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 #:	206352 21567
Supplement #:	S-003 S-038
Drug Name:	Reyataz® (atazanavir sulphate, ATV)
Proposed Indication:	Reyataz for use in combination with other antiretroviral agents for the treatment of HIV-1 infection for patients 3 months and older weighing at least 5 kg
Applicant:	Bristol-Myers Squibb
Date(s):	Submission Date: 03/27/2015 Primary Review Date: 09/03/2015 PDUFA Date: 09/25/2015
Review Priority:	Priority
Biometrics Division:	DB4
Statistical Reviewer:	Fraser Smith, Ph.D.
Concurring Reviewers:	Greg Soon, Ph.D.
Medical Division:	Division of Antiviral Products.
Clinical Team:	Medical Reviewer: Alan Shapiro, M.D. Medical Team Leader: Mary Singer, M.D., Ph.D.

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Project Manager: Suzanne Strayhorn, M.Sc.

Keywords:

PRINCE I, PRINCE II, atazanavir, powder cohort, snapshot algorithm, last observation carried forward

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1 EXECUTIVE SUMMARY

Atazanavir (ATV) in combination with other antiretroviral agents has been approved to treat HIV-infected adults and pediatric patients ≥ 6 years of age. The applicant has developed the ATV powder formulation for oral use in pediatric patients who are unable to swallow a solid oral dosage form to fulfill a post-marketing commitment. The pediatric indication and dosage recommendation for children was based on the results of Study PACTG 1020-A (AI424020) which was a single-arm, dose-finding, pharmacokinetics (PK) study. Two Phase 3B pediatric studies, i.e., PRINCE I (Study AI42439) and PRINCE II (Study AI424451), were conducted to confirm the dose of ATV powder formulation with ritonavir (RTV) in infant and children ≥ 3 months to 11 years who were either HIV treatment-naïve (TN) or treatment-experienced (TE).

The ATV dosing depended on the subject's baseline body weight, namely, 150 mg in PRINCE I and 150 mg or 200 mg in PRINCE II for subjects weighing 5 to less than 10 kg, 200 mg for subjects weighing 10 to less than 15 kg, 250 mg for subjects weighing 15 to less than 25 kg, and 300 mg for subjects weighing 25 to less than 35 kg. After the 48 weeks of the powder treatment, the subjects in both studies would switch to the ATV capsule treatment which they could take until the subjects reached 18 years of age. In terms of study conduct, the 48-week ATV powder treatment phase had completed in the PRINCE I study; however subjects in the PRINCE II study completed 24 weeks of ATV powder treatment but the final clinical study report was submitted before all subjects to the opportunity to complete their Week 48 visit. In addition, many subjects in PRINCE I were reclassified from ARV naïve (TN) to ARV experienced (TE) after the interim analysis that was used for the initial label.

The two Phase 3B studies included in the submission supported the recommended ATV powder dosage for the pediatric patients weighing 10 to less than 25 kg. However, response rates for the 5 to less than 10 kg group were lower than in higher weight categories. Information about a higher dose of 200 mg for subjects in the 5 to less than 10 kg group became available for the PRINCE II study after the interim results and was also not encouraging. The PRINCE II study had even less data at Week 48 and therefore could not confirm that the 200 mg dose was more effective at Week 48 as there was only one subject with efficacy results in this group nor could PRINCE II confirm that the ATV powder dose was effective after 48 weeks for pediatric patients weighing 25 to less than 35 kg since there were only two subjects in that weight group.

Using a modified ITT analysis, the proportions of patients with HIV RNA <50 copies/mL at Week 24 by weight band in patients receiving REYATAZ oral powder with ritonavir in the PRINCE I study were 33% (7/21) for 5 kg to less than 10 kg, 53% (10/19) for 10 kg to less than 15 kg, and 56% (9/16) for 15 kg to less than 25 kg. Similarly efficacy results in the PRINCE II study were 43% (10/23) for 5 kg to less than 10 kg (ATV 150 mg), 17% (2/12) for 5 kg to less than 10 kg (ATV 200 mg), 48% (10/21) for 10 kg to less than 15 kg, 54% (19/35) for 15 kg to less than 25 kg, and 63% (5/8) for 25 kg to less than 35 kg.

Using a modified ITT analysis, the proportions of patients with HIV RNA <400 copies/mL at Week 24 by weight band in patients receiving REYATAZ oral powder with ritonavir in the PRINCE I study were 57% (12/21) for 5 kg to less than 10 kg, 79% (15/19) for 10 kg to less than

15 kg, and 69% (11/16) for 15 kg to less than 25 kg. Similarly efficacy results in the PRINCE II study were 65% (15/23) for 5 kg to less than 10 kg (ATV 150 mg), 42% (5/12) for 5 kg to less than 10 kg (ATV 200 mg), 71% (15/21) for 10 kg to less than 15 kg, 69% (24/35) for 15 kg to less than 25 kg, and 75% (6/8) for 25 kg to less than 35 kg.

2 INTRODUCTION

2.1 Overview

ATV is an azapeptide protease inhibitor of HIV-1. It has been approved for the treatment of HIV-1 infected adult subjects and pediatric patients ≥ 6 years of age. The applicant has developed the ATV powder for oral use in pediatric patients who are unable to swallow a solid oral dosage form to fulfill a post-marketing commitment. The pediatric indication and dosage recommendation for children was based on the results of Study PACTG 1020-A which was a single-arm, dose-finding study investigating the safety, PK, and optimal dose of ATV powder and capsules in 182 pediatric subjects aged 91 days to 21 years. A population modeling and simulation study using the observed data from Study PACTG 1020-A led to the recommended doses that were expected to achieve exposures considered close to that of adults and therefore sufficient for efficacy. The applicant conducted two Phase 3B studies, PRINCE I and II, to confirm the proposed dose of ATV powder formulation with RTV in optimized regimens given in infants and children ≥ 3 months to 11 years. The two studies consisted of a 48-week ATV powder treatment phase and an ATV capsule treatment phase that could last until the subjects reached 18 years of age. The 48-week ATV powder treatment phase had completed in the PRINCE I study but was ongoing in the PRINCE II study. Table 1 below briefly summarizes the key elements in the study design for the two studies.

The purpose of this sNDA submission is to provide data for review to support dosing recommendations for the Oral Powder formulation in patients who are 5 to < 10 kg and ≥ 25 kg, to provide a corresponding labeling supplement to the Capsule NDA (21-567) for labeling consistency (via cross-reference), to fulfill post-marketing commitment number 2153-1 for NDA 206352, and to fulfill the Written Request for Exclusivity (official determination of exclusivity was requested). In their request for priority review, the applicant claimed that the approval of this sNDA would provide an important and 'significant improvement' for the treatment of HIV-infected patients over the currently approved dosing recommendations. The applicant claimed

- there is a clear need for potent, safe, simplified and well tolerated, once-a-day therapies for treatment naive and treatment experienced HIV-infected pediatric patients,
- approval of this application will provide new dose recommendations for a pediatric-appropriate formulation for younger pediatric patients who cannot yet swallow a capsule or tablet

The applicant also noted that Priority Review of the ATV Oral Powder sNDA would facilitate the fastest possible availability of a new pediatric formulation with dosing recommendations for pediatric patients who are between 5 and < 10 kg and ≥ 25 kg.

Table 1: List of all studies included in analysis

Study	PRINCE I (Study AI424397)	PRINCE II (Study AI424451)
Study design	single arm, open-label, international, multicenter	single arm, open-label, international, multicenter
Treatment regimen	The study consisted of two stages. In the first stage, ATV powder (50 mg/sachet) boosted with Ritonavir (RTV) liquid with an optimized NRTI background therapy for up to 48 weeks. The ATV doses were 150 mg for 5 - <10 kg; 200 mg for 10 - <15 kg; 250 mg for 15 - <25 kg weight once daily. In the second stage, the dosing of ATV was transitioned from power to capsules. The subjects continued the treatment until they reached 18 years of age of pediatric indication was locally approved and subjects met requirements to receive appropriate formulation.	The study consisted of two stages. In the first stage, the subjects received ATV powder (50 mg/sachet) boosted with Ritonavir (RTV) with an optimized NRTI background therapy for up to 48 weeks. The ATV doses were 150 or 200 mg for 5 - <10 kg; 200 mg for 10 - <15 kg; 250 mg for 15 - <25 kg weight once daily. In the second stage, the dosing of ATV was transitioned from power to capsules. The subjects continued the treatment until they reached 18 years of age of pediatric indication was locally approved and subjects met requirements to receive appropriate formulation.
Patient population	HIV infected TE and TN pediatric patients greater than or equal to 3 months to less than 5 1/2 years and weighing ≥ 5 – < 25 kg	HIV infected TE and TN pediatric patients greater than or equal to 3 months to less than 11 years and weighing ≥ 5 - < 35 kg
Sample size	Eighty-two subjects were enrolled and 56 subjects were treated.	The study enrolled 160 subjects and 99 subjects were treated with ATV powder.

2.2 Data Sources

The final clinical study report for PRINCE II, Addendum 02 to the final clinical study report for PRINCE I and SAS datasets for PRINCE I and II are located in \\CDSESUB1\evsprod\NDA206352\0019 while the final clinical study report for PRINCE I was submitted earlier with the interim results and can be found in \\CDSESUB1\evsprod\NDA206352\0000

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The efficacy datasets for the PRINCE I study were well defined and clear as were most of the summary tables and figures in the clinical study reports. In terms of study conduct, the 48-week ATV powder treatment phase had completed in the PRINCE I study; however subjects in the PRINCE II study completed 24 weeks of ATV powder treatment but the final clinical study report was submitted before all subjects had the opportunity to complete their Week 48 visit. In addition, many subjects in PRINCE I were reclassified from ARV naïve (TN) to ARV experienced (TE) after the interim analysis that was used for the initial label.

3.2 Evaluation of Efficacy

The two studies had similar study designs, efficacy endpoints and statistical methods. Therefore, they are summarized together in the following sections.

3.2.1 Study Design and Endpoints

Figure 3 and Figure 4 in the Appendix display the study designs for the two studies. Both studies were Phase 3b prospective, international, multicenter, non-randomized trials. The primary objective in the two studies was to describe the safety of ATV powder formulation boosted with RTV based highly active antiretroviral therapy (HAART) regimen in pediatric subjects dosed through 48 week. However given the early termination of the PRINCE II trial after 24 weeks the primary efficacy analysis focused on the Week 24 visit.

Both studies consisted of two stages. In the first stage, the subjects received the ATV powder boosted with RTV liquid with an optimized NRTI background therapy for up to 48 weeks. The dose of ATV depended on the subject's body weight at baseline. Specifically, subjects with the baseline body weight of 5 to less than 10 kg were administered with 150 mg ATV, subjects with the baseline body weight of 10 to less than 15 kg were administered with 200 mg ATV, subjects with the baseline body weight of 15 to less than 25 kg were administered with 250 mg ATV, and subjects with the baseline body weight of 25 to less than 35 kg were administered with 300 mg ATV. Of note, there was an exception regarding the ATV dose for the subjects with body weight of 5 to less than 10 kg in the PRINCE II study. According to the protocol, a minimum of 5 subjects were supposed to receive 150 mg ATV and a minimum 6 of subjects were supposed to receive 200 mg ATV in this baseline body weight group in the PRINCE II study.

After the completion of the first stage, the subjects in the PRINCE 1 and PRINCE II studies entered the second stage during which they switched to take ATV capsules until the subjects reached 18 years of age or the pediatric indication was locally approved and the subjects met requirements to receive appropriate formulation.

In addition to the difference in the ATV dose in the group of subjects with the baseline body weight of 5 to less than 10 kg as mentioned above, there were two other main differences regarding the study design between the two studies:

1) The PRINCE I study enrolled the pediatric patients from ≥ 3 months to < 5 1/2 years old weighing ≥ 5 - < 25 kg, while the PRINCE II study recruited the pediatric patients from ≥ 3 months to < 11 years old and weighing ≥ 5 - < 35 kg.

2) The criteria to enter the second stage to take ATV capsule were different. Subjects age 6 years or weighing ≥ 25 kg in the PRINCE I study were allowed to enter the second stage, while subjects who weighed ≥ 35 kg were permitted to enter the second stage in the PRINCE II study.

3.2.2 Statistical Methodologies

The efficacy analysis for Week 48 was performed in the powder cohort at Week 48. The Week 48 powder cohort in the PRINCE I and PRINCE II studies included all subjects who received at least one dose of ATV powder and did not switch to ATV capsule at or before analysis Week 48 or before their HIV RNA Week 48 assessment. In the PRINCE II study the Week 48 powder cohort had an additional criterion which was that subjects must have initiated treatment at least 48 weeks prior to the last patient's last visit. This would ensure that all subjects in this cohort would have had the opportunity to be followed up for 48 weeks.

The proportions of HIV RNA < 50 copies/mL and < 400 copies/mL at each scheduled visit on ATV powder through Weeks 24 and 48 were evaluated using the snapshot algorithm which applied the last HIV RNA in the pre-specified visit window to determine the response. The two studies had the same specification of visit windows shown in Table 22 in the Appendix.

The CD4 cell counts and percent were assessed at Week 48 as were the changes from baseline. The value closest to the target day of the analysis week window was utilized in the analysis. The first value measured based on collection date was used if there was tie. In addition to using only observed values, the last observation carried forward (LOCF) approach was also used to summarize the change from baseline in CD4 cell counts and CD4 percent. For LOCF, missing values were replaced with the last on-treatment value in the previous visit windows; if a subject did not have any on-treatment value, then the baseline value was carried forward. For the LOCF analyses, missing baseline values were replaced with the first on-treatment value (i.e., Week 4).

Of note, the efficacy analyses were not only carried out for all treated subjects but also were performed by the baseline body weight in the clinical study reports since the ATV dose was based on the baseline body weight.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Since the ATV dose was administered based on the baseline body weight, the patient disposition, demographics and baseline disease characteristics were summarized for all treated subjects as well as for each of the baseline weight group per the medical reviewer, Dr. Shapiro's request.

Table 2 shows the patient disposition for the PRINCE I study. Among all 56 treated subjects 100% of the subjects in the first two weight categories and 88% (14/16) of the subjects in the 15-<25 kg weight category completed the first stage of 48 weeks of ATV powder treatment. The Week 48 powder cohort which was used to analyze the efficacy endpoints at Week 48 included almost all treated subjects except for two subjects who had switched to the ATV capsule before Week 48.

Patient disposition for PRINCE II is shown in Table 3. The Week 24 ATV powder cohort was completed in the PRINCE II study but the final clinical study report was submitted before all subjects had the opportunity to complete their Week 48 visit. The study enrolled 160 subjects and 99 subjects were treated with ATV powder. In this submission, the applicant included the final study report for 48 weeks of ATV powder treatment for the PRINCE I study and summarized the results for subjects with an opportunity to be dosed through a minimum of 24 weeks based on a data cutoff date of 09-Oct-2014 for the PRINCE II study. The Week 24 powder cohort in the PRINCE II trial included 100% of all treated subjects but the Week 48 powder cohort only included 8% (1/12) of the subjects in the lowest weight category who were to receive the 200 mg dose, and only 25% (2/8) of the subjects in the highest weight category.

Table 2: Patient Disposition for PRINCE I (Study AI424397)

	B/L Wt 5 - <10kg	B/L Wt 10 - <15kg	B/L Wt 15 - <25kg
Treated	21	19	16
Completed 48-wk ATV powder trt	17 (81%)	15 (79%)	15 (94%)
Reason for discont. 48-wk trt			
AE	4 (19%)	1 (5%)	0
Lack of efficacy	0	2 (10.5%)	0
Poor / non-Compliance	0	1 (5%)	0
Consent withdrawn	0	0	1 (6%)
Week 48 powder cohort	21 (100%)	19 (100%)	14 (88%)

Source: Tables 1 and 4 in the Final Clinical Study Report

Table 3 Patient Disposition for PRINCE II (Study AI424451)

	B/L Wt 5 - <10kg (ATV 150mg)	B/L Wt 5 - <10kg (ATV 200mg)	B/L Wt 10 - <15kg	B/L Wt 15 - <25kg	B/L Wt 25 - <35kg
Treated	23	12	21	35	8
Completed Stage 1 Treatment Period	15 (65%)	4 (33%)	16 (76%)	26 (74%)	6 (75%)
Reason for not completing Stage 1 treatment period					
AE	1 (4%)	2 (17%)	2 (10%)	1 (3%)	1 (13%)
Lack of efficacy	3 (13%)	1 (8%)	3 (14%)	3 (9%)	1 (13%)
Poor / non-compliance	0	1 (8%)	0	2 (6%)	0
Consent withdrawn	1 (4%)	2 (17%)	0	1 (3%)	0
Loss to follow-up	1 (4%)	1 (8%)	0	0	0
Subject no longer met study criteria	1 (4%0	1 (8%)	0	1 (3%)	0
Other	1 (4%)	0	0	1 (3%)	0
Week 24 powder cohort	23 (100%)	12 (100%)	21 (100%)	35 (100%)	8 (100%)
Week 48 powder cohort	23 (100%)	1 (8%)	20 (95%)	34 (97%)	2 (25%)

Source: Tables 1, 4 and 7.3.1-3 of the Final Clinical Study Report

Table 4 to Table 7 display the patient demographics and baseline HIV disease characteristics for all of the subjects who received at least one dose of study medication (all treated) in the two studies. In the PRINCE I study, the mean age was 30 [standard deviation (SD) = 21] months. Half of the treated subjects were male. The majority of the subjects were from Africa (68%). Also, the majority of the subjects were ARV treatment-naïve (39%). The overall median HIV RNA was 5 $\log_{10}$ copies/mL, and 57% of the subjects had HIV RNA > 100,000 copies/mL (ranging from only 25% in the 15 - <25 kg weight group to 86% in the 5 - <10 kg weight group). The overall median absolute CD4 count was 1004 cells/mm^3 (ranging from 669 in the 15 - <25 kg weight group to 1815 in the 5 - < 10 kg weight group) while the median CD4 percent was fairly constant across the three weight categories with an overall median of 24%.

In the PRINCE II study, the mean age for all treated subjects was 42.5 (SD=32) months. Slightly more than half of the subjects were female (52%). The majority of the subjects were from Africa (65%). Thirty-seven percent of the subjects were treatment-naïve. The overall median HIV RNA was 5 $\log_{10}$ copies/mL, and 52% of the subjects had HIV RNA > 100,000 copies/mL (ranging from 25% in the 25 - <35 kg group to 83% in the 5 - <10 kg (ATV 200 mg) weight group. The median absolute CD4 count was 928 cells/mm^3 [ranging from 605 in the 25 - <35 kg weight group to 2235 in the 5 - <10 kg (ATV 150) mg weight group]. The median CD4 percent was 27% and was fairly consistent across the five weight (and ATV dose) categories.

Table 4: Patient Demographics in PRINCE I (All Treated)

	All (N=56)	baseline weight 5 - < 10 kg (N=21)	baseline weight 10 - <15 kg (N=19)	baseline weight 15 - <25 kg (N=16)
Age (month)				
n	56	21	19	16
Mean (SD)	30 (21)	7 (4)	35 (12)	52 (10)
Median	28.5	6	35	55
Gender				
Male	28 (50%)	11 (52%)	7 (37%)	10 (62.5%)
Femalee	28 (50%)	10 (48%)	12 (63%)	6 (37.5%)
Race				
White	11 (20%)	2 (9.5%)	3 (16%)	6 (37.5%)
Black / African American	32 (57%)	13 (62%)	12 (63%)	7 (44%)
Asian	1 (2%)	0	1 (5%)	0
Other	12 (21%)	6 (29%)	3 (16%)	3 (19%)
Ethnicity				
Hispanic/Latino	0	0	0	0
Not Hispanic/Latino	1 (2%)	0	0	1 (6%)
Not reported	55 (98%)	21 (100%)	19 (100%)	15 (94%)
Region				
Africa	38 (68%)	17 (81%)	13 (68%)	8 (50%)
Asia	1 (2%)	0	1 (5%)	0
North America	9 (16%)	2 (9.5%)	3 (16%)	4 (25%)
South America	8 (14%)	2 (9.5%)	2 (10.5%)	4 (25%)

Source: Results from Table 2 in Final Clinical Study Report for PRINCE I (Study AI424397)

Table 5: Patient Demographics in PRINCE II (All Treated)

	All (N=99)	baseline weight 5 - < 10 kg (ATV 150 mg) (N=23)	baseline weight 5 - < 10 kg (ATV 200 mg) (N=12)	baseline weight 10 - <15 kg (N=21)	baseline weight 15 - <25 kg (N=35)	baseline weight 25 - <35 kg (N=8)
Age (month)						
n	99	23	12	21	35	8
Mean (SD)	42.5 (32)	8 (6)	10.5 (9)	37 (12)	67 (17)	93 (16)
Median	41.0	5	5.5	36	68	87
Gender						
Male	48 (48%)	11 (48%)	6 (50%)	9 (43%)	17 (49%)	5 (63%)
Female	51 (52%)	12 (52%)	6 (50%	12 (57%)	18 (51%)	3 (38%)
Race						
White	32 (32%)	2 (9%)	2 (17%)	12 (57%)	13 (37%)	3 (38%)
Black / African American	57 (58%)	19 (83%)	6 (50%)	7 (33%)	20 (57%)	5 (63%)
Other	10 (10%)	2 (9%)	4 (33%)	2 (10%)	2 (6%)	0
Ethnicity						
Hispanic/Latino	4 (4%)	0	1 (8%)	2 (10%)	1 (3%)	0
Not Hispanic/Latino	4 (4%)	1 (4%)	1 (8%)	1 (5%)	1 (3%)	0
Not reported	91 (92%)	22 (96%)	10 (83%)	18 (86%)	33 (94%)	8 (100%)
Region						
Africa	64 (65%)	20 (87%)	10 (83%)	8 (38%)	21 (60%)	5 (63%)
Europe	9 (9%)	0	0	3 (14%)	6 (17%)	0
North America	18 (18%)	2 (9%)	1 (8%)	9 (43%)	4 (11%)	2 (25%)
South America	8 (8%)	1 (4%)	1 (8%)	1 (5%)	4 (11%)	1 (13%)

Source: Results from Table 2 in Final Clinical Study Report for PRINCE II (Study AI424451)

Table 6: Baseline HIV Disease Characteristics in PRINCE I (All Treated)

	All (N=56)	baseline weight 5 - < 10 kg (N=21)	baseline weight 10 - <15 kg (N=19)	baseline weight 15 - <25 kg (N=16)
HIV RNA (log_{10} copies/mL)				
n	56	21	19	16
Mean (SD)	4.6 (0.6)	4.8 (0.6)	4.8 (0.3)	4.2 (0.7)
Median	5.0	5.0	5.0	4.3
< 30,000 copies/mL	14 (25%)	3 (14%)	2 (10.5%)	9 (56%)
30,000 – 100,000 copies/mL	10 (18%)	0	7 (37%)	3 (19%)
>100,000 copies/mL	32 (57%)	18 (86%)	10 (53%)	4 (25%)
CD4 count (cells/mm^3)				
n	39	16	13	10
Mean (SD)	1193 (784)	1594 (897)	1107 (643)	661 (303)
Median	1004	1814.5	1002	668.5
CD4 percent				
n	41	16	14	11
Mean (SD)	25 (11)	25 (12)	22 (9)	27.5 (10)
Median	24	23.5	22	27
Prior ARV use				
ARV naïve	22 (39%)	8 (38%)	7 (37%)	7 (44%)
ARV experienced	34 (61%)	13 (62%)	12 (63%)	9 (56%)

Source: Results from Table 3 in Final Clinical Study Report for PRINCE II (Study AI424451)

Table 7: Baseline HIV Disease Characteristics in PRINCE II (All Treated)

	All (N=99)	baseline weight 5 - < 10 kg (ATV 150 mg) (N=23)	baseline weight 5 - < 10 kg (ATV 200 mg) (N=12)	baseline weight 10 - <15 kg (N=21)	baseline weight 15 - <25 kg (N=35)	baseline weight 25 - <35 kg (N=8)
HIV RNA (log_{10} copies/mL)						
n	99	23	12	21	35	8
Mean (SD)	4.8 (0.7)	4.6 (0.9)	5.5 (0.5)	4.9 (0.5)	4.8 (0.4)	4.4 (0.9)
Median	5.0	5.0	5.4	5.0	4 9	4.5
< 30,000 copies/mL	26 (26%)	6 (26%)	1 (8%)	5 (24%)	10 (29%)	4 (50%)
30,000 – 100,000 copies/mL	22 (22%)	5 (22%)	1 (8%)	3 (14%)	11 (31%)	2 (25%)
>100,000 copies/mL	51 (52%)	12 (52%)	10 (83%)	13 (62%)	14 (40%)	2 (25%)
CD4 count (cells/mm^3)						
n	79	20	11	13	27	8
Mean (SD)	1314 (1015)	2245 (1233)	2139 (736)	842 (488)	723 (283)	611 (116)
Median	928	2234.5	2168	888	724	605
CD4 percent						
n	85	21	11	15	30	8
Mean (SD)	26 (11)	29 (11)	31 (11)	21 (11)	24.5 (10)	31 (11)
Median	27	29	30	21	25	32
Prior ARV use						
ARV naïve	37 (37%)	5 (22%)	2 (17%)	13 (62%)	14 (40%)	3 (38%)
ARV experienced	62 (63%)	18 (78%)	10 (83%)	8 (38%)	21 (60%)	5 (63%)

Sources: Results from Table.3 in Final Clinical Study Report for PRINCE II (Study AI424451)

3.2.4 Results and Conclusions

A. HIV RNA

Table 8 through Table 11 summarize the applicant's outcomes for the proportion of HIV RNA <50 copies/mL and <400 copies/mL using the snapshot algorithm at Week 24 in the Week 24 Powder Cohort and at Week 48 in the Week 48 Powder cohort. The reviewer has confirmed the results (See reviewer's summaries in Figure 1 and Figure 2.

In the PRINCE I study, 46% of the subjects achieved HIV RNA < 50 copies/mL and 68% of the subjects had HIV RNA < 400 copies/mL at Week 24 while 61% of the subjects achieved HIV RNA < 50 copies/mL and 74% of the subjects had HIV RNA < 400 copies/mL at Week 48. Also, the virologic response rates at Weeks 24 and 48 increased with the higher baseline weight band.

In the PRINCE II study, 47% of the subjects had HIV RNA < 50 copies/mL and 66% had HIV RNA < 400 copies/mL at Week 24 while 45% of the subjects had HIV RNA < 50 copies/mL and 65% had HIV RNA < 400 copies/mL at Week 48. The response rates in each weight category for PRINCE II study were fairly consistent with corresponding response rates in the PRINCE I study.

Data for PRINCE I and PRINCE II were pooled and the statistics reviewer performed an exploratory Cochran-Mantel-Haenszel (CMH) analysis using modified ridit scores stratified by study and found a statistically significant increase in response rates across the five ordinal baseline weight categories using a cutoff of 50 copies/mL (p=0.031). However this finding was not statistically significant for the cutoff of 400 copies/mL (p=0.22). Without stratification similar findings were observed with a statistically significant weight effect for the 50 copies/mL threshold (p=0.033) and a non-statistically significant trend for the 400 copies/mL threshold (p=0.24). Similar but slightly more significant findings were observed after combining the two weight categories for the subjects weighing 5 to <10 kg (i.e., ATV 150 mg and 200 mg combined) (the corresponding p-values were 0.017, 0.15, 0.017 and 0.16 respectively).

The applicant also plotted the percentage of time on ATV powder, the proportion of subjects with HIV RNA < 50 copies/mL and < 400 copies/mL as well as mean HIV RNA viral loads and corresponding changes from baseline at each visit in the two studies (see Appendix). In general, the response rates increased with the duration of treatment in the first 16-24 weeks of treatment.

Table 8: Snapshot Outcomes at Week 24 for ALL Subjects in PRINCE I (Week 24 Powder Cohort)

Treatment Outcomes	B/L Weight 5 - < 10 kg N=21	B/L Weight 10 - < 15 kg N=19	B/L Weight 15 - < 25 kg N=16	Combined 10 - < 25 kg N=35	TOTAL N=56
HIV RNA < 50 c/mL					
VIROLOGIC SUCCESS	7 (33.3)	10 (52.6)	9 (56.3)	19 (54.3)	26 (46.4)
VIROLOGIC FAILURE	11 (52.4)	9 (47.4)	7 (43.8)	16 (45.7)	27 (48.2)
HIV RNA >= 50c/mL	11 (52.4)	8 (42.1)	6 (37.5)	14 (40.0)	25 (44.6)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	0	0	0	0
DISCONTINUED DUE TO OTHER REASONS AND HIV >= 50 c/mL AT TIME OF DISCONTINUATION	0	1 (5.3)	1 (6.3)	2 (5.7)	2 (3.6)
OBT CHANGED	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	3 (14.3)	0	0	0	3 (5.4)
DISCONTINUED DUE TO AE OR DEATH	3 (14.3)	0	0	0	3 (5.4)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50c/mL AT TIME OF DISCONTINUATION	0	0	0	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0	0	0
HIV RNA < 400 c/mL					
VIROLOGIC SUCCESS	12 (57.1)	15 (78.9)	11 (68.8)	26 (74.3)	38 (67.9)
VIROLOGIC FAILURE	6 (28.6)	4 (21.1)	5 (31.3)	9 (25.7)	15 (26.8)
HIV RNA >= 400c/mL	6 (28.6)	3 (15.8)	4 (25.0)	7 (20.0)	13 (23.2)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	0	0	0	0
DISCONTINUED DUE TO OTHER REASONS AND HIV >= 400 c/mL AT TIME OF DISCONTINUATION	0	1 (5.3)	1 (6.3)	2 (5.7)	2 (3.6)
OBT CHANGED	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	3 (14.3)	0	0	0	3 (5.4)
DISCONTINUED DUE TO AE OR DEATH	3 (14.3)	0	0	0	3 (5.4)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400c/mL AT TIME OF DISCONTINUATION	0	0	0	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0	0	0

Source: Appendix 5.1G of the Final Clinical Study Report

Table 9: Snapshot Outcomes at Week 24 for ALL Subjects in PRINCE II (Week 24 Powder Cohort)

Treatment Outcomes	B/L Weight 5 - < 10 kg (ATV 150mg) N=23	B/L Weight 5 - < 10 kg (ATV 200mg) N=12	B/L Weight 10 - < 15 kg N=21	B/L Weight 15 - < 25 kg N=35	B/L Weight 25 - < 35 kg N=8	Total N=99
HIV RNA < 50 C/ML						
VIROLOGIC SUCCESS	10 (43.5)	2 (16.7)	10 (47.6)	19 (54.3)	5 (62.5)	46 (46.5)
VIROLOGIC FAILURE	12 (52.2)	8 (66.7)	9 (42.9)	13 (37.1)	2 (25.0)	44 (44.4)
HIV RNA >= 50 C/ML	11 (47.8)	5 (41.7)	9 (42.9)	10 (28.6)	2 (25.0)	37 (37.4)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	0	0	0	0	0
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 50 C/ML AT TIME OF DISCONTINUATION	1 (4.3)	3 (25.0)	0	3 (8.6)	0	7 (7.1)
OBT CHANGED	0	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	1 (4.3)	2 (16.7)	2 (9.5)	3 (8.6)	1 (12.5)	9 (9.1)
DISCONTINUED DUE TO AE OR DEATH	0	2 (16.7)	2 (9.5)	1 (2.9)	1 (12.5)	6 (6.1)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50 C/ML AT TIME OF DISCONTINUATION	1 (4.3)	0	0	0	0	1 (1.0)
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0	2 (5.7)	0	2 (2.0)
HIV RNA < 400 C/ML						
VIROLOGIC SUCCESS	15 (65.2)	5 (41.7)	15 (71.4)	24 (68.6)	6 (75.0)	65 (65.7)
VIROLOGIC FAILURE	7 (30.4)	5 (41.7)	4 (19.0)	8 (22.9)	1 (12.5)	25 (25.3)
HIV RNA >= 400 C/ML	6 (26.1)	2 (16.7)	4 (19.0)	5 (14.3)	1 (12.5)	18 (18.2)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	0	0	0	0	0
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 400 C/ML AT TIME OF DISCONTINUATION	1 (4.3)	3 (25.0)	0	3 (8.6)	0	7 (7.1)
OBT CHANGED	0	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	1 (4.3)	2 (16.7)	2 (9.5)	3 (8.6)	1 (12.5)	9 (9.1)
DISCONTINUED DUE TO AE OR DEATH	0	2 (16.7)	2 (9.5)	1 (2.9)	1 (12.5)	6 (6.1)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400 C/ML AT TIME OF DISCONTINUATION	1 (4.3)	0	0	0	0	1 (1.0)
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0	2 (5.7)	0	2 (2.0)

Source: Table 4 of the Final Clinical Study Report

Table 10: Snapshot Outcomes at Week 48 for ALL Subjects in PRINCE I (Week 48 Powder Cohort)

Treatment Outcomes	B/L Weight 5 - < 10 kg N=21	B/L Weight 10 - < 15 kg N=19	B/L Weight 15 - < 25 kg N=14	Combined 10 - < 25 kg N=33	TOTAL N=54
HIV RNA < 50 c/mL					
VIROLOGIC SUCCESS	10 (47.6)	13 (68.4)	10 (71.4)	23 (69.7)	33 (61.1)
VIROLOGIC FAILURE	7 (33.3)	5 (26.3)	4 (28.6)	9 (27.3)	16 (29.6)
HIV RNA >= 50c/mL	7 (33.3)	2 (10.5)	3 (21.4)	5 (15.2)	12 (22.2)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	2 (10.5)	0	2 (6.1)	2 (3.7)
DISCONTINUED DUE TO OTHER REASONS AND HIV >= 50 c/mL AT TIME OF DISCONTINUATION	0	1 (5.3)	1 (7.1)	2 (6.1)	2 (3.7)
OBT CHANGED	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	4 (19.0)	1 (5.3)	0	1 (3.0)	5 (9.3)
DISCONTINUED DUE TO AE OR DEATH	4 (19.0)	1 (5.3)	0	1 (3.0)	5 (9.3)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50c/mL AT TIME OF DISCONTINUATION	0	0	0	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0	0	0
HIV RNA < 400 c/mL					
VIROLOGIC SUCCESS	14 (66.7)	14 (73.7)	12 (85.7)	26 (78.8)	40 (74.1)
VIROLOGIC FAILURE	3 (14.3)	4 (21.1)	2 (14.3)	6 (18.2)	9 (16.7)
HIV RNA >= 400c/mL	3 (14.3)	1 (5.3)	1 (7.1)	2 (6.1)	5 (9.3)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	2 (10.5)	0	2 (6.1)	2 (3.7)
DISCONTINUED DUE TO OTHER REASONS AND HIV >= 400 c/mL AT TIME OF DISCONTINUATION	0	1 (5.3)	1 (7.1)	2 (6.1)	2 (3.7)
OBT CHANGED	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	4 (19.0)	1 (5.3)	0	1 (3.0)	5 (9.3)
DISCONTINUED DUE TO AE OR DEATH	4 (19.0)	1 (5.3)	0	1 (3.0)	5 (9.3)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400c/mL AT TIME OF DISCONTINUATION	0	0	0	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0	0	0

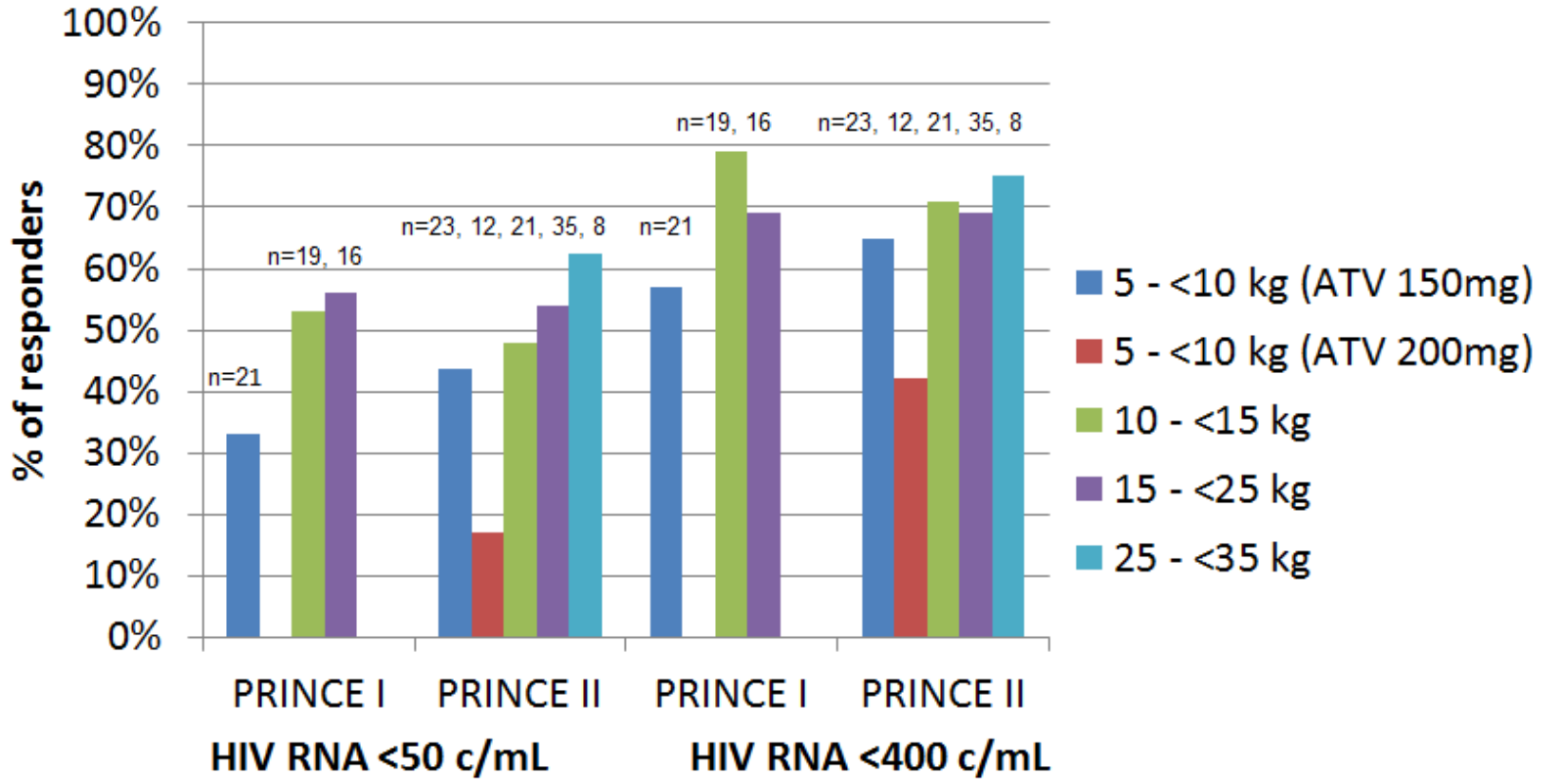
Source: Table 4 of the Final Clinical Study Report

Table 11: Snapshot Outcomes at Week 48 for ALL Subjects in PRINCE II (Week 48 Powder Cohort)

Treatment Outcomes	B/L Weight 5 - < 10 kg (ATV 150mg) N=23	B/L Weight 5 - < 10 kg (ATV 200mg) N=1	B/L Weight 10 - < 15 kg N=20	B/L Weight 15 - < 25 kg N=34	B/L Weight 25 - < 35 kg N=2	Total N=80
HIV RNA < 50 C/ML						
VIROLOGIC SUCCESS	11 (47.8)	0	6 (30.0)	18 (52.9)	1 (50.0)	36 (45.0)
VIROLOGIC FAILURE	9 (39.1)	1 (100.0)	11 (55.0)	15 (44.1)	1 (50.0)	37 (46.3)
HIV RNA >= 50 C/ML	5 (21.7)	1 (100.0)	9 (45.0)	7 (20.6)	0	22 (27.5)
DISCONTINUED DUE TO VIROLOGIC FAILURE	2 (8.7)	0	2 (10.0)	3 (8.8)	1 (50.0)	8 (10.0)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 50 C/ML AT TIME OF DISCONTINUATION	2 (8.7)	0	0	5 (14.7)	0	7 (8.8)
OBT CHANGED	0	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	3 (13.0)	0	3 (15.0)	1 (2.9)	0	7 (8.8)
DISCONTINUED DUE TO AE OR DEATH	1 (4.3)	0	2 (10.0)	1 (2.9)	0	4 (5.0)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50 C/ML AT TIME OF DISCONTINUATION	1 (4.3)	0	0	0	0	1 (1.3)
MISSING DATA IN WINDOW BUT ON TREATMENT	1 (4.3)	0	1 (5.0)	0	0	2 (2.5)
HIV RNA < 400 C/ML						
VIROLOGIC SUCCESS	14 (60.9)	1 (100.0)	14 (70.0)	22 (64.7)	1 (50.0)	52 (65.0)
VIROLOGIC FAILURE	6 (26.1)	0	3 (15.0)	10 (29.4)	1 (50.0)	20 (25.0)
HIV RNA >= 400 C/ML	2 (8.7)	0	1 (5.0)	3 (8.8)	0	6 (7.5)
DISCONTINUED DUE TO VIROLOGIC FAILURE	2 (8.7)	0	2 (10.0)	3 (8.8)	1 (50.0)	8 (10.0)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 400 C/ML AT TIME OF DISCONTINUATION	2 (8.7)	0	0	4 (11.8)	0	6 (7.5)
OBT CHANGED	0	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	3 (13.0)	0	3 (15.0)	2 (5.9)	0	8 (10.0)
DISCONTINUED DUE TO AE OR DEATH	1 (4.3)	0	2 (10.0)	1 (2.9)	0	4 (5.0)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400 C/ML AT TIME OF DISCONTINUATION	1 (4.3)	0	0	1 (2.9)	0	2 (2.5)
MISSING DATA IN WINDOW BUT ON TREATMENT	1 (4.3)	0	1 (5.0)	0	0	2 (2.5)

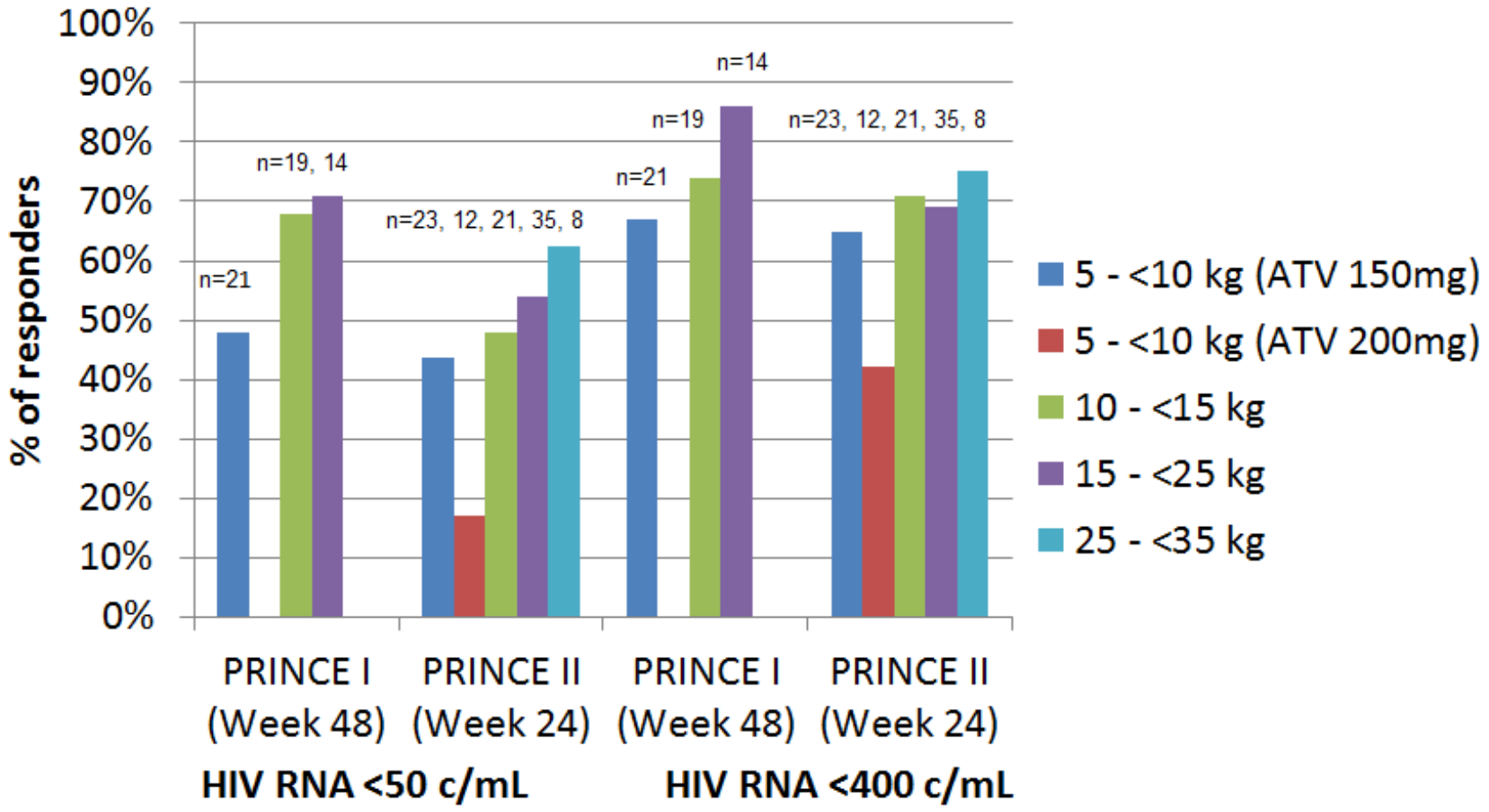
Source: Table 7.3.1-3 of the Final Clinical Study Report

Figure 1: Week 24 Efficacy Results by Weight Category



Source: Reviewer's Analysis

Figure 2: Primary Efficacy Results by Weight Category



N.B. primary efficacy analysis visit changed in PRINCE II from Week 48 to Week 24 after interim analysis due to PREA deadlines

Source: Reviewer's Analysis

Table 12: Mean and Median change in log_{10} (HIV RNA) for 150 and 200 mg doses in the 5-<10 kg Weight Category

(Observed Data for PRINCE I and PRINCE II combined)

	Week 24	Week 48
150 mg	N=39, Mean=-2.25 (sd=1.19) Median=-2.49	N=33 Mean=-2.46 (sd=1.27) Median=-3.09
200 mg	N=7 Mean=-3.07 (sd=1.27) Median=-3.68	N=1 Mean=-3.90 (sd=n/a) Median=-3.90

(Baseline Observation Carried Forward Data for PRINCE I and PRINCE II combined)

	Week 24 Powder Cohort	Week 48 Powder Cohort
150 mg	N=44, Mean=-1.99 (sd=1.33) Median=-2.21	N=44 Mean=-1.85 (sd=1.53) Median=-2.50
200 mg	N=12 Mean=-1.79 (sd=1.84) Median=-1.25	N=1 Mean=-3.90 (sd=n/a) Median=-3.90

Source: Reviewer's Analysis

The medical officer requested a summary of mean and median change from baseline in log_{10} HIV RNA for the two dose groups in the 5-<10 kg weight group at Weeks 24 and 48. The 200 mg dose looked more effective than the 150 mg dose using only observed data and the applicant's plot for the PRINCE II study (see Figure 16 in the Appendix) was misleading because it showed 95% confidence intervals that did not overlap. However after adjusting for dropouts by assuming that children who stopped taking their medication would rebound to baseline levels, the mean and median decreases from baseline for the 150 mg dose were slightly larger than those of the 200 mg dose for the Week 24 Powder Cohort. (The Week 48 Powder Cohort only had one subject eligible to complete 48 weeks of treatment who took 200 mg.)

B. CD4

Table 13 and Table 14 summarize the applicant's results for change from baseline in CD4 count and percent at Week 48. Approximately 30% of the subjects in the PRINCE I study had missing baseline CD4 data in contrast to PRINCE II where only 6% of the baseline values were missing. The mean and median changes were positive in the PRINCE I study but negative in the PRINCE II study for the 5-<10 kg (ATV 150 mg) weight group, perhaps due to the higher mean baseline CD4 counts in the PRINCE II study. The mean and median changes from baseline in CD4 percent were positive in both studies with the exception of a slightly negative change from baseline in the 25-<35 kg weight group in PRINCE II. The applicant also plotted median CD4 cell counts and corresponding changes from baseline data at each visit for the two studies (see Appendix).

Table 13: Change from Baseline in CD4 Count and Percent at Week 48 in PRINCE I (Week 48 Powder Cohort)

	baseline weight 5 - < 10 kg N=21	baseline weight 10 - <15 kg N=19	baseline weight 15 - <25 kg N=14
Baseline absolute CD4 count			
n	16	13	10
mean (SD)	1594 (897)	1107 (643)	661 (303)
median	1814.5	1002	668.5
Change from baseline in absolute CD4 count			
Observed approach[1]			
n	13	11	5
mean (SE)	550 (285)	225 (198)	374 (69)
median	491	274	363
Last observation carried forward (LOCF)[2]			
n	16	13	10
mean (SE)	507 (233)	176 (170)	235.5 (63)
median	389	0	228
Baseline CD4 percent			
n	16	14	11
mean (SE)	25 (12)	22 (9)	27.5 (10)
median	23.5	22	27
Change from baseline in CD4 percent			
Observed approach[1]			
n	14	12	6
mean (SE)	6 (2)	7 (2)	9 (1)
median	6	7.5	9.5
LOCF[2]			
n	16	14	11
mean (SE)	6 (1)	6 (2)	6 (1)
median	4.5	5.5	5

[1]The results for Study AI424397 were obtained from Appendices 5.3A and 5.3C in the final clinical study report.
[2]LOCF approach replaced the missing values with the last on-treatment value in the previous visit window; and the baseline value was carried forward if subject did not have on-treatment value. The LOCF results for change from baseline in CD4 counts in Study AI424397 were obtained from Appendix 5.3 E in final clinical study report. The LOCF results for change from baseline in CD4 percent were obtained by the statistics reviewer using the applicant's derived analysis dataset (adcd4).

Table 14: Change from Baseline in CD4 Count and Percent at Week 48 in PRINCE II (Week 48 Powder Cohort)

	baseline weight 5 - < 10 kg (ATV 150 mg) N=21	baseline weight 5 - <10 kg (ATV 200 mg) N=11	baseline weight 10 - <15 kg N=15	baseline weight 15 - < 25 kg N=30	baseline weight 25 - <35 kg N=8
Baseline absolute CD4 count					
n	20	11	13	27	8
mean (SD)	2245 (1233)	2139 (736)	842 (488)	723 (283)	611 (116)
median	2235	2168	888	724	604.5
Change from baseline in absolute CD4 count					
Observed approach[1]					
n	10	0	8	16	1
mean (SE)	-410 (438)		400 (156)	335 (109)	213 (N/A)
median	-353.5		288.5	227.5	213
Last observation carried forward (LOCF)[2]					
n	20	11	13	27	8
mean (SE)	-139 (245)	235 (239)	280 (107)	238 (72)	155 (78)
median	-220	75	230	173	69
Baseline CD4 percent					
n	21	11	15	30	8
mean (SE)	29 (11)	31 (11)	21 (11)	24.5 (10)	31 (11)
median	29	30	2217	25	31.5
Change from baseline in CD4 percent					
Observed approach[1]					
n	12	0	9	19	1
mean (SE)	3 (3)		9 (2)	7.5 (2)	1 (N/A)
median	2.5		8	8	1
LOCF[2]					
n	21	11	15	30	8
mean (SE)	6 (2)	3 (2)	5 (2)	6 (1)	-2 (3)
median	4	4	6	6	-0.5

[1]The results for Study AI424451 were obtained from Appendices 5.3A and 5.3C in the final clinical study report.

[2]LOCF approach replaced the missing values with the last on-treatment value in the previous visit window; and the baseline value was carried forward if subject did not have on-treatment value. The LOCF results for change from baseline in CD4 counts in Study AI424451 were obtained from Appendices 5.3E and 5.3F in the final clinical study report.

3.3 Evaluation of Safety

The statistical reviewer did not evaluate the safety data. For a detailed safety evaluation, please refer to Dr. Alan Shapiro's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 23 in the Appendix shows the reviewer's subgroup analyses by gender, race and geographic region. In the pooled analysis of both studies, there appeared to be no differences with gender or race (Black/African American vs. other races). For the subgroup analysis by region, the three biggest regions (Africa, N. America, and S. America) had similar response rates; sample sizes for Europe and Asia were too small to make any conclusions. Also, the sample sizes in subgroups with each baseline weight group were too small to be informative. Finally, the reviewer did not perform the subgroup analysis by age since the age is highly correlated with the baseline body weight.

4.2 Other Special/Subgroup Populations

The previous HIV treatment history (i.e., TN versus TE) was expected to affect the virologic response rate. The applicant proposed to present the response rates by the previous HIV treatment history in the label. Therefore the applicant performed snapshot analyses by the previous HIV treatment history (See Table 24 to Table 27 in the Appendix).

Note however that many subjects in PRINCE I were reclassified from ARV naïve (TN) to ARV experienced (TE) after the interim analysis that was used for the initial label and this had a fairly high impact on the percentage of responders in both subgroups as shown below (in red font). The applicant said the subjects were reclassified because additional data on prior medications became available after the interim. At the time of the interim, the percentage of responders in TN and TE subjects were about the same with fewer failures in the TE subjects compared to TN subjects. However after the interim, a higher percentage of TN subjects compared to TE subjects were classified as responders.

Table 15: Summary of Week 48 Snapshot Responders by Prior ARV Use in the PRINCE I trial (Week 48 ATV Powder Cohort)

Outcome	Interim Results		Final Results	
	ARV Naive N=34 n (%)	ARV Experienced N=20 n (%)	ARV Naive N=22 n (%)	ARV Experienced N=32 n (%)
Virologic Success (<50 copies/mL)	21 (62%)	12 (60%)	15 (68%)	18 (56%)
(<400 copies/mL)	25 (74%)	15 (75%)	19 (86%)	21 (66%)

Source: Reviewer's Analysis

There were about the same number of TN and TE subjects at the time of the interim analysis in the PRINCE II study, but after the interim there was only one additional TN subject but there were almost twice as many TE subjects as there were before the interim.

Table 16: Summary of Week 24 Snapshot Responders by Prior ARV Use in the PRINCE II trial (Week 24 ATV Powder Cohort)

Outcome	Interim Results		Final Results	
	ARV Naive N=36 n (%)	ARV Experienced N=32 n (%)	ARV Naive N=37 n (%)	ARV Experienced N=62 n (%)
Virologic Success (<50 copies/mL)	17 (47%)	17 (53%)	17 (46%)	29 (47%)
(<400 copies/mL)	25 (69%)	22 (69%)	25 (68%)	40 (65%)

Source: Reviewer's Analysis

The medical division was more interested in subgroup analyses in the lowest weight category where suboptimal responses were observed. Previous ARV treatment and baseline HIV RNA were two subgroups considered likely to have an effect on responses. The division had hoped that increasing the atazanavir dose from 150 to 200 mg after the interim would increase the response rate. However observed responses for the atazanavir dose of 200 mg in the lowest weight category were consistently lower than the corresponding responses for the atazanavir dose of 150 mg (See Table 17 - Table 20).

Table 17: Summary of Week 24 Snapshot Responders (<50 copies/mL) for 5-<10 kg Weight Group, by selected Baseline Subgroups

Subgroup	PRINCE I and II		PRINCE II	
	ATV 150 mg	ATV 200 mg	ATV 150 mg	ATV 200 mg
ARV Experienced	38% (12/32)	20% (2/10)	44% (8/18)	20% (2/10)
ARV Naive	42% (5/12)	0% (0/2)	40% (2/5)	0% (0/2)
Baseline HIV RNA(copies/mL)				
≤100,000	50% (7/14)	0% (0/2)	64% (7/11)	0% (0/2)
>100,000	33% (10/30)	20% (2/10)	25% (3/12)	20% (2/10)

Source: Reviewer's Analysis

Table 18: Summary of Week 24 Snapshot Responders (<400 copies/mL) for 5-<10 kg Weight Group, by selected Baseline Subgroups

Subgroup	PRINCE I and II		PRINCE II	
	ATV 150 mg	ATV 200 mg	ATV 150 mg	ATV 200 mg
ARV Experienced	56% (18/32)	50% (5/10)	67% (12/18)	50% (5/10)
ARV Naive	75% (9/12)	0% (0/2)	60% (3/5)	0% (0/2)
Baseline HIV RNA(copies/mL)				
≤100,000	71% (10/14)	0% (0/2)	73% (8/11)	0% (0/2)
>100,000	57% (17/30)	50% (5/10)	58% (7/12)	50% (5/10)

Source: Reviewer's Analysis

Table 19: Summary of Week 48 Snapshot Responders (<50 copies/mL) for 5-<10 kg Weight Group, by selected Baseline Subgroups

Subgroup	PRINCE I and II		PRINCE II	
	ATV 150 mg	ATV 200 mg	ATV 150 mg	ATV 200 mg
ARV Experienced	53% (17/32)	0% (0/1)	56% (10/18)	0% (0/1)
ARV Naive	33% (4/12)	0	20% (1/5)	0
Baseline HIV RNA(copies/mL)				
≤100,000	57% (8/14)	0	64% (7/11)	0
>100,000	43% (13/30)	0% (0/1)	33% (4/12)	0% (0/1)

Source: Reviewer's Analysis

Table 20: Summary of Week 48 Snapshot Responders (<400 copies/mL) for 5-<10 kg Weight Group, by selected Baseline Subgroups

Subgroup	PRINCE I and II		PRINCE II	
	ATV 150 mg	ATV 200 mg	ATV 150 mg	ATV 200 mg
ARV Experienced	59% (19/32)	100% (1/1)	61% (11/18)	100% (1/1)
ARV Naive	75% (9/12)	0	60% (3/5)	0
Baseline HIV RNA(copies/mL)				
≤100,000	64% (9/14)	0	73% (8/11)	0
>100,000	63% (19/30)	100% (1/1)	50% (6/12)	100% (1/1)

Source: Reviewer's Analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In terms of study conduct, the 48-week ATV powder treatment phase had completed in the PRINCE I study; however subjects in the PRINCE II study completed 24 weeks of ATV powder treatment but the final clinical study report was submitted before all subjects had the opportunity to complete their Week 48 visit. In addition, many subjects in PRINCE I were reclassified from ARV naïve (TN) to ARV experienced (TE) after the interim analysis that was used for the initial label.

5.2 Collective Evidence

Using a modified ITT analysis, the proportions of patients with HIV RNA <50 copies/mL at Week 24 by weight band in patients receiving REYATAZ oral powder with ritonavir in the PRINCE I study were 33% (7/21) for 5 kg to less than 10 kg, 53% (10/19) for 10 kg to less than 15 kg, and 56% (9/16) for 15 kg to less than 25 kg. Similarly efficacy results in the PRINCE II study were 43% (10/23) for 5 kg to less than 10 kg (ATV 150 mg), 17% (2/12) for 5 kg to less than 10 kg (ATV 200 mg), 48% (10/21) for 10 kg to less than 15 kg, 54% (19/35) for 15 kg to less than 25 kg, and 63% (5/8) for 25 kg to less than 35 kg.

Using a modified ITT analysis, the proportions of patients with HIV RNA <400 copies/mL at Week 24 by weight band in patients receiving REYATAZ oral powder with ritonavir in the PRINCE I study were 57% (12/21) for 5 kg to less than 10 kg, 79% (15/19) for 10 kg to less than 15 kg, and 69% (11/16) for 15 kg to less than 25 kg. Similarly efficacy results in the PRINCE II study were 65% (15/23) for 5 kg to less than 10 kg (ATV 150 mg), 42% (5/12) for 5 kg to less than 10 kg (ATV 200 mg), 71% (15/21) for 10 kg to less than 15 kg, 69% (24/35) for 15 kg to less than 25 kg, and 75% (6/8) for 25 kg to less than 35 kg.

5.3 Conclusions and Recommendations

The pediatric indication and dosage for the use of ATV in children has been approved based on a dosing-finding, PK study (i.e., Study PACTG 1020-A) and the population modeling and simulation study. The two Phase 3B studies included in the submission supported the recommended ATV powder dosage for the pediatric patients weighing 10 to less than 25 kg. However, response rates for the 5 to less than 10 kg group were lower than in higher weight categories. Information about a higher dose of 200 mg for subjects in the 5 to less than 10 kg group became available for the PRINCE II study after the interim results and was also not encouraging. The PRINCE II study had even less data at Week 48 and therefore could not confirm that the 200 mg dose was more effective at Week 48 as there was only one subject with efficacy results in this group nor could PRINCE II confirm that the ATV powder dose was

effective after 48 weeks for pediatric patients weighing 25 to less than 35 kg since there were only two subjects in that weight group.

5.4 Labeling Recommendations (as applicable)

Section 14.3 of the draft label for this supplement was updated by the applicant at the time of the submission as shown below:

Pediatric Trials with REYATAZ Oral Powder

Assessment of the pharmacokinetics, safety, tolerability, and virologic response of REYATAZ oral powder was based on data from two open-label, multicenter clinical trials.

- AI424-397 (PRINCE I): In pediatric patients from 3 months to less than 6 years of age
- AI424-451 (PRINCE II): In pediatric patients from 3 months to less than 11 years of age

In these studies (b) (4) 155 patients (b) (4) 59 antiretroviral-naive and (b) (4) 96 antiretroviral-experienced) received once daily REYATAZ oral powder and ritonavir, in combination with two NRTIs.

For inclusion in both trials, treatment-naive patients had to have genotypic sensitivity to REYATAZ and two NRTIs, and treatment-experienced patients had to have documented genotypic and phenotypic sensitivity at screening to REYATAZ and at least 2 NRTIs. Patients exposed only to antiretrovirals *in utero* or intrapartum were considered treatment-naive. Patients who received REYATAZ or REYATAZ/ritonavir at any time prior to study enrollment or who had a history of treatment failure on two or more protease inhibitors were excluded from the trials.

(b) (4) One hundred thirty-four (b) (4) 134) patients from both studies weighing (b) (4) 5 kg to less than (b) (4) 35 kg treated with REYATAZ oral powder with ritonavir were evaluated. Patients (b) (4) kg to less than 15 kg received 200 mg REYATAZ and 80 mg ritonavir oral solution, (b) (4) patients 15 kg to less than 25 kg received 250 mg REYATAZ and 80 mg ritonavir oral solution, and patients 25 kg to less than 35 kg received 300 mg REYATAZ and 100 mg ritonavir oral solution. Using a modified ITT analysis, the overall proportions of antiretroviral-naive and antiretroviral-experienced patients with HIV RNA <400 copies/mL at Week 48 were (b) (4) 79% (b) (4) 41/52) and (b) (4) 62% (b) (4) 51/82), respectively in patients who received REYATAZ oral powder with ritonavir. The overall proportions of antiretroviral-naive and antiretroviral-experienced patients with HIV RNA <50 copies/mL at Week 48 were (b) (4) 54% (b) (4) 28/52) and (b) (4) 50% (b) (4) 41/82),

respectively in patients who received REYATAZ oral powder with ritonavir. The median increase from baseline in absolute CD4 count (percent) at 48 weeks of therapy was (b) (4) 288 cells/mm^3 (b) (4) 9%) in antiretroviral-naive patients and (b) (4) 240 cells/mm^3 (6%) in antiretroviral-experienced patients who received REYATAZ oral powder with ritonavir.

The reviewer has the following comments.

1) The applicant summarized pooled Week 48 PRINCE I and II HIV RNA response rates (snapshot algorithm) by treatment naïve and treatment experienced subjects. However the medical division was most concerned with efficacy results in each baseline weight category rather than by treatment history. In addition, there was only one subject who was treated with 200 mg in the 5 to <10 kg group and there were only two subjects treated with 25 to <35 kg who were followed up at Week 48. At the time of this writing the medical division decided to use the same approach that was used for the interim label and summarize by TN and TE subjects rather than weight categories.

2) The statistics reviewer added a snapshot table to Section 14 of the draft label instead of summarizing percentages and corresponding numbers of responders in the text, as shown below. Subsequently the medical division decided against using the snapshot table and kept the original text in the label.

3) The results for the change from baseline in absolute CD4 count at 48 weeks of therapy proposed by the applicant were based on what the applicant referred to as an observed values analysis. The observed values analysis did not impute any missing data and Week 48 change scores were missing for almost half of the patients. Since the CD4 counts usually are maintained for a while after the treatment, the LOCF approach is usually used to analyze the change from baseline in CD4 in the adult studies and results using the LOCF approach are presented in the label. The median change from baseline in absolute CD4 count at Week 48 using the LOCF approach was 215 cells/mm^3 (n=43) for TN subjects and 172 cells/mm^3 (n=78) for TE subjects.

4) Per Dr. Shapiro, the absolute CD4 count could be confounded with age in the younger pediatric patients. The younger children usually have higher absolute CD4 counts and the counts decrease with age. The CD4 percent is a more stable measurement. Therefore the change from baseline in CD4 percent is more appropriate than the change from baseline in absolute CD4 counts in the younger pediatric subjects, and should also be presented in the label. Using the LOCF approach, the median change in CD4 percent at Week 48 was 8.0% (n=49) for TN subjects and 4.0% (n=84) for TE subjects.

Table 21: Example of Snapshot Table for Section 14 of the label

Outcomes of Randomized Treatment Through Week 24

(Studies AI424-397 and AI424-451)

	Baseline Weight				
	5-<10 kg (ATV 150mg) N=44	5-<10 kg (ATV 200mg) N=12	10-<15 kg N=40	15-<25 kg N=51	25-<35 kg N=8
Outcome					
Responder[a]	39% (61%)	17% (42%)	50% (75%)	55% (69%)	63% (75%)
Virologic Failure[b]	52% (30%)	67% (42%)	45% (20%)	39% (25%)	25% (13%)
No virologic data	9%	17%	5%	6%	13%
Discontinued due to adverse event or death	7%	17%	5%	2%	13%
Discontinued for other reasons[c]	2%	0	0	0	0
Missing data during window but on study	0	0	0	4%	0

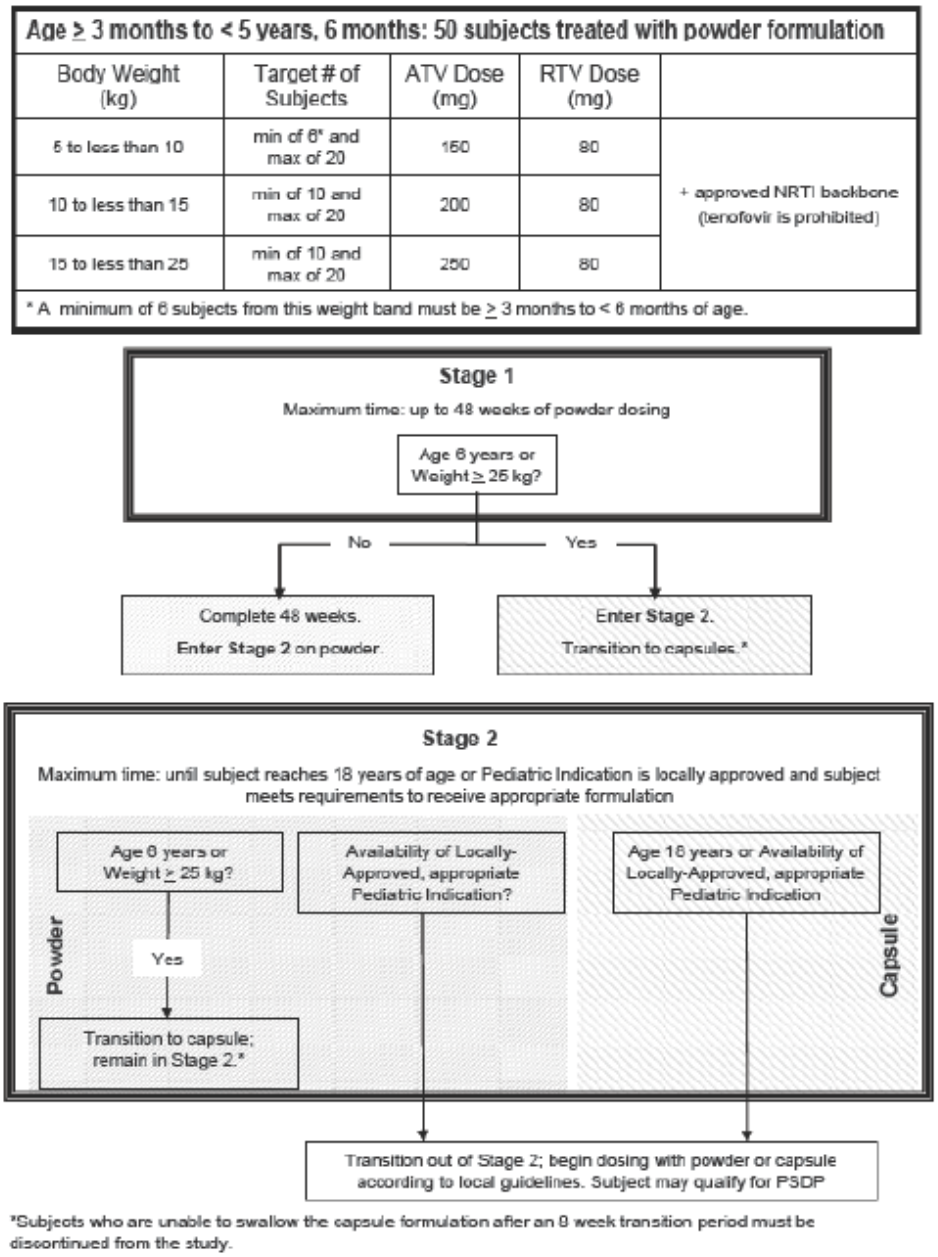
[a] HIV-1 RNA less than 50 copies/mL (less than 400 copies/mL) through Week 24

[b] Includes viral rebound, failure to achieve confirmed less than 50 copies per mL (less than 400 copies per mL) by Week 24, insufficient viral load response.

[c] Includes consent withdrawn, lost to follow-up, protocol violations, clinical progression, and other.Source: Reviewer's Analysis

APPENDIX

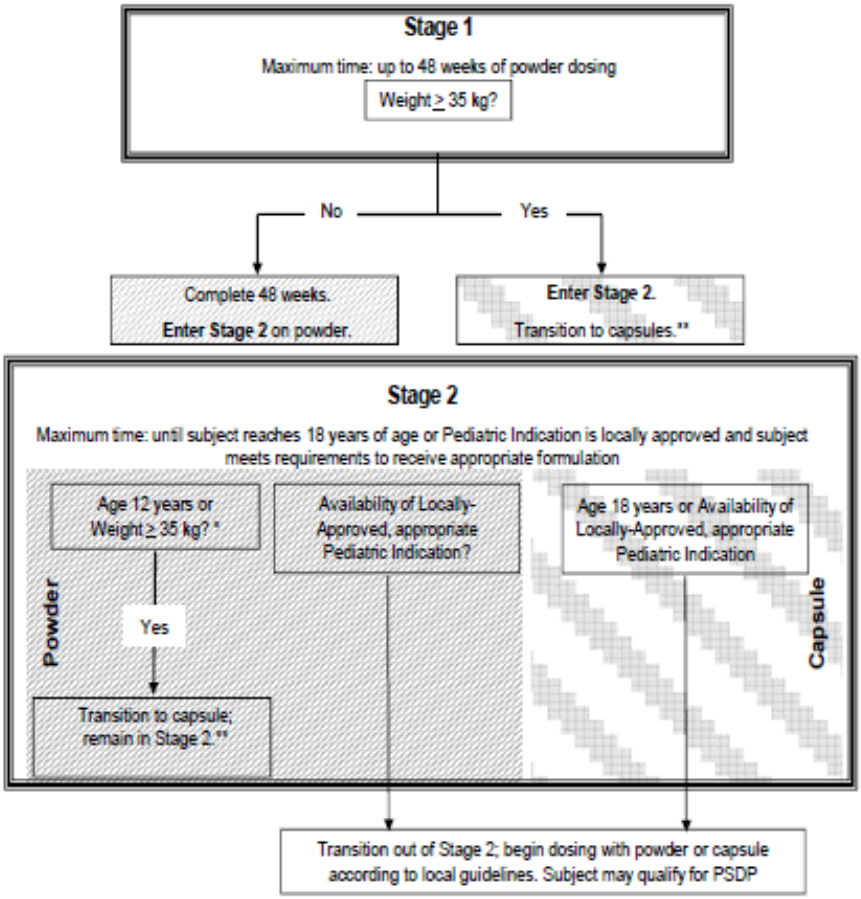
Figure 3: Study Schema in PRINCE I



Source: Figure 3.1 in Final Clinical Study Report for PRINCE I (Study AI424397)

Figure 4: Study Schema in PRINCE II

Age ≥ 3 months to < 11 years: Minimum 56 subjects treated with ATV powder formulation for 48 weeks				
Body Weight (kg)	Target # of Subjects	ATV Dose (mg)	RTV Dose (mg)	
5 to less than 10	Minimum of 5	150	80	+ approved NRTI backbone (tenofovir is prohibited)
	Minimum of 6	200	80	
10 to less than 15	Minimum of 10	200	80	
15 to less than 25	Minimum of 10	250	80	
25 to less than 35	Minimum of 6	300	100	
The study will commit to enroll a minimum of 30 ARV experienced patients .				



* Subjects are required to switch to capsules when they reach 35 kg and/or become 12 years of age. However, subjects who reach a weight of 25 kg and/or 6 years of age during Stage 2 may, at the discretion of the investigator and caregiver, choose to attempt switch to the solid dosage forms of ATV/RTV. Careful consideration should be given to the time of switch as subjects who are unable to swallow capsule after an 8-week transition period must be discontinue from Stage 2.

** Subjects who are unable to swallow the capsule formulation after an 8 week transition period must be discontinued from the study.

Source: Figure 3.1 in Interim Clinical Study Report for PRINCE II (Study AI424451)

Table 22: Visit Windows for Snapshot Analysis for HIV Virologic Response in PRINCE I and PRINCE II

Week	Label	Analysis Week Window on ATV Powder
-1	SCREENING	≤ 1 day not at baseline
0	BASELINE	≤ 1 day at baseline
4	WEEK 4	Day 2 - < 6
8	WEEK 8	6 - < 10
12	WEEK 12	10 - < 14
16	WEEK 16	14 - < 18
24	WEEK 24	18 - < 30
32	WEEK 32	30 - < 36
40	WEEK 40	36 - < 42
48	WEEK 48	42 - < 54
60	WEEK 60	54 - < 66
72	WEEK 72	66 - < 78
84	WEEK 84	78 - < 90
96	WEEK 96	90 - < 102
108	WEEK 108	102 - < 114
120	WEEK 120	114 - < 126
X	WEEK X	(X - 6) - < (X + 6)

Source: Statistical Analysis Plan Version 2.0 in Appendix of Final Clinical Study Report for PRINCE I

Figure 5 Survival Analysis Plot of Time on Atazanavir Powder for the PRINCE I Study

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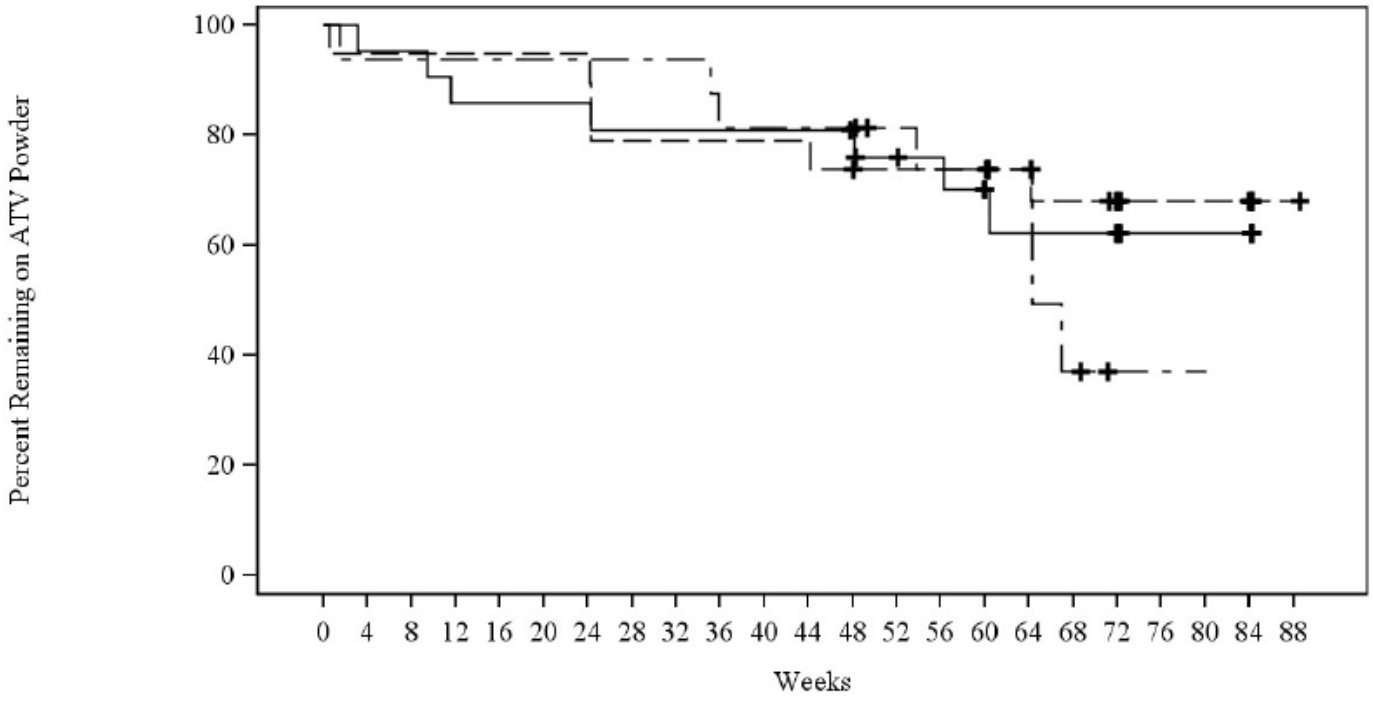
Figure S.4.2
Time on ATV Powder
Treated Subjects



Number at risk

B/L Weight 5 - < 10 kg	21	20	20	18	18	18	18	17	17	17	17	17	16	14	13	9	8	8	7	4	4	4	0
B/L Weight 10 - < 15 kg	19	18	18	18	18	18	18	15	15	15	15	15	13	13	13	13	13	12	9	7	7	6	1
B/L Weight 15 - < 25 kg	16	15	15	15	15	15	15	15	15	13	13	13	13	11	10	10	7	3	1	1	1	0	0

Source: Final Clinical Study Report

Figure 6: Plot of Virologic Response (HIV RNA <50 copies/mL) by Visit through Week 48 for the PRINCE I study

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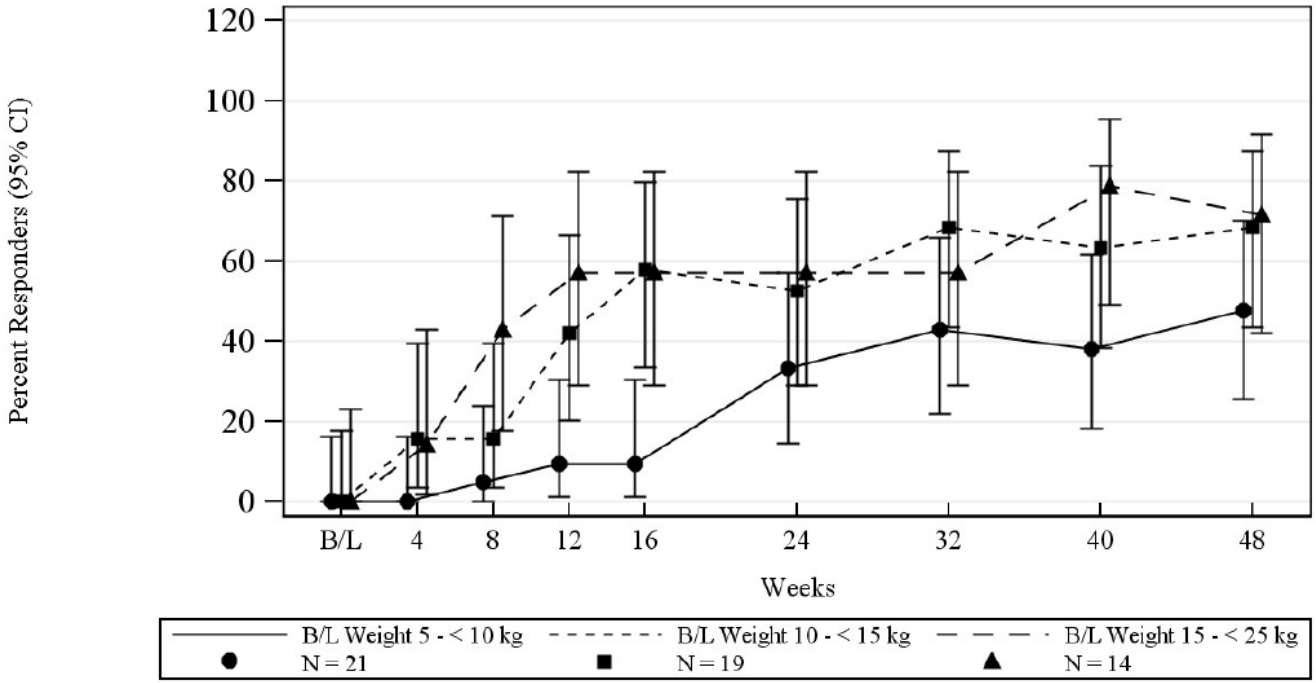
Figure S.5.1A
Virologic Response (HIV RNA < 50 c/mL)
Modified ITT on ATV Powder through Week 48
Week 48 ATV Powder Cohort



Number of Responders

B/L Weight 5 - < 10 kg	0	0	1	2	2	7	9	8	10
B/L Weight 10 - < 15 kg	0	3	3	8	11	10	13	12	13
B/L Weight 15 - < 25 kg	0	2	6	8	8	8	8	11	10

Source: Final Clinical Study Report

Figure 7: Plot of Virologic Response (HIV RNA <400 copies/mL) by Visit through Week 48 for the PRINCE I study

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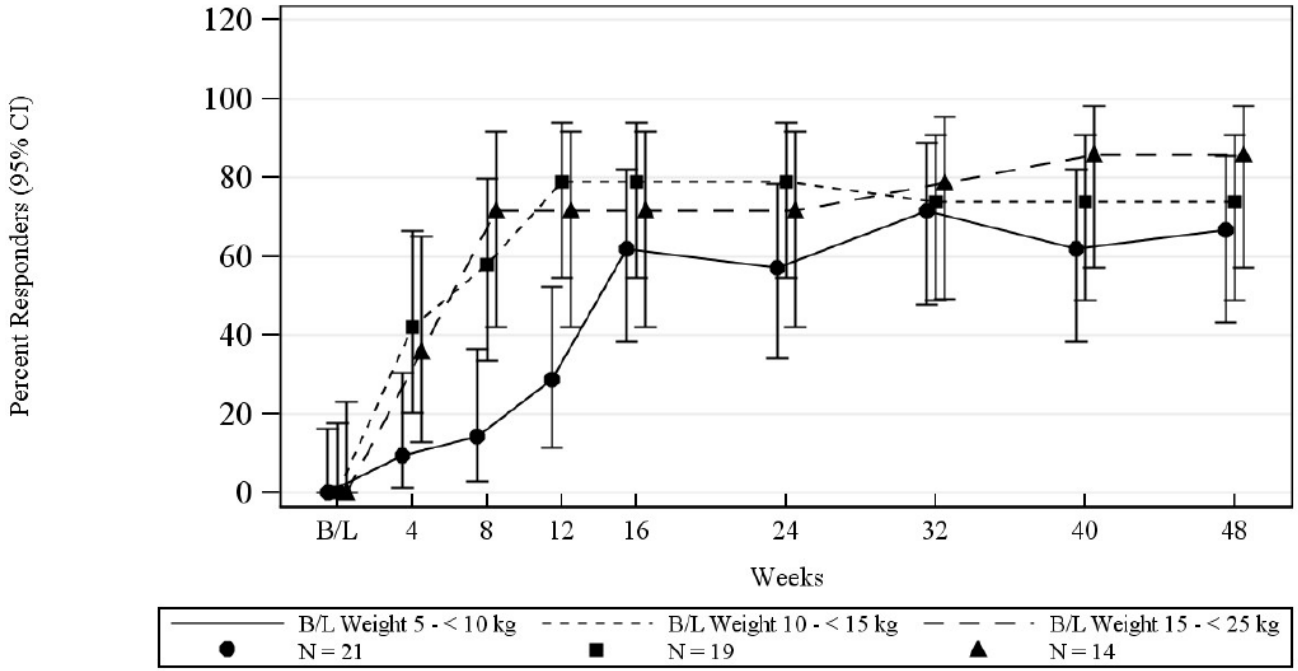
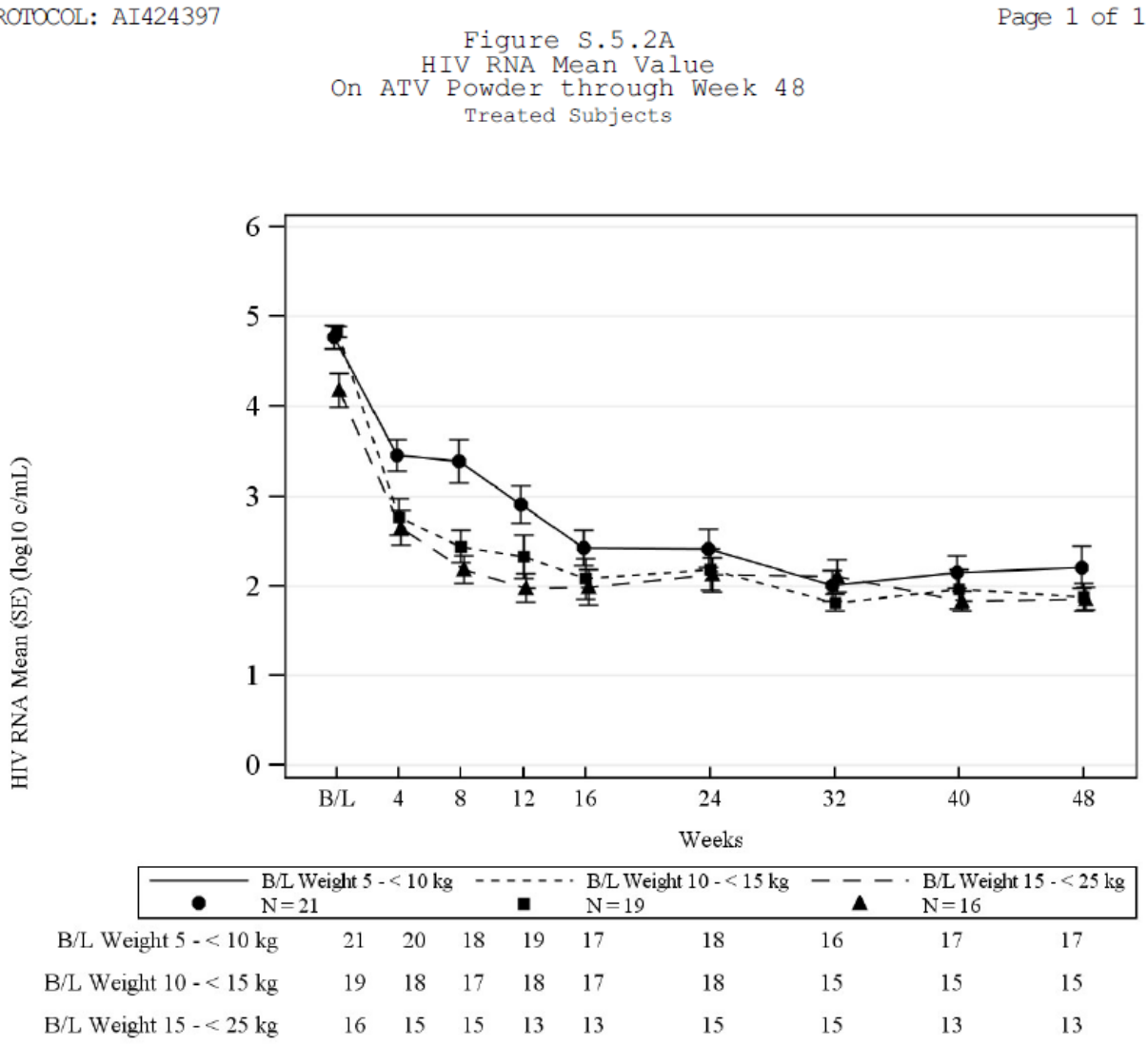
Figure S.5.1B
Virologic Response (HIV RNA < 400 c/mL)
Modified ITT on ATV Powder through Week 48
Week 48 ATV Powder Cohort



Number of Responders									
B/L Weight 5 - < 10 kg	0	2	3	6	13	12	15	13	14
B/L Weight 10 - < 15 kg	0	8	11	15	15	15	14	14	14
B/L Weight 15 - < 25 kg	0	5	10	10	10	10	11	12	12

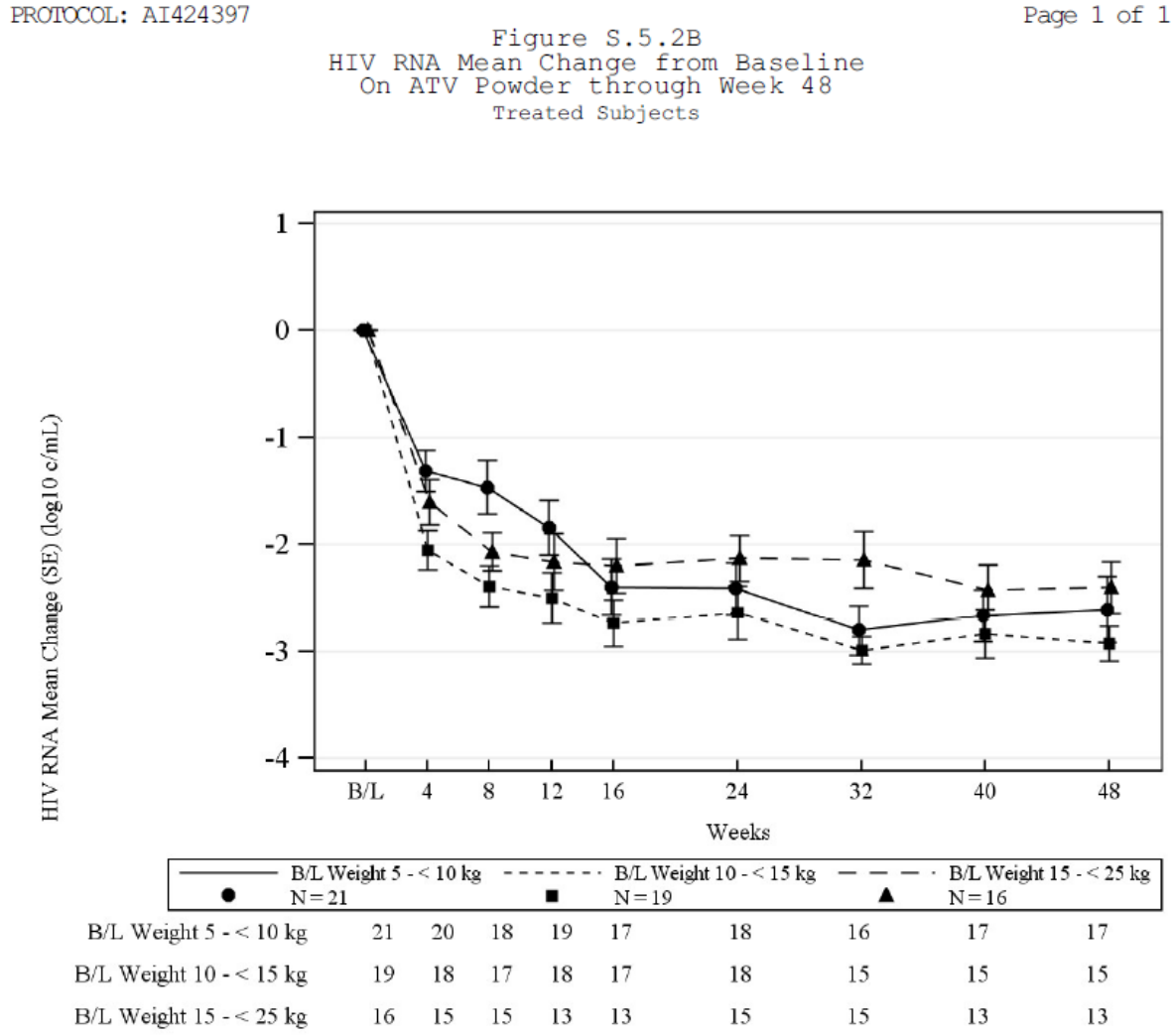
Source: Final Clinical Study Report

Figure 8: Plot of mean (+/-se) log10 HIV RNA values at each visit through Week 48 for the PRINCE I study



Source: Final Clinical Study Report

Figure 9: Plot of mean change from baseline (+/-se) in log10 scale of HIV RNA values at each visit through Week 48 for the PRINCE I study



Source: Final Clinical Study Report

Figure 10: Plot of median CD4 cell counts (+/- se) by visit through Week 48 for the PRINCE I study

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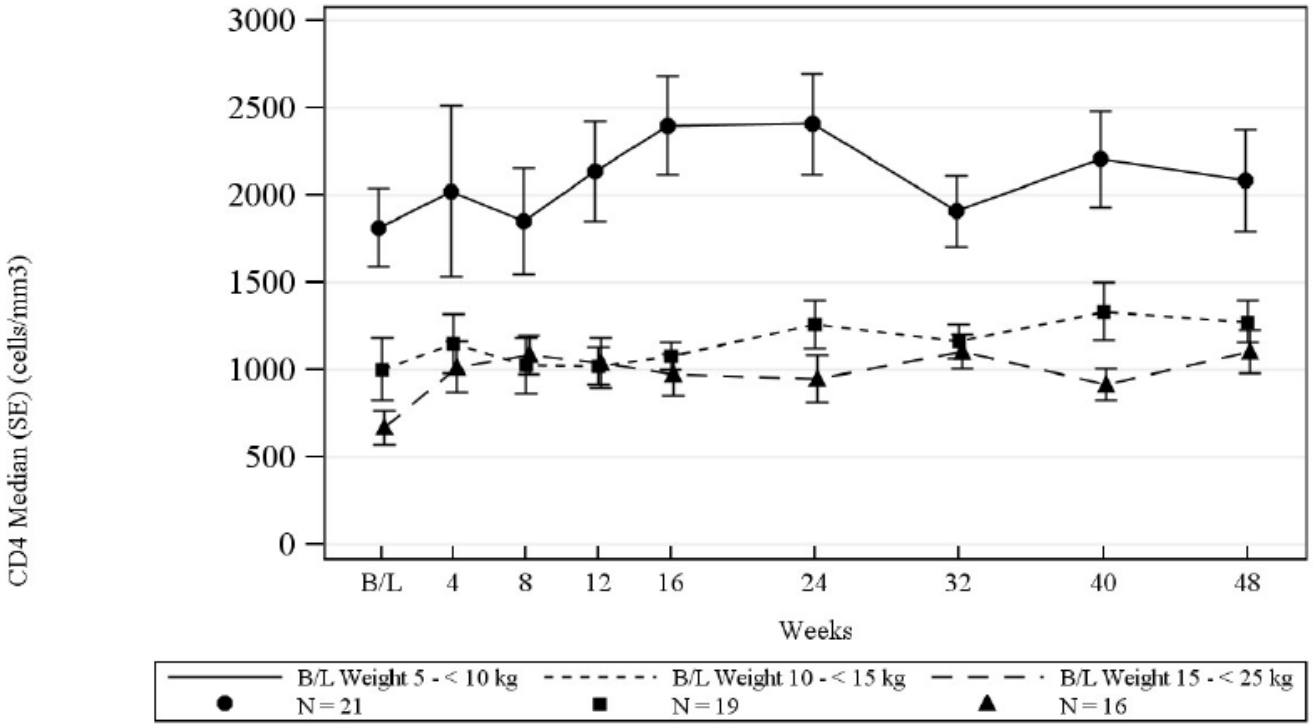
Figure S.5.3A
CD4 Median Cell Count
On ATV Powder through Week 48
Treated Subjects



B/L Weight 5 - < 10 kg	16	13	15	18	16	16	13	13	15
B/L Weight 10 - < 15 kg	13	11	13	15	16	15	13	14	13
B/L Weight 15 - < 25 kg	10	12	11	10	12	11	12	12	11

Source: Final Clinical Study Report

Figure 11: Plot of median change from baseline of CD4 cell counts (+/- se) by visit through Week 48 for the PRINCE I study

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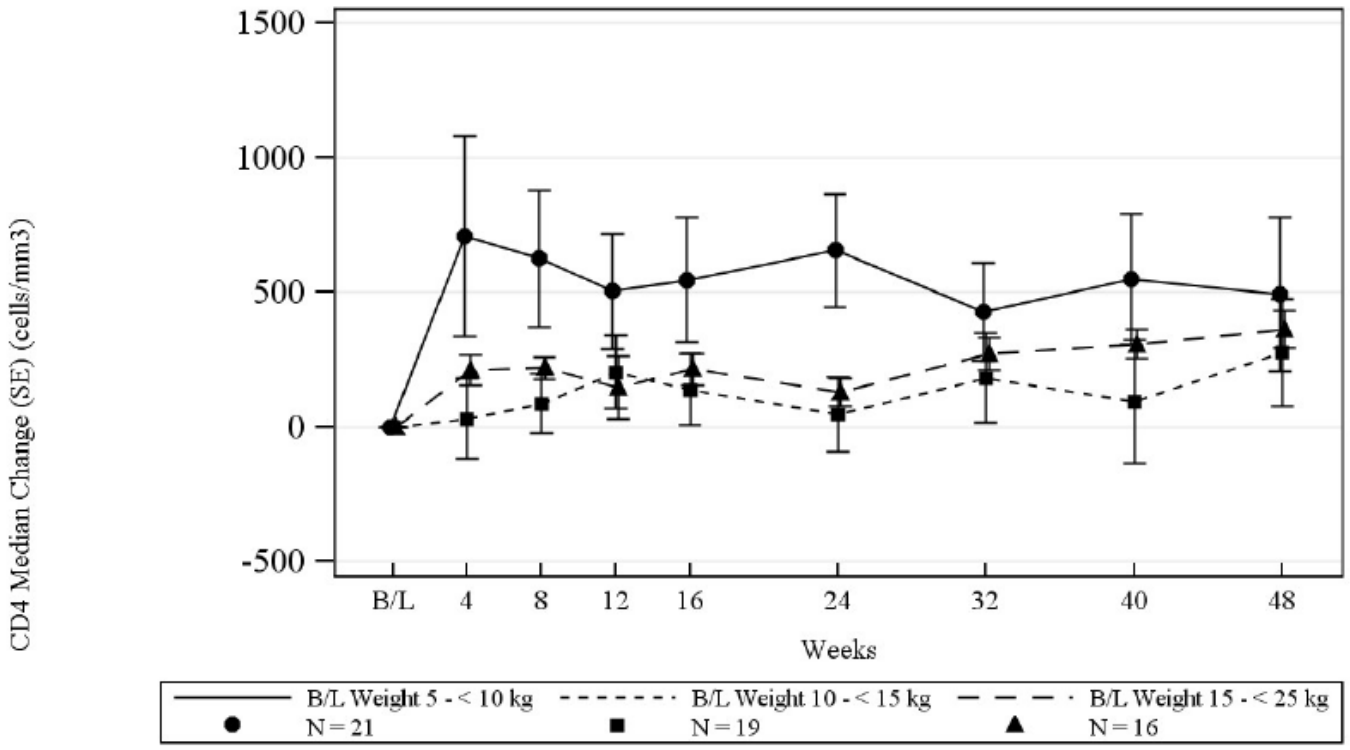
Figure S.5.3B
CD4 Median Change from Baseline
On ATV Powder through Week 48
Treated Subjects



B/L Weight 5 - < 10 kg	16	11	12	15	14	14	11	11	13
B/L Weight 10 - < 15 kg	13	8	11	10	11	11	10	11	11
B/L Weight 15 - < 25 kg	10	8	6	6	7	6	7	7	5

Source: Final Clinical Study Report

Figure 12: Survival Analysis Plot of Time on Atazanavir Powder for the PRINCE II Study

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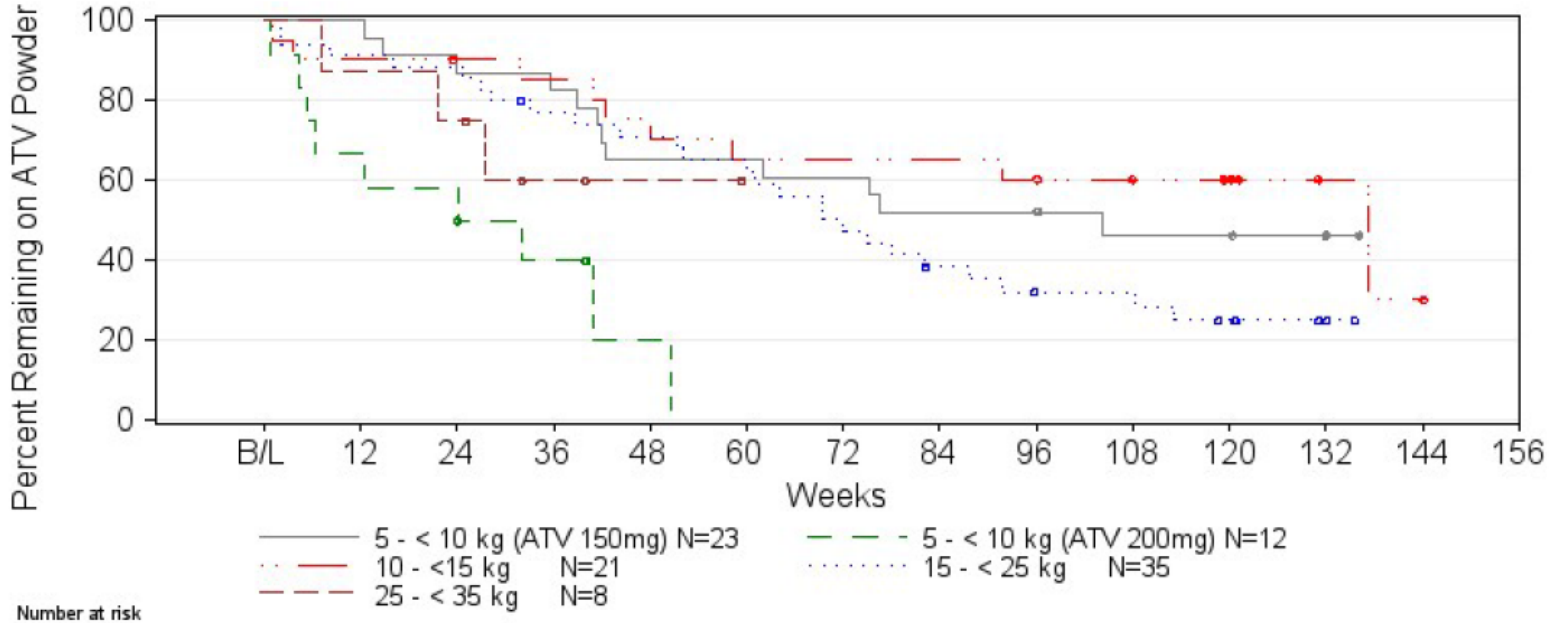
Figure S.4.2
Time on ATV Powder
Treated Subjects



Number at risk

5 -< 10 kg (150mg)	23	23	20	19	15	15	14	12	12	8	8	3	0	0
5 -< 10 kg (200mg)	12	8	7	4	1	0	0	0	0	0	0	0	0	0
10 -< 15 kg	21	19	18	17	15	13	13	13	12	8	6	2	1	0
15 -< 25 kg	35	32	31	26	24	21	16	12	9	9	5	2	0	0
25 -< 35 kg	8	7	6	2	1	0	0	0	0	0	0	0	0	0

Source: Final Clinical Study Report

Figure 13: Plot of Virologic Response (HIV RNA <50 copies/mL) by Visit through Week 48 for the PRINCE II study

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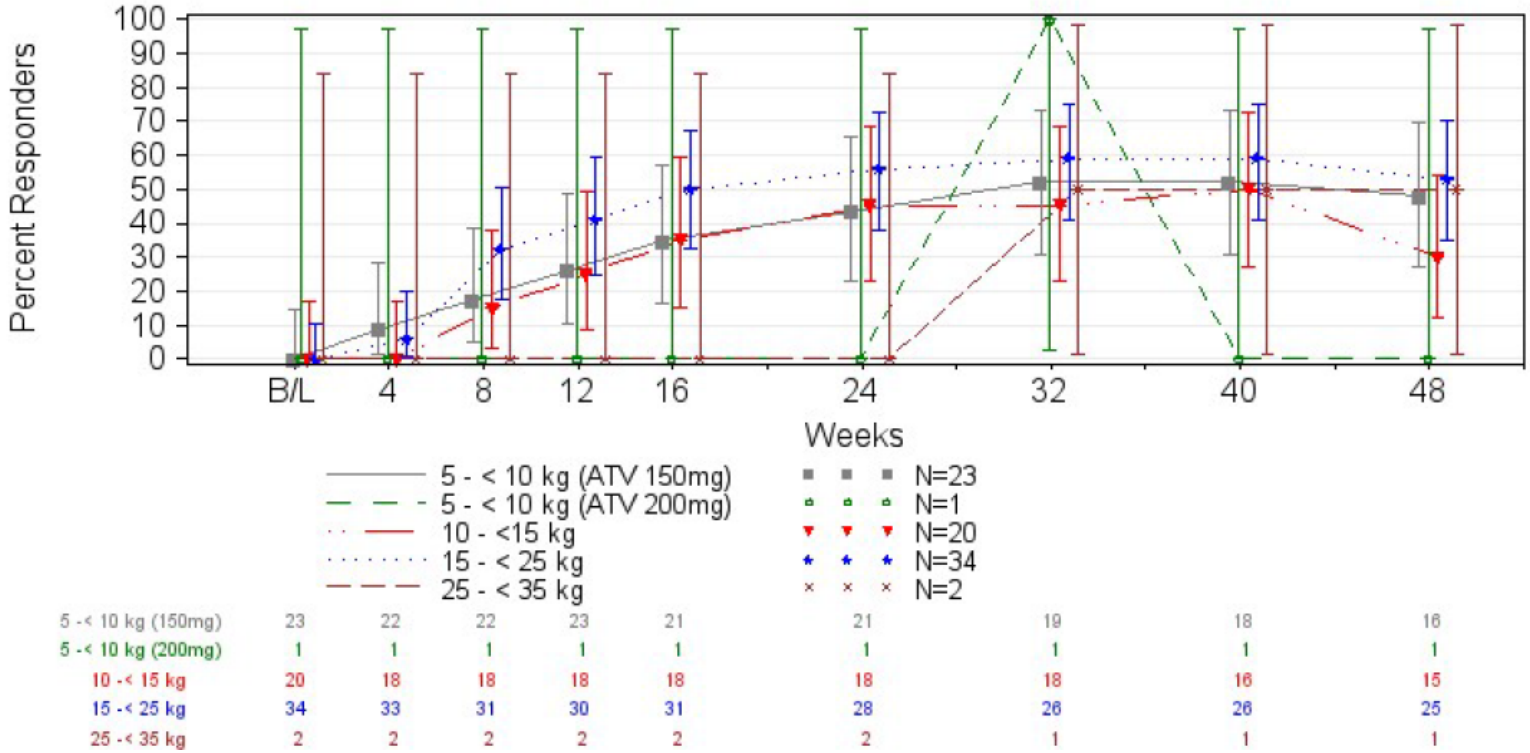
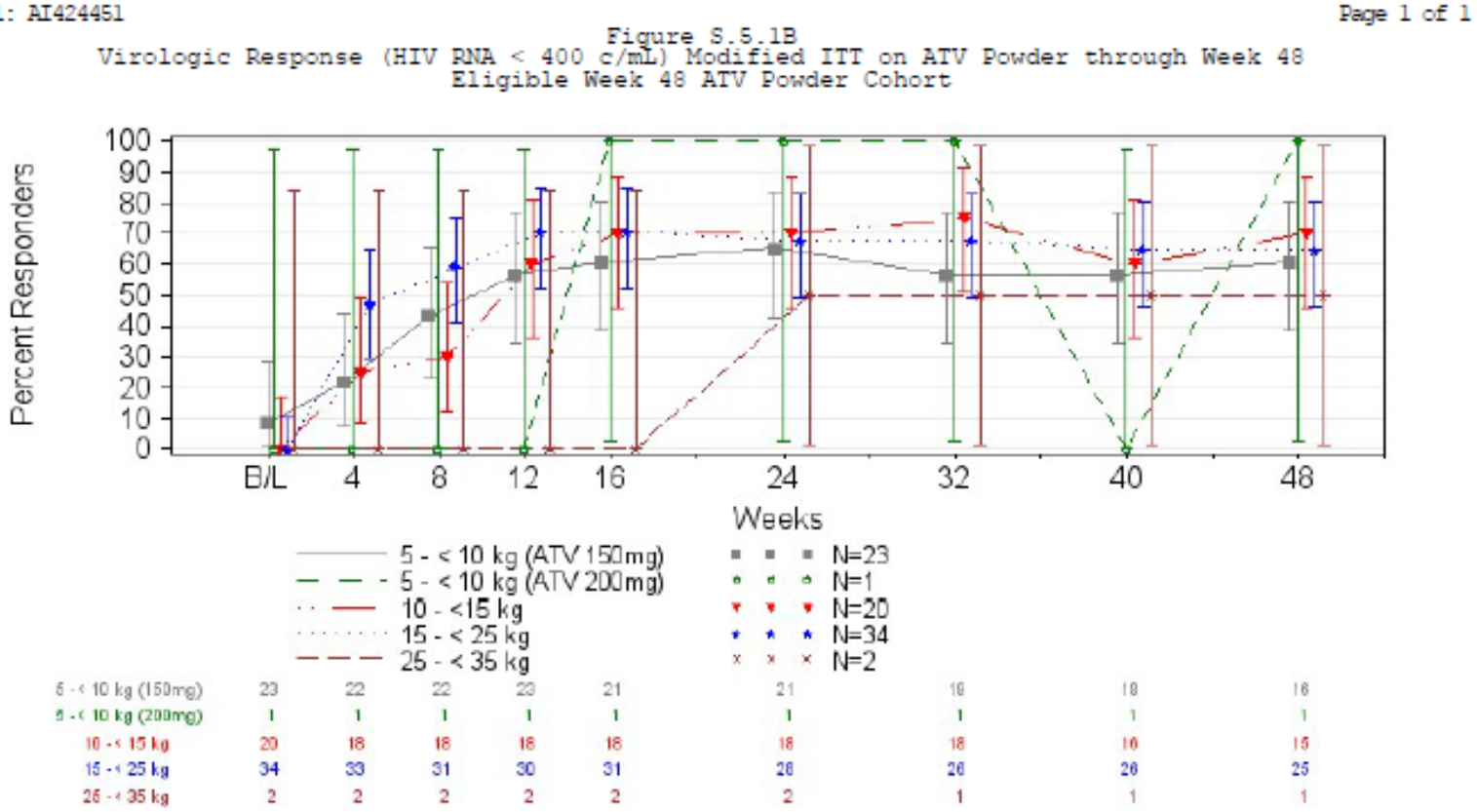
Figure S.5.1A
Virologic Response (HIV RNA < 50 c/mL) Modified ITT on ATV Powder through Week 48
Eligible Week 48 ATV Powder Cohort



5 -< 10 kg (150mg)	23	22	22	23	21	21	19	18	16
5 -< 10 kg (200mg)	1	1	1	1	1	1	1	1	1
10 -< 15 kg	20	18	18	18	18	18	18	16	15
15 -< 25 kg	34	33	31	30	31	28	26	26	25
25 -< 35 kg	2	2	2	2	2	2	1	1	1

Source: Final Clinical Study Report

Figure 14: Plot of Virologic Response (HIV RNA <400 copies/mL) by Visit through Week 48 for the PRINCE II study



Source: Final Clinical Study Report

Figure 15: Plot of mean (+/-se) log10 HIV RNA values at each visit through Week 48 for the PRINCE II study

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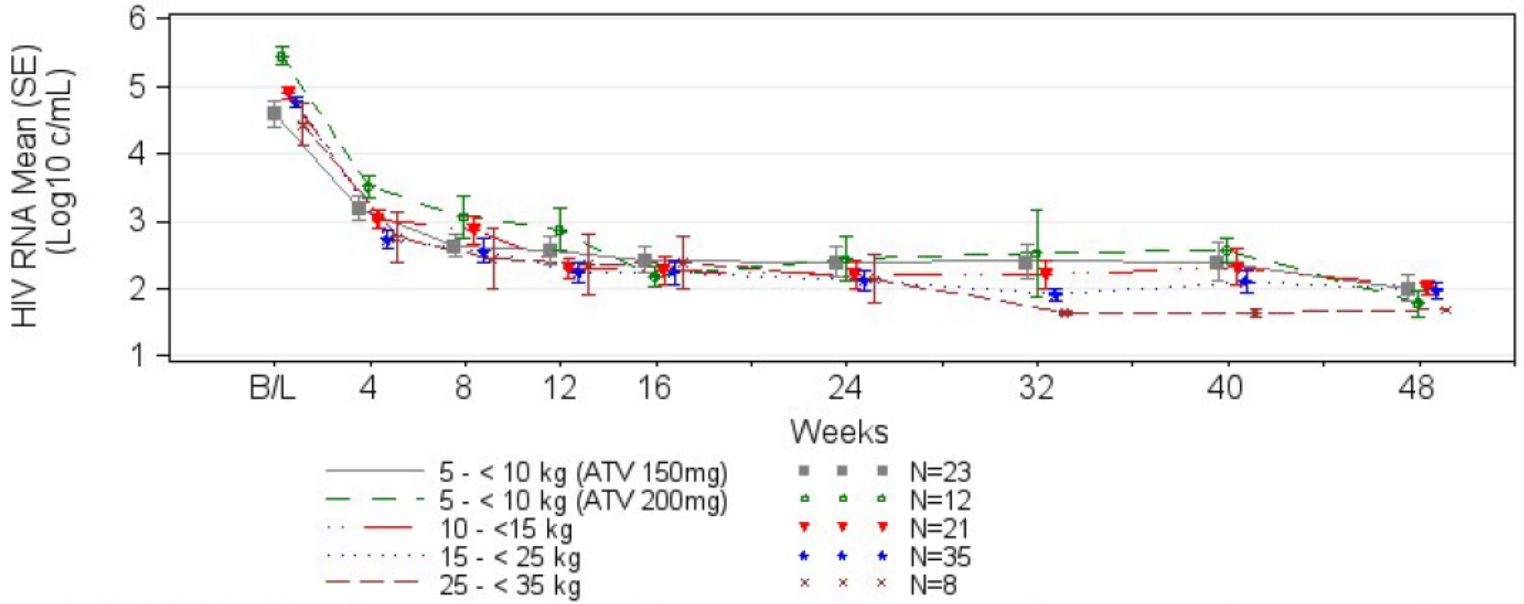
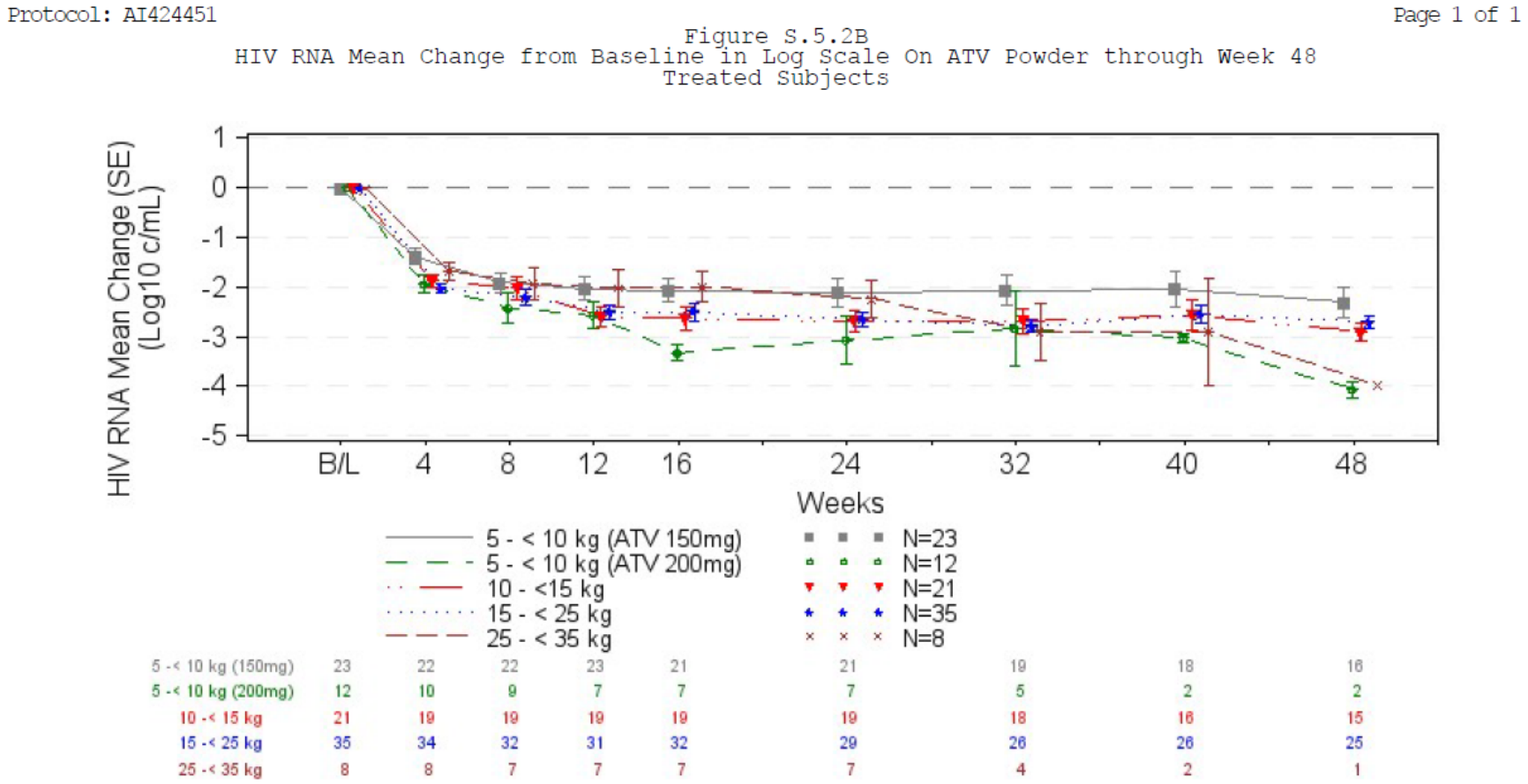
Figure S.5.2A
HIV RNA Mean Value in Log Scale On ATV Powder through Week 48
Treated Subjects



5 -< 10 kg (150mg)	23	22	22	23	21	21	19	18	16
5 -< 10 kg (200mg)	12	10	9	7	7	7	5	2	2
10 -< 15 kg	21	19	19	19	19	19	18	16	15
15 -< 25 kg	35	34	32	31	32	29	26	26	25
25 -< 35 kg	8	8	7	7	7	7	4	2	1

Source: Final Clinical Study Report

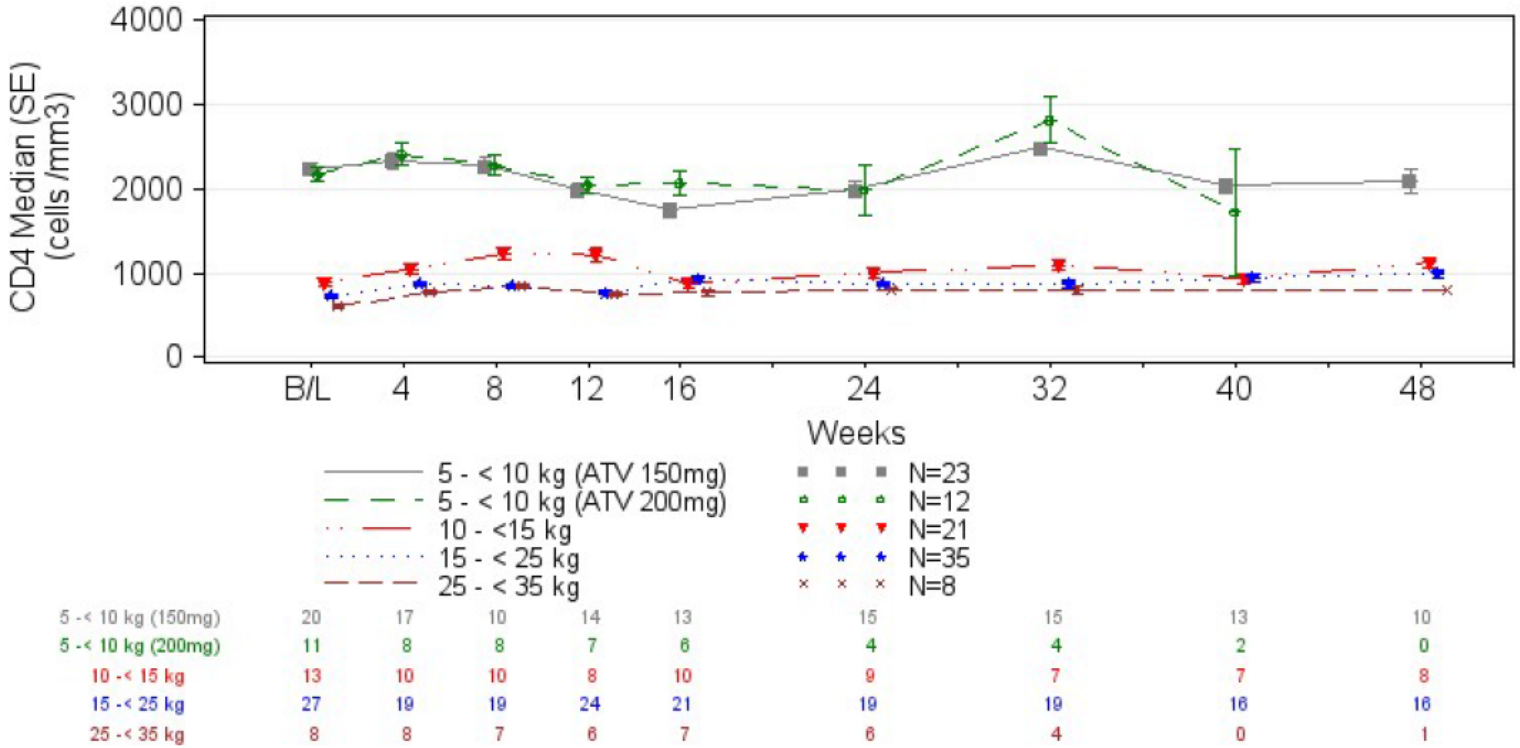
Figure 16: Plot of mean change from baseline (+/-se) in log10 scale of HIV RNA values at each visit through Week 48 for the PRINCE II study



Source: Final Clinical Study Report

Figure 17: Plot of median CD4 cell counts (+/- se) by visit through Week 48 for the PRINCE II study

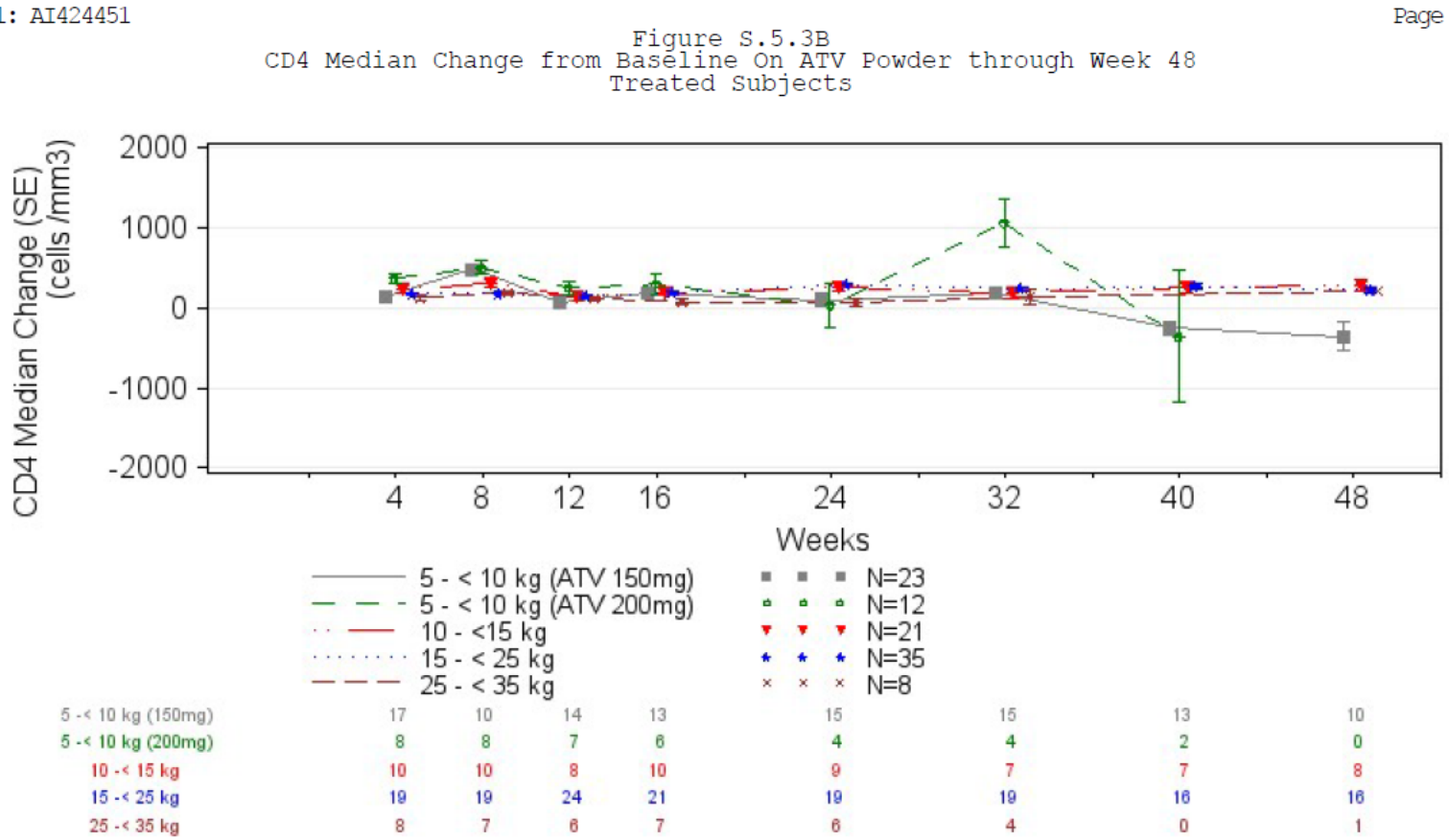
Figure S.5.3A
CD4 Median Cell Count On ATV Powder through Week 48
Treated Subjects



5 -< 10 kg (150mg)	20	17	10	14	13	15	15	13	10
5 -< 10 kg (200mg)	11	8	8	7	6	4	4	2	0
10 -< 15 kg	13	10	10	8	10	9	7	7	8
15 -< 25 kg	27	19	19	24	21	19	19	16	16
25 -< 35 kg	8	8	7	6	7	6	4	0	1

Source: Final Clinical Study Report

Figure 18: Plot of median change from baseline of CD4 cell counts (+/- se) by visit through Week 48 for the PRINCE II study



Source: Final Clinical Study Report

Table 23: Subgroup Analysis for Proportion of Subjects with HIV RNA < 50 copies/mL by Gender, Race and Region (Week 48 Powder Cohort)

	PRINCE I and II combined					
	All (N=54)	**baseline weight 5 - < 10 kg (ATV 150 mg) (N=22)**	**baseline weight 5 - <10 kg (ATV 200 mg) (N=6)**	**baseline weight 10 - <15 kg (N=24)**	**baseline weight 15 - <25 kg (N=24)**	**baseline weight 25 - < 35 kg (N=3)**
Gender						
Male	42% (32/76)	36% (8/22)	17% (1/6)	44% (7/16)	48% (13/27)	60% (3/5)
Female	51% (40/79)	41% (9/22)	17% (1/6)	54% (13/24)	63% (15/24)	67% (2/3)
Race						
Black/African American	46% (41/89)	44% (14/32)	0% (0/6)	37% (7/19)	59% (16/27)	80% (4/5)
Other	47% (31/66)	25% (3/12)	33% (2/6)	62% (13/21)	50% (12/24)	33% (1/3)
Region						
Africa	47% (48/102)	43% (16/37)	20% (2/10)	48% (10/21)	55% (16/29)	80% (4/5)
Asia	100% (1/1)	0	0	100% (1/1)	0	0
Europe	25% (2/8)	0	0	33% (1/3)	20% (1/5)	0
North America	48% (13/27)	25% (1/4)	0% (0/1)	50% (6/12)	63% (5/8)	50% (1/2)
South America	44% (7/16)	0% (0/3)	0% (0/1)	67% (2/3)	63% (5/8)	0% (0/1)

Source: Reviewer's analysis

Table 24: Snapshot Outcomes at Week 24 for ALL Subjects in PRINCE I by Prior ARV Use (Week 24 Powder Cohort)

Treatment Outcomes	ARV Naive N=22	ARV Experienced N=34
HIV RNA < 50 C/ML		
VIROLOGIC SUCCESS	13 (59.1)	13 (38.2)
VIROLOGIC FAILURE	9 (40.9)	18 (52.9)
HIV RNA >= 50 C/ML	9 (40.9)	16 (47.1)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	0
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 50 C/ML AT TIME OF DISCONTINUATION	0	2 (5.9)
OBT CHANGED	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	0	3 (8.8)
DISCONTINUED DUE TO AE OR DEATH	0	3 (8.8)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50 C/ML AT TIME OF DISCONTINUATION	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0
HIV RNA < 400 C/ML		
VIROLOGIC SUCCESS	19 (86.4)	19 (55.9)
VIROLOGIC FAILURE	3 (13.6)	12 (35.3)
HIV RNA >= 400 C/ML	3 (13.6)	10 (29.4)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	0
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 400 C/ML AT TIME OF DISCONTINUATION	0	2 (5.9)
OBT CHANGED	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	0	3 (8.8)
DISCONTINUED DUE TO AE OR DEATH	0	3 (8.8)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400 C/ML AT TIME OF DISCONTINUATION	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0

Source: Table 6.1-1 of Addendum 02 to the Final Clinical Study Report

Table 25: Snapshot Outcomes at Week 24 for ALL Subjects in PRINCE II by Prior ARV Use (Week 24 Powder Cohort)

Treatment Outcomes	ARV Naive N=37	ARV Experienced N=62
HIV RNA < 50 C/ML		
VIROLOGIC SUCCESS	17 (45.9)	29 (46.8)
VIROLOGIC FAILURE	14 (37.8)	30 (48.4)
HIV RNA >= 50 C/ML	13 (35.1)	24 (38.7)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	0
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 50 C/ML AT TIME OF DISCONTINUATION	1 (2.7)	6 (9.7)
OBT CHANGED	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	6 (16.2)	3 (4.8)
DISCONTINUED DUE TO AE OR DEATH	4 (10.8)	2 (3.2)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50 C/ML AT TIME OF DISCONTINUATION	0	1 (1.6)
MISSING DATA IN WINDOW BUT ON TREATMENT	2 (5.4)	0
HIV RNA < 400 C/ML		
VIROLOGIC SUCCESS	25 (67.6)	40 (64.5)
VIROLOGIC FAILURE	6 (16.2)	19 (30.6)
HIV RNA >= 400 C/ML	5 (13.5)	13 (21.0)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	0
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 400 C/ML AT TIME OF DISCONTINUATION	1 (2.7)	6 (9.7)
OBT CHANGED	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	6 (16.2)	3 (4.8)
DISCONTINUED DUE TO AE OR DEATH	4 (10.8)	2 (3.2)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400 C/ML AT TIME OF DISCONTINUATION	0	1 (1.6)
MISSING DATA IN WINDOW BUT ON TREATMENT	2 (5.4)	0

Source: Table 5 in the Final Clinical Study Report

Table 26: Snapshot Outcomes at Week 48 for ALL Subjects in PRINCE I by Prior ARV Use (Week 48 Powder Cohort)

Treatment Outcomes	ARV Naive N=22	ARV Experienced N=32
HIV RNA < 50 C/ML		
VIROLOGIC SUCCESS	15 (68.2)	18 (56.3)
VIROLOGIC FAILURE	6 (27.3)	10 (31.3)
HIV RNA >= 50 C/ML	5 (22.7)	7 (21.9)
DISCONTINUED DUE TO VIROLOGIC FAILURE	1 (4.5)	1 (3.1)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 50 C/ML AT TIME OF DISCONTINUATION	0	2 (6.3)
OBT CHANGED	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	1 (4.5)	4 (12.5)
DISCONTINUED DUE TO AE OR DEATH	1 (4.5)	4 (12.5)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50 C/ML AT TIME OF DISCONTINUATION	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0
HIV RNA < 400 C/ML		
VIROLOGIC SUCCESS	19 (86.4)	21 (65.6)
VIROLOGIC FAILURE	2 (9.1)	7 (21.9)
HIV RNA >= 400 C/ML	1 (4.5)	4 (12.5)
DISCONTINUED DUE TO VIROLOGIC FAILURE	1 (4.5)	1 (3.1)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 400 C/ML AT TIME OF DISCONTINUATION	0	2 (6.3)
OBT CHANGED	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	1 (4.5)	4 (12.5)
DISCONTINUED DUE TO AE OR DEATH	1 (4.5)	4 (12.5)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400 C/ML AT TIME OF DISCONTINUATION	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0

Source: Table 6.1-2 of Addendum 02 to the Final Clinical Study Report

Table 27: Snapshot Outcomes at Week 48 for ALL Subjects in PRINCE II by Prior ARV Use (Week 48 Powder Cohort)

Treatment Outcomes	ARV Naive N=30	ARV Experienced N=50
HIV RNA < 50 C/ML		
VIROLOGIC SUCCESS	13 (43.3)	23 (46.0)
VIROLOGIC FAILURE	14 (46.7)	23 (46.0)
HIV RNA >= 50 C/ML	11 (36.7)	11 (22.0)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	8 (16.0)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 50 C/ML AT TIME OF DISCONTINUATION	3 (10.0)	4 (8.0)
OBT CHANGED	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	3 (10.0)	4 (8.0)
DISCONTINUED DUE TO AE OR DEATH	2 (6.7)	2 (4.0)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50 C/ML AT TIME OF DISCONTINUATION	0	1 (2.0)
MISSING DATA IN WINDOW BUT ON TREATMENT	1 (3.3)	1 (2.0)
HIV RNA < 400 C/ML		
VIROLOGIC SUCCESS	22 (73.3)	30 (60.0)
VIROLOGIC FAILURE	4 (13.3)	16 (32.0)
HIV RNA >= 400 C/ML	2 (6.7)	4 (8.0)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	8 (16.0)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA >= 400 C/ML AT TIME OF DISCONTINUATION	2 (6.7)	4 (8.0)
OBT CHANGED	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	4 (13.3)	4 (8.0)
DISCONTINUED DUE TO AE OR DEATH	2 (6.7)	2 (4.0)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400 C/ML AT TIME OF DISCONTINUATION	1 (3.3)	1 (2.0)
MISSING DATA IN WINDOW BUT ON TREATMENT	1 (3.3)	1 (2.0)

Source: Table 7.3.1-4 of the Final Clinical Study Report

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/s/

FRASER B SMITH
09/02/2015

GUOXING SOON
09/02/2015