U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 021567/S026
Drug Name:	Reyataz™, Atazanavir
Indication(s):	Treatment of HIV infected Infants, Children and Adolescents
Applicant:	BRISTOL-MYERS SQUIBB
Date(s):	• Stamp date 12/17/10 • PDUFA goal date - 10/17/11 • Primary reviews due by 09/12/11
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Biometrics Division:	DB IV
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Phase I/II, Open-Label, Pharmacokinetic and Safety Study; Protease Inhibitor; pediatrics; geographic difference; multiple centers; missing data; adverse events (AE); stratification; subgroup analyses; antiretroviral-naive, HIV-1 infected; Pediatric study.

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1. EXECUTIVE SUMMARY

Bristol-Myers Squibb (BMS) submitted a Supplemental New Drug Application (sNDA) to NDA 21567: Reyataz®(atazanavir sulfate) Capsules, which received US FDA approval on June 20, 2003. The submission included a single clinical trial (AI424020) to provide clinical support of the revised dosing recommendations that are higher than those currently approved (in the 15 to 20 kg and 20 to 25 kg weight bands), in additional to the modeling and simulation analysis.

BMS acknowledged that there are only a total of seven (7) subjects between these two weight bands who received the newly proposed recommended dose or higher and provided several options to FDA for consideration. FDA agreed for BMS to proceed with one option, which was to submit a supplement with an updated AI424020 database for an updated Clinical Study Report focusing on subjects receiving the recommended doses or higher along with the Modeling and Simulation report.

All but one of the seven (7) subjects who were administered the recommended dose or higher had virologic success (HIV RNA < 50 c/mL) at Week 96. A similarly high virologic success rate was also observed in the other than the recommended doses in a matched population. Although subjects who were administered the recommended dose or higher had numerically higher virologic success rate than in other cohorts, we cannot draw any conclusion by only comparing the recommended doses to other doses in terms of the virologic success due to the small sample size.

This review mainly focuses on the sponsor's proposal on presenting the virologic response of Week 96 on the label, resulted from all 105 subjects in the capsule cohort in AI424020. We agree with the sponsor to report the efficacy data, but at the same time we caution not to interpret these data as if they were obtained from a well controlled, double blinded, randomized trial. This is basically a nonrandomized, open label, single arm trial. It is well known that the efficacy data generated from this type of trials may be subject to bias, therefore the results should not be considered as the equal value as those obtained from well controlled, double blind, randomized trials.

As one example to illustrate the difficultly to interpret the data, we report that there is a significant geographic difference between the United States and the South Africa, the two exclusive regions in the trial and acknowledge that we do not know exactly what is responsible for the difference. The geographic difference could be due to a combination of the following factors: differences in compliance and drug adherence (adherence data from the South Africa is not collected); different laboratories in two regions used to measure HIV RNA levels and different recording systems; drug availability difference; and potential confounders such as age, dosage, anti-retroviral drug experience, or other conscious or subconscious factors, or random errors. However, the nature of the nonrandomized, open label, single arm trial makes it difficult to make a conclusion with high confidence.

2. INTRODUCTION

2.1 Overview

The atazanavir (ATV, a protease inhibitor) capsule dosing recommendation for pediatric subjects was approved by the US Food and Drug Administration (FDA) in March 2008 and in other countries, for treatment of HIV.

The sponsor submitted a single trial AI424020 (see Table 1) to FDA and one of the sponsor's intentions is to include this study's Week 96 efficacy data to update the label. The same study, with an earlier cut of data (Week 24), was submitted before to support the indication of ATV in children with HIV.

Although it looks like there are two arms: ATV, ATV with Ritonavir (RTV) in the trial, it is more appropriate to consider it a single arm trial. This is a trial focusing on ATV and there basically is no randomization between two groups. At the time of initial protocol development, only the ATV arm was included and the study was later modified to include regimens of ATV with RTV arm. Among all 105 subjects, most subjects in the ATV arm were enrolled in years 2001-2004; most subjects in the ATV with RTV arm were enrolled in years 2005-2007.

Table 1: list of studies

Study	Phase and Design	Study Period	Design	# of Subjects per Arm	Study Population
AI424020	Phase I/II	Start: 16-Nov-2000; cutoff date: 21-Sep-2010	Single arm	105	HIV-Infected Infants, Children and Adolescents

Trial AI424020 is a Phase I/II, open-label, pharmacokinetic and safety study in combination regimens in antiretroviral therapy (ART)-naive and experienced HIV-infected infants, children and adolescents. It is basically a nonrandomized and single arm study in which subjects were assigned to the treatment without randomization. A total of 105 subjects were enrolled in the United States (72 subjects) and the South Africa (33 subjects).

2.2 Data Sources

Study report and Datasets

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3. STATISTICAL EVALUATION

3.1 The quality of the Submission

The reviewer is able to reproduce the primary endpoint, the HIV RNA level, from the raw dataset. On the other hand, the sponsor's define file can be defined better to facilitate the regulatory review. For example, in the define file for the raw data, the important variable "QUALIF" (the censoring indicator of the HIV RNA level) from the HIV RNA dataset has no definition. We finally understood the importance of the variable but it took several rounds of communications with the sponsor before we were able to trace to this variable and understand its importance. For another example, on the TXW0097 (the dataset of study medication) page of the file blackcrf_raw.pdf, it is stated "Refer to Appendix 3" but Appendix 3 was not submitted until we requested after we realize it is missing. These types of problems exist abundantly in the submission and created unnecessarily extra work.

3.2 Evaluation of Efficacy

Study Design and Endpoints

This is a multicenter, open-label trial conducted in the United States and South Africa to determine the safety, PK, and optimal dose of ATV powder and capsules, administered with or without RTV, in pediatric subjects (age 91 days to 21 years) infected with HIV. Subjects were ARV-naive or experienced.

Design

Subjects were enrolled by age, ATV formulation, and concomitant administration of RTV into 8 groups as shown in Table 2.

Table 2: enrollments

ATV without RTV	ATV with RTV	Formulation	Age Ranges
Group 1	Group 5	Powder	Infants 3 months to ≤ 2 years
Group 2	Group 6	Powder	Children > 2 to ≤ 13 years
Group 3	Group 7	Capsules	Children > 2 to ≤ 13 years
Group 4	Group 8	Capsules	Adolescents > 13 to ≤ 21 years

At the time of initial protocol development, only Groups 1-4 were implemented. The starting data is the end of 2000. The study was later modified in the year of 2003, in the protocol version 4, to include regimens of ATV with RTV in Groups 5-8. The study was closed to accrual on 24-Jan-2007, and the final accrual was 183 subjects.

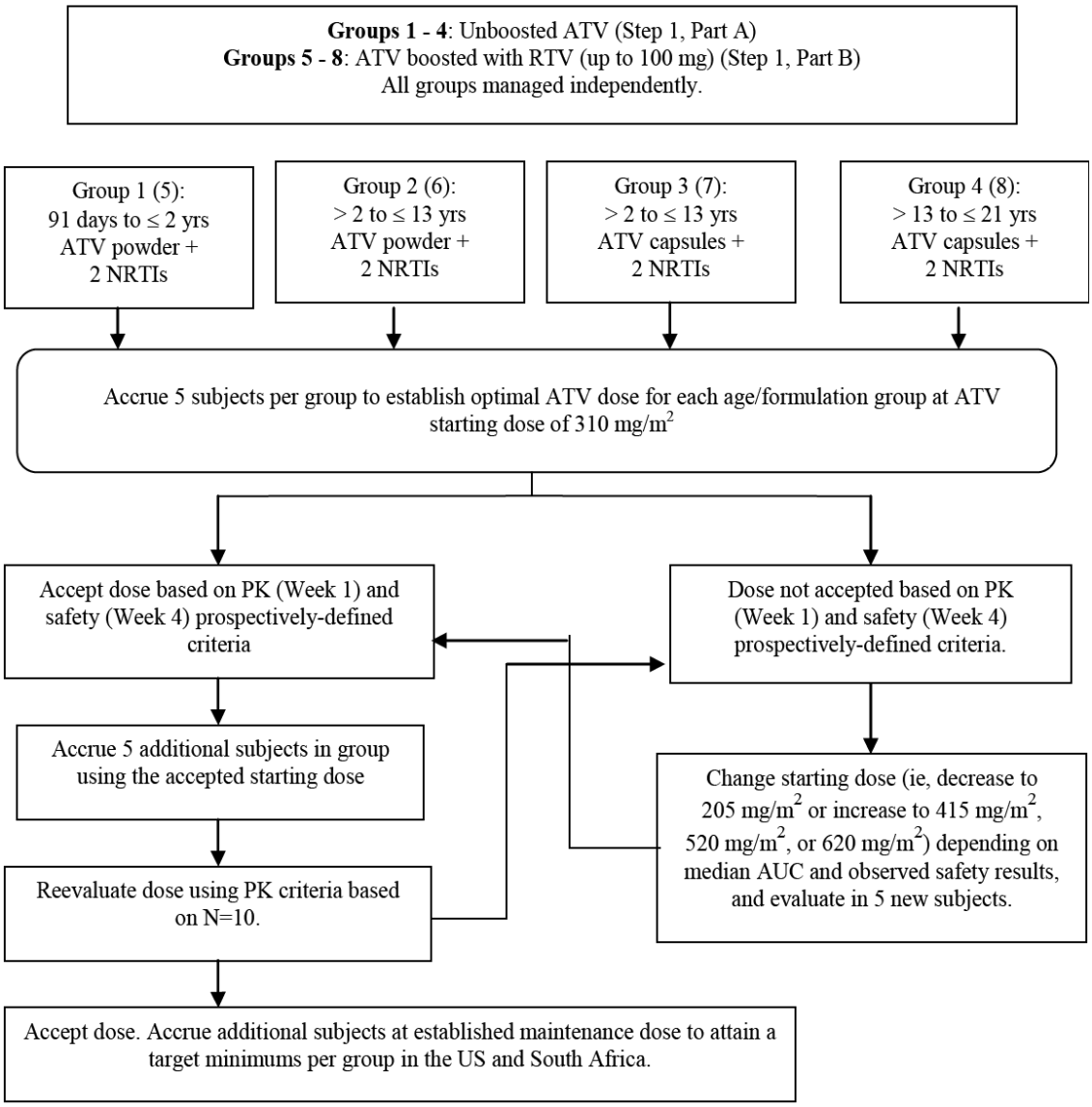
Eligible subjects were assigned to dose based on body surface area. Step 1 (dose-finding) was conducted in the US and South Africa, and consisted of 2 parts:

Part A: ATV plus 2 NRTIs (excluding abacavir sulfate and tenofovir disoproxil fumarate).

Part B: ATV/RTV plus 2 NRTIs (excluding abacavir sulfate and tenofovir disoproxil fumarate).

Nucleoside backbone therapy was determined on the basis of the viral genotypic and phenotypic resistance profile and/or the subject's treatment history. All groups began at 310 mg/m^2 of ATV QD; the boosted groups also received RTV 100 mg/m^2 QD. All groups escalated or decreased ATV doses based on PK exposure targets and safety criteria. See Figure 1.

Figure 1: study design



In January 2009, Step 2 was opened to South African subjects who were virologically responding to treatment when the last enrollee into either part of Step 1 (Part A or Part B) had completed 96 weeks of treatment (end of Step 1). Step 2 is ongoing, at the time of the submission, in South Africa until ATV is approved and readily available.

Subjects were basically assigned into different groups without randomization. Only if both the ATV and ATV/RTV groups still needed subjects for a particular age category, the subject was randomized to determine which treatment regimen was to be assigned. The randomization department used the subject enrollment system (computer generated permuted block algorithm: block size of 4, 2 of each treatment in a block) to randomly select the treatment.

In this submission, the sponsor only provides information on the ATV Capsule Cohort. That is, only subjects enrolled into group 3, 4, 7, and 8 were included in this submission.

Endpoints

Efficacy variables included the percentage of subjects who achieved virologic response (VR) among all enrolled subjects and the percentage of subjects who achieved virologic response-observed cases (VR-OC) (HIV RNA < 50 or < 400 c/ml) among all subjects with observed viral load measurements at Week 96, as well as CD4 counts and changes from baseline through Week 96 for the ATV Capsule Cohort only. VR-OC is the percentage of subjects who achieved virologic response among subjects who remained on study therapy through Week 96 and who had no missing measurements (subjects with missing measurements are excluded from the analysis).

Safety variables for this interim analysis included AEs (all grades and Grade 2-4), serious adverse events (SAEs), deaths, discontinuations due to AEs, laboratory abnormalities (hematology, liver function tests, serum chemistry, including lipids and glucose) cardiac disorders, ECG evaluations (abnormalities, individual parameters, and changes from baseline at Weeks 1 and 56), and the frequency of acquired immunodeficiency syndrome-related events.

HIV RNA was measured using the Roche Amplicor polymerase chain reaction (PCR). The lower and upper limits of quantification (LOQ) of the ultra sensitive assay are 50 c/mL and 100,000 c/mL, respectively. The HIV RNA levels were measured in difference central laboratories and were reported using different systems in South Africa and the United States (reference: support document number 322, dated June 09, 2011). All HIV RNA levels from South Africa were measured in a single International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) certified central laboratory. In South Africa, HIV RNA level was entered on the case report form (CRF). In the United States, HIV RNA came directly from the Laboratory Data Management System (LDMS). After the sample was assayed by the laboratory, the HIV RNA value was input into the LDMS, which assigned a censor code to HIV RNA < 50 c/mL.

Discontinuation:

Subjects were to be discontinued from Step 1 for any of the following reasons:

1. Treatment failure as defined by:

a. Less than 1 log10 reduction from baseline in plasma HIV RNA level by Week 16, confirmed by a second plasma HIV RNA level obtained within 30 days.
b. Plasma HIV RNA level > 10,000 c/mL on 2 successive determinations in a subject who had previously achieved a HIV RNA level of < 400 c/mL, confirmed by a second plasma HIV RNA level obtained within 30 days.

Subjects who met the above criteria for treatment failure could have remained in the study if the protocol chairperson, investigator, and subject (or parent/legal guardian) agreed that it was in the subject's *best* interest to remain on his/her current treatment.

2. Discontinuations mandated by protocol-defined safety parameters.

3. Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicated that continued treatment with study therapy was not in the best interest of the subject.

4. Withdrawal of informed consent (subject's or parent/legal guardian's decision to withdraw for any reason).

5. Failure to comply with study requirements that would have resulted in harm to the subject or seriously interfered with validity of study results.

6. Required treatment with disallowed medications.

7. Pregnancy.

A cohort of a few subjects in the 15 to 20 kg and 20 to 25 kg weight bands received revised dosing recommendations that are higher than those currently approved. This cohort is a subset of the ATV Capsule Cohort and includes subjects 6 to < 18 years in the 15 to < 20 kg weight band who were taking >=150 mg of ATV capsule plus >=100 mg of RTV (solution or capsule) for at least 24 weeks or subjects 6 to < 18 years in the 20 - 25 kg weight band who were taking >=200 mg of ATV capsule plus >=100 mg of RTV (solution or capsule) for at least 24 weeks.

Comments:

- The trial is designed as a single arm, nonrandomized, and open label trial, similar to many other pediatric trials. Results from the trial may not have the equal credibility as a well controlled, randomized, double blind trial.

- The endpoint, HIV RNA level, and the assay used for RNA level determination are standard. However, it would be preferable if all measurements of HIV RNA levels could be performed in one central laboratory as the sponsor planned and if results were reported using the same system, which did not happen in this trial.

- The cohort of subjects is rather small in the 15 to 20 kg and 20 to 25 kg weight bands received revised dosing recommendations that are higher than those currently approved. Consequently, we do not expect any conclusion could be made only based these limited clinical information obtained from this trial.

Patient Disposition, Demographic and Baseline Characteristics

A total of 105 subjects were enrolled into the trial. Among them, 46 subjects discontinued due to different reasons: 6 subjects discontinued due to virologic failures; 14 due to AEs, and 26 due to other reasons such as protocol compliance, loss to follow up, etc. All subjects in the recommended dose cohort completed the Week 96 study.

Table 3: Patient disposition by week 96

TREATMENT REGIMEN			
	ATV N = 63	ATV/RTV N = 42	TOTAL N = 105
Completed	**35 (56%)**	**24 (57%)**	**59 (56%)**
Discontinued	**28 (44%)**	**18 (43%)**	**46 (44%)**
Failure	6 (9%)	0 (0%)	6 (6%)
AEs	8 (12%)	6 (15%)	14 (13%)
Others	14 (22%)	12 (29%)	26 (25%)

Source: reviewer's analysis, generally match the sponsor's result in Table 5.1.A.

The primary efficacy analysis population is the entire enrolled population of 105 subjects. Of the 105 subjects in the ATV Capsule Cohort, 72 (69%) were treated at sites in the United States and 33 (31%) were treated at sites in South Africa. Demographic characteristics are listed by subject in Table 4.

Table 4: Demography

TREATMENT REGIMEN			
	ATV N = 63	ATV/RTV N = 42	TOTAL N = 105
Age (Years) MEAN (SD)	11.9 (3.5)	11.6 (3.6)	11.8 (3.5)
Gender: N (%)			
FEMALE	33 (52)	22 (52)	55 (52)
MALE	30 (48)	20 (48)	50 (48)
Race Group: N (%)			
BLACK	38 (60)	29 (69)	67 (64)
WHITE	14 (22)	10 (24)	24 (23)
OTHER	11 (17)	3 (7)	14 (13)
Region: N (%)			
NORTH AMERICA	42 (67)	30 (71)	72 (69)
AFRICA	21 (33)	12 (29)	33 (31)

Source: reviewer's analysis, matches with the sponsor's results if reported**.**

The median baseline HIV RNA plasma level was 4.49 log10 copies/ml. Overall, about a quarter (24%) of the subjects had baseline HIV RNA levels >= 100,000 c/ml. The median baseline CD4 counts was 386 and 24% of the subjects had baseline CD4 counts < 200 cells/mm^3. See Table 5.

Table 5: Baseline characteristics

TREATMENT REGIMEN			
	ATV N = 63	ATV/RTV N = 42	TOTAL N = 105
Baseline viral loads (log10) MEAN (SD)	4.5 (0.5)	4.3(0.6)	4.4 (0.5)
Baseline CD4 cell counts MEAN (SD)	386 (251)	454(257)	414(254)
Baseline viral loads: N(%)			
≤100,000 copies/ml	45(71%)	35(83%)	80(76%)
>100,000 copies/ml	18(29%)	7(17%)	25(24%)
CD4 cell counts: N(%)			
≤200 cells/mm^3	16 (25%)	9(21%)	25(24%)
>200 cells/mm^3	47(75%)	33 (79%)	80(76%)

Source: reviewer's analysis based on analysis data, matches with the sponsor's results if reported.

Statistical Methodologies

The original statistical analysis plan includes no formal test of statistical significance. Only descriptive statistics are presented. It also states that Time to Loss of Virologic Response

(TLOVR) at Week 24 will be reported. However, the original statistical analysis plan does not specify any analysis for Week 96 data.

The analyses that the sponsor provided at the initial submission are as follow. Efficacy variables include the percentage of subjects who achieved virologic response (VR) or virologic response-observed cases (VR-OC) (HIV RNA < 50 or < 400 c/mL) at Week 96, as well as CD4 counts and changes from baseline through Week 96 for the ATV Capsule Cohort only. In the VR analysis, subjects with missing measurements are treated as failures; In the VR-OC analyses, subjects with missing measurements are excluded from the analysis. The sponsor also conducted observed case analysis for CD4 in which subjects with missing measurements are excluded from the analysis as well.

Comments:

1. We disagree with the label (b) (4) originally proposed by the sponsor. (b) (4)

2. In order to report efficacy results using our current labeling paradigm for efficacy in HIV, we requested the sponsor analyze the efficacy data using the snapshot algorithm. The reviewer performs the snapshot algorithm as well. The snapshot algorithm, which separates discontinuation due to virologic failure, AEs from other reasons of discontinuation such as loss-to follow up, withdrew consent; expect to covey more information (b) (4).

3. The sponsor reported the observed case analysis for CD4 counts as well. However, because subjects with missing measurements were excluded from the analysis, this unlikely provides the best description of the efficacy results.

4. We conducted some more sensitivity analyses for CD4 analyses, such as last observation carry forward (LOCF), baseline observation carry forward (BOCF), and multiple imputation (MI). Because there are different ways of conducting MIs and the underlying assumption may not be satisfied, we shall briefly comment on the results but do not report the actual numbers.

Results and Conclusions

The sponsor reported the VR-OC analysis that, among 105 subjects in the ATV Capsule Cohort (6 to < 18 years of age) were treated with the ATV capsule formulation, with or without RTV, the overall proportions of antiretroviral (ARV)-naive and -experienced subjects with HIV RNA < 400 copies/mL at Week 96 were 78% (21/27) and 66% (21/32), respectively. The overall proportions of ARV-naive and -experienced subjects with HIV RNA < 50 copies/mL at Week 96 were 74% (20/27) and 47% (15/32), respectively. See Table 6 for details. Table 6 also reports the VR analysis results.

Table 6: virologic response

Method LOQ	**ARV-naive** **N = 43**	**ARV-experienced** **N = 62**
VR at Week 96 <400 c/mL <50 c/mL	 21/43 (49%) 20/43 (47%)	 21/62 (34%) 15/62 (24%)
VR-OC at Week 96 <400 c/mL <50 c/mL	 21/27 (78%) 20/27 (74%)	 21/32 (66%) 15/32 (47%)

Reference: Table 7.3.1. Study report.

(b) (4)

Following our request, the sponsor analyzed the efficacy data using the snapshot algorithm. The overall proportions of ARV-naive and -experienced subjects with HIV RNA < 50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The overall proportions of ARV-naive and -experienced subjects with virologic failure at Week 96 were 30% (13/43) and 58% (36/62), respectively. The overall proportions of ARV-naive and -experienced subjects discontinued due to AEs prior to Week 96 were 12% (5/43) and 18% (11/62), respectively. Note that AEs counts for all discontinuations due to reasons other than virologic failure in ARV-experienced subjects. See Table 7 for details.

Table 7: snapshot results by ARV experience at Week 96

	ARV-naive **N = 43**	**ARV-experienced** **N = 62**
Success (less than 50 copies/ml)	**20 (47%)**	**15 (24%)**
Failure	**13 (30%)**	**36 (58%)**
No Virologic Data at Week 96 Window Discontinued study due to AE Discontinued study for Other Reasons	**10 (23%)** 5 (12%) 5 (12%)	**11 (18%)** 11 (18%) 0

Reference: SDN 318, dated May 6, 2011. Results are consistent with the reviewer's analysis.

Results by treatment are presented in Table 8.

Table 8: snapshot results by treatment (<50 c/ml) at Week 96

	ATV N=63	**ATV/RTV N=42**
Virologic Success (less than 50 copies/ml)	**17 (27%)**	**18 (43%)**
Virologic Failure	**33 (52%)**	**16 (38%)**
No Virologic Data at week 96 Window Discontinued study due to AE Discontinued study for Other Reasons	**13 (21%)** 10 (16%) 3 (5%)	**8 (19%)** 6 (14%) 2 (5%)

Reference: Reviewer's analysis

All but one of the seven (7) subjects who were administered the recommended dose or higher had virologic success. The failed subject suppressed during the study, rebounded, reached < 50 c/mL again, but ultimately remained above 50 c/mL. Because all seven subjects were in the ATV/RTV group and they are from South Africa and all ARV naive, we compared them to the four (4) subjects from South Africa who are ARV naïve and were administered ATV/RTV. The results are given in
Table 9. There appears no significant difference in two comparing groups. On the other hand, no conclusion can be drawn by comparing the recommended doses to other doses in terms of the virologic success due to the small sample size.

Table 9: snapshot results by treatment (recommended does vs others then recommended doses) at Week 96

Treatment=ATV/RTV, ARV naïve; South Africa;	Recommended dose N=7	Other than recommended dose N=4
Virologic Success (less than 50 copies/ml)	**6 (86%)**	**3 (75%)**
Virologic Failure	**1 (14%)**	**0 (0%)**
No Virologic Data at week 96 Window Discontinued study due to AE Discontinued study for Other Reasons	**0 (0%)** 0 (0%) 0 (0%)	**1 (25%)** 0 (0%) 1 (25%)

Reference: Reviewer's analysis

We also conducted a further study comparing the cohort with recommended dose to 25 subjects who are ARV- naïve from South Africa. Among them, 13 (52%) had virologic success. Again, numerically the virologic response rate in the cohort of recommended is higher, however the difference in virologic success between the cohorts of recommended and other than recommended doses is not statistically different,

The sponsor reported the observed case analysis for CD4 counts. The mean increase from baseline in absolute CD4 count at 96 weeks of therapy was 394 cells/mm^3 in ARV-naive subjects and 252 cells/mm^3 in ARV-experienced subjects. See Table 10. However, since subjects with missing measurements were excluded from the analysis, it does not provide the best description of the efficacy results.

Table 10: CD4 changes from baseline to Week 96

TREATMENT REGIMEN			
MEAN (SD)	ATV N = 63	ATV/RTV N = 42	TOTAL N = 105
increase of CD4 counts Observed case	306 (261)	339(296)	319(273)
	ARV-Naive N =43	ARV-experienced N = 62	TOTAL N = 105
increase of CD4 counts Observed case	394 (310)	252(220)	319(273)

Reference: reviewer's analysis, which matches the sponsor's result.

We conducted some more sensitivity analyses, such as last observation carry forward (LOCF), baseline observation carry forward (BOCF), and multiple imputation (MI) (results not shown). The results (except for MI) are given in Table 11. As we can see from Table 11, results are fairly different. Although we do not consider the observed case analysis is preferable, we cannot claim that LOCF and BOCF are preferable too. Results from MI are also different from any of these methods and the missing at random assumption that validates MI is unlikely the reality from some ad hoc analyses we assessed (results not shown).

Table 11: Changes of CD4 counts from baseline to Week 96

TREATMENT REGIMEN			
MEAN (SD)	ATV N = 63	ATV/RTV N = 42	TOTAL N = 105
Increase of CD4 counts			
Observed case	306 (261)	339(296)	319(273)
BOCF	173(248)	194(279)	181(260)
LOCF	238(239)	214(298)	228(263)
ARV-EXPERIENCE			
	ARV-Naive N =43	ARV-experienced N = 62	TOTAL N = 105
increase of CD4 counts			
Observed case	394 (310)	252(220)	319(273)
BOCF	256(313)	128(201)	181(260)
LOCF	343(272)	147(225)	228(263)

Reference: reviewer's analysis, match the sponsor's results if reported.

3.3 Evaluation of Safety

Please refer to clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Among 55 female subjects, 15 (27%) had virologic success; among 50 male subjects, 20 (40%) had virologic success. The rates of virologic success among female and male subjects are not significantly different (p=0.21). Similarly, no significant difference is observed among subjects with different races. See Table 12.

On the other hand, the virologic response rate is higher in younger (<=13 years old) kids than older kids (>13 years old). The rates of 15% observed in older kids is significantly (p-value=0.00072) smaller than the rate of 47% observed in younger kids. See Table 12.

The virologic response rate is higher in kids from South Africa than kids from the United States. The rates of 58% observed in kids from South Africa is significantly (p-value=0.00068) smaller than the rate of 22% observed in kids from the United States. See Table 12.

Table 12: Subgroup analysis of virologic success

TREATMENT REGIMEN			
MEAN (SD)	ATV N = 63	ATV/RTV N = 42	TOTAL N = 105
Gender			
Female	24% (8/33)	32% (7/22)	27%(15/55)
Male	30% (9/30)	55% (11/20)	40%(20/50)
Race			
Black	29% (11/38)	42% (12/29)	34% (23/67)
Other	18% (2/11)	67% (2/3)	29% (4/14)
White	29% (4/14)	40% (4/10)	33% (8/24)
Age			
>13-18 years old	16% (5/32)	14% (2/14)	15% (7/46)
> 2-13 years old	39% (12/31)	57% (16/28)	47% (28/59)
Region			
South Africa	48% (10/21)	75% (9/12)	58% (19/33)
US	17% (7/42)	30% (9/30)	22% (16/72)

Reference: reviewer's analysis.

We do not understand why the virologic response rates between two regions are different and further investigate for possible confounding in this non-randomized trial. We list results for two regions stratified by some key factors: treatment, antiretroviral (ARV) experience, and age group. The results are given in Table 13. It appears that the inferior results in the US sites happen in applicable categories, except in the subgroup of ARV experienced subjects administered ATV/RTV who are between 13-18 years old. Thus, the geographic difference is unlikely caused only by confounding of these key factors we investigated. Some additional factors may contribute to the geographic difference. See Table 13.

Table 13: stratified analysis of regional difference.

Virologic response rate (<50 copies/ml at Week 96)	South Africa (N=33)	USA (N=72)
ATV, naïve, >13-18 years old	36% (4/11)	0% (0/4)
ATV, naïve, >2-13 years old	60% (6/10)	0% (0/1)
ATV, experienced, >13-18 years old	NA (0/0)	6% (1/17)
ATV, experienced, >2-13 years old	NA (0/0)	30% (6/20)
ATV/RTV, naïve, >13-18 years old	NA (0/0)	0% (0/4)
ATV/RTV, naïve, >2-13 years old	82% (9/11)	50% (1/2)
ATV/RTV, experienced, >13-18 years old	0% (0/1)	22% (2/9)
ATV/RTV, experienced, >2-13 years old	NA (0/0)	40% (6/15)

Reference: reviewer's analysis.

Next, we focus on 30 ARV-naïve black subjects from South Africa and nine (9) ARV-naïve black subjects from the United States, in a hope to identify reasons for the geographic difference. The results from Table 14 further confirm that results are significantly favorable in South Africa than in the United States.

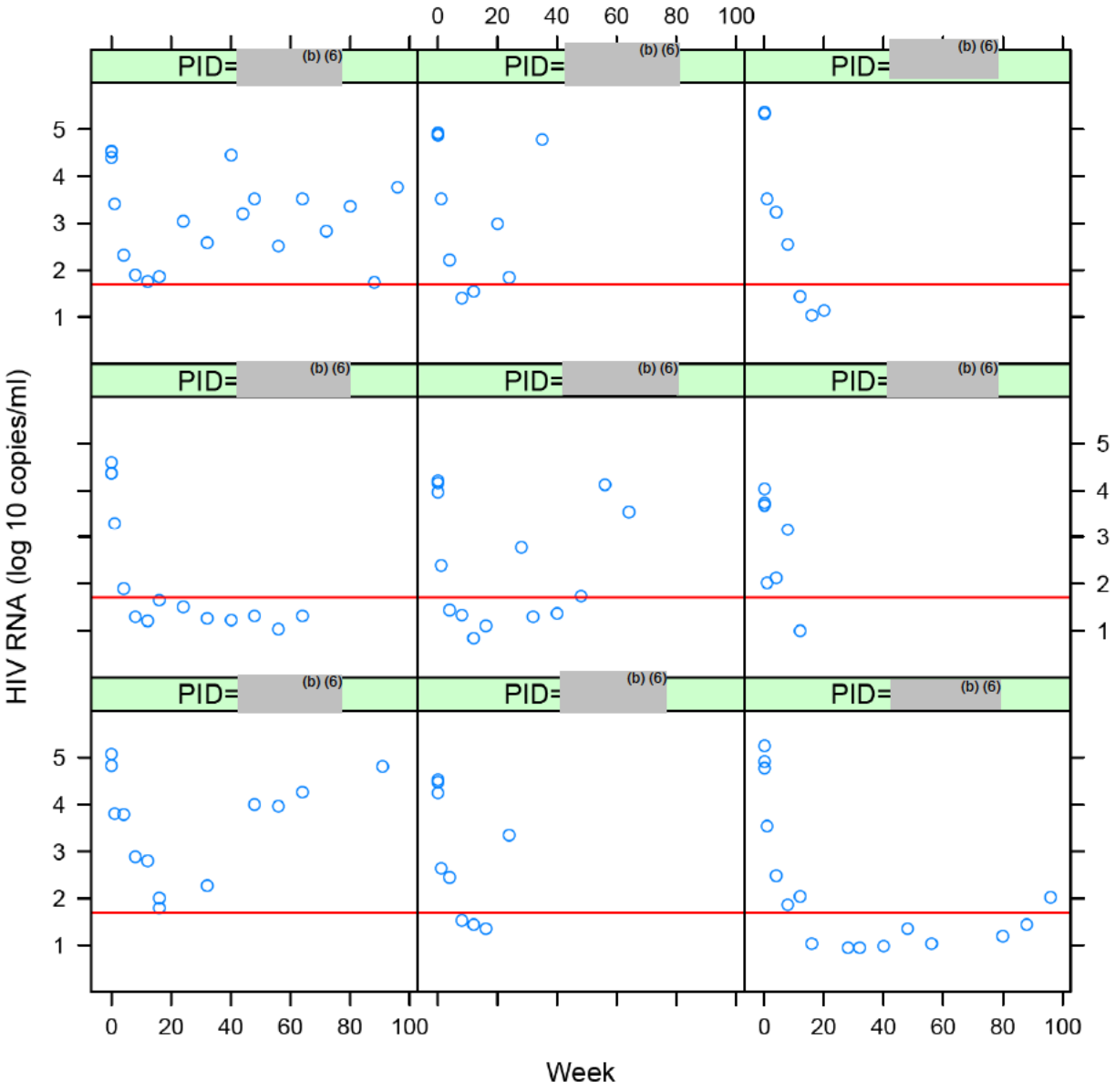
Table 14: 30 ARV-naïve blacks subjects from south Africa and 9 ARV-naïve black subjects

Virologic response rate (<50 copies/ml at Week 96)	USA/ATV N=4	Africa/ATV N=20
Virologic Success	0 (0%)	9 (45%)
Virologic Failure	2 (50%)	5 (25%)
Discontinued study due to AE	0 (0%)	5 (25%)
	USA/ATV+RTV N=5	Africa/ATV+RTV N=10
Virologic Success	0 (0%)	8 (80%)
Virologic Failure	4 (80%)	1 (10%)
Discontinued study due to AE	0 (0%)	0 (0%)

Reference: reviewer's analysis.

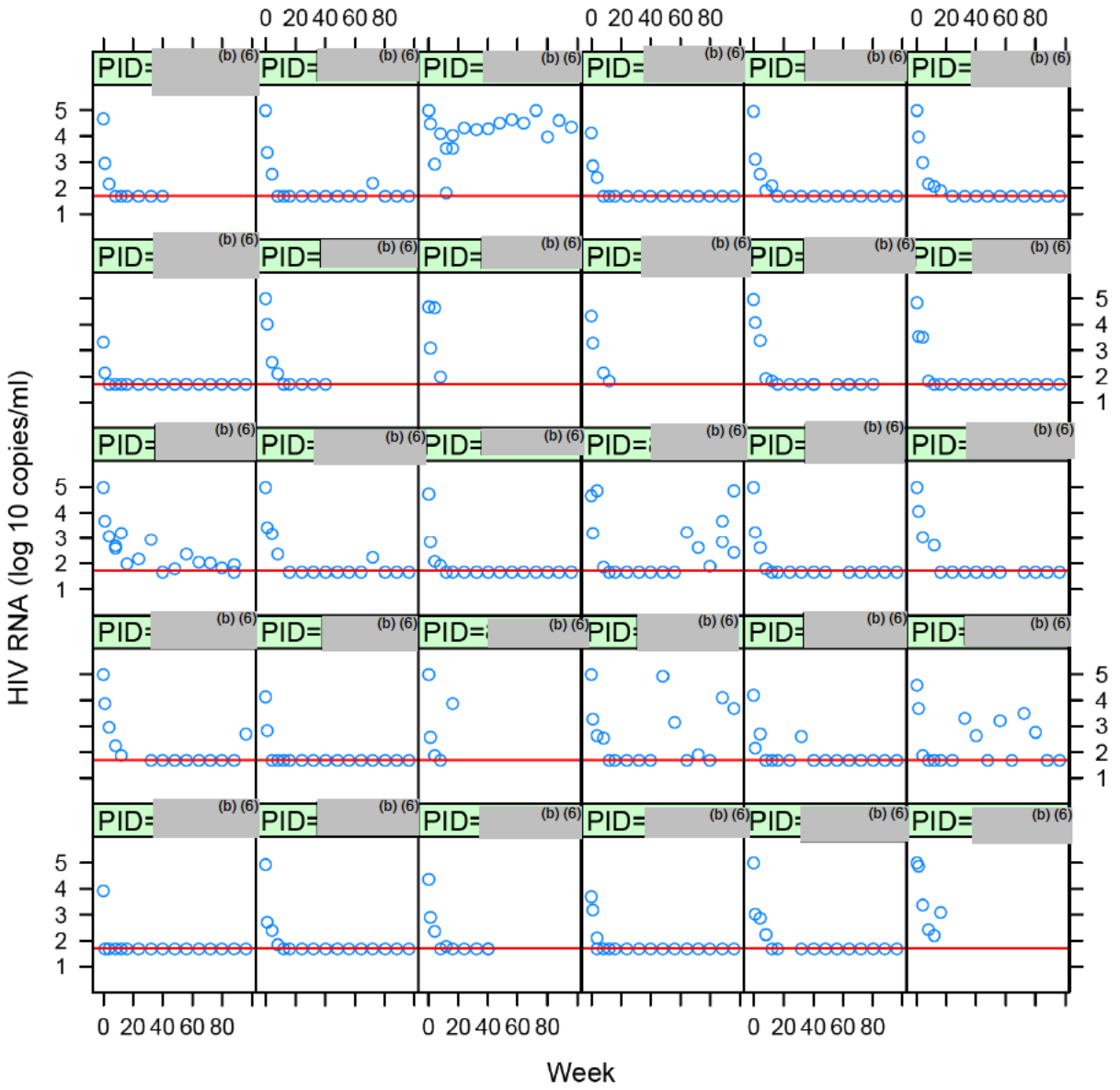
We below conduct some exploratory analyses for these 39 subjects to understand more about the geographic difference. Among the nine subjects from the United States, three completed and they are failures (completed the study up to the Week 96 windows but their viral load is above 50 copies/ml at Week 96). All other six (6) subjects discontinued earlier (three had no viral loads suppression at time of discontinuation and the remaining three are either loss to follow up or unwilling to participate after site closure). Among these six (6) discontinued subjects, two (2) subjects are related to non-compliance; two (2) subjects lost to follow-up; One subject was pregnant; one subject did not want to transfer after the original site the subject participated is closed. See Figure 2 for the viral load profile for these nine subjects.

Figure 2: virologic responses for the 9 ARV-naïve black subjects from the United States (the red line is reference line of log10(50 copies/ml)).



Among 30 black subjects who are ARV-naïve, 17 had virologic success at Week 96. Among the 13 subjects did not have virologic success at Week 96, five (5) discontinued due to AEs; 1 for doctor's decision to switch treatment; 1 loss to follow up; 3 non-compliances. See Figure 3 for the viral load profile for these 30 subjects.

Figure 3. Virologic responses for the 9 ARV-naïve black subjects from the South Africa (the red line is reference line of log10(50 copies/ml)).



As a summary, we report the following exploratory results for the ARV-naïve black subjects from two regions: 1) US. Subjects had a higher non-compliance rate (20%) that subjects from South Africa (10%); 2) US. Subjects had a loss to follow-up rate (20%) those subjects from South Africa (3%); 3) US. Subjects had a lower AE rate (0%) that subjects from South Africa (17%). 4) US. Subjects had a higher rate (20%) of random events (pregnancy, site closure, doctor's decision) that subjects from South Africa (3%).

Consequently, the geographic difference could be driven by non-compliance, loss to follow-up, and some other events happened in a random manner. However, the natural of the single arm and open label makes a conclusion difficult.

4.2 Other Special/Subgroup Populations

Like what we observed in other trials, subjects with higher baseline viral loads are more likely to fail than subjects with low baseline viral loads. See Table 15 for details. Again, on the other hand, the results further confirm the geographic difference.

Table 15: stratified analysis of response (higher or low baseline viral loads)

Virologic response rate (<50 copies/ml at Week 96)	South Africa N=33	USA N=72
ATV, naïve, baseline HIV RNA>100,000 copies/ml	33% (3/9)	0% (0/1)
ATV, naïve, baseline HIV RNA<=100,000 copies/ml	58% (7/12)	0% (0/4)
ATV, experienced, HIV RNA>100,000 copies/ml	NA (0/0)	0% (0/8)
ATV, experienced, HIV RNA<=100,000 copies/ml	NA (0/0)	24% (7/29)
ATV/RTV, naïve, HIV RNA>100,000 copies/ml	83% (5/6)	NA (0/0)
ATV/RTV, naïve, HIV RNA<=100,000 copies/ml	80% (4/5)	17% (1/6)
ATV/RTV, experienced, HIV RNA>100,000 copies/ml	0% (0/1)	NA (0/0)
ATV/RTV, experienced, HIV RNA<=100,000 copies/ml	NA (0/0)	33% (8/24)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

All but one of the seven (7) subjects who were administered the recommended dose or higher had virologic success (HIV RNA < 50 c/mL) at Week 96. A similarly high virologic success rate was also observed in the other than the recommended doses in a matched population. Although subjects who were administered the recommended dose or higher had numerically higher virologic success rate than in other cohorts, we cannot draw any conclusion by only comparing the recommended doses to other doses in terms of the virologic success due to the small sample size.

We found that some virologic response results obtained from this trial are difficult to interpret. First, we note that there is a significant geographic difference between the United States and the South Africa, the two exclusive regions and acknowledge that we do not know what contributed to the difference. The geographic difference could be due to the following factors or a combination of these factors: drug adherence (adherence data from the south Africa is not collected); difference laboratories in two regions used to measure HIV RNA levels and different

recording systems; drug availability; and potential confounders such as age, dosage, anti-retroviral drug experience, or random errors in additional to other factors. However, the nature of the nonrandomized, open label single trial makes it difficult to make a conclusion. Second, the sponsor proposed analysis of CD 4 counts may not be the preferred analysis. On the other hand, results from different sensitivity analyses are very different. Drawing a conclusion from them seems to be difficult due to the missing CD4 counts data.

5.2 Conclusions and Recommendations

No conclusion can be drawn by only comparing the recommended doses to other doses in terms of the virologic success due to the small sample size. We agree with the sponsor to report the efficacy data, but the same time we caution not to interpret these data as they were obtained from a well controlled, double doubling, randomized trials. This is basically a nonrandomized, open label, single arm trial. As we were cautioned for all of this type of studies, the efficacy data generated from these studies may subject to bias and therefore the results should not be considered as the equal value as those obtained from well controlled, double blind, randomized trials.

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