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 Serial Number:	206352-S00, 21567-S35
Drug Name:	Reyataz® (atazanavir sulphate, ATV)
Indication(s):	ATV powder for oral use formulation in pediatric patients
Applicant:	Bristol-Myers Squibb
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Keywords: pediatric patients, Reyataz, atazanavir sulfate, powder, HIV, snapshot algorithm

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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 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). In the two studies, the subjects received the ATV powder for up to 48 weeks. The ATV dosing depended on the subject's baseline body weight, namely, 150 or 200 mg for the subjects with 5 to less than 10 kg, 200 mg for the subjects with 10 to less than 15 kg, 250 mg for the subjects with 15 to less than 25 kg, and 300 mg for the subjects with 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 could last until the subjects reached 18 years old. The 48-week ATV powder treatment phase has completed in the PRINCE I study but was ongoing in the PRINCE II study. In this submission, the applicant included the final and interim study reports for the 48 weeks of ATV powder treatment for the PRINCE I and II studies, respectively. These study reports included the results for the pediatric subjects with baseline body weight of 5 to less than 35 kg although the applicant is seeking the approval of the pediatric indication of the ATV powder for oral use formulation in pediatric patients who are 10 to less than 25 kg.

There is no statistical issue. The outcomes for the proportions of HIV RNA < 50 copies/mL and < 400 copies/mL at Week 48 are displayed in Table 1 below. The reviewer has performed separate analyses and got the same results as the applicant's. In the PRINCE I study, the overall virologic response rates at Week 48 increased with the higher baseline body weight band. Similar trend was observed in the PRINCE II study except for the group of 10 to less than 15 kg where the response rates were low possibly due to temporary "viral blips". Please note that these interim results for the PRINCE II study only represented the approximately 53% of the planned sample size. Also, there was only one subject in the 25 to less than 35 kg weight group in the two studies. Therefore the studies cannot confirm the dosing in that weight group.

Table 1: HIV RNA Response Rates at Week 48 in PRINCE I and PRINCE II

	PRINCE I			PRINCE II			
	baseline weight (kg) 5 - < 10	baseline weight (kg) 10 - <15	baseline weight (kg) 15 - <25	baseline weight (kg) 5 - < 10	baseline weight (kg) 10 - <15	baseline weight (kg) 15 - <25	baseline weight (kg) 25 - <35
All (TN + TE)							
% of subjects with HIV RNA < 50 c/mL	48% (10/21)	68% (13/19)	71% (10/14)	47% (8/17)	31% (4/13)	74% (14/19)	0% (0/1)
% of subjects with HIV RNA < 400 c/mL	67% (14/21)	74% (14/19)	86% (12/14)	65% (11/17)	62% (8/13)	79% (15/19)	0% (0/1)

to be continued

Table 1: HIV RNA Response Rates in PRINCE I and PRINCE II (to be continued)

	PRINCE I			PRINCE II			
	baseline weight (kg) 5 - < 10	baseline weight (kg) 10 - <15	baseline weight (kg) 15 - <25	baseline weight (kg) 5 - < 10	baseline weight (kg) 10 - <15	baseline weight (kg) 15 - <25	baseline weight (kg) 25 - <35
TN							
% of subjects with HIV RNA < 50 c/mL	46% (6/13)	75% (9/12)	67% (6/9)	0% (0/4)	38% (3/8)	75% (9/12)	0% (0/1)
% of subjects with HIV RNA < 400 c/mL	69% (9/13)	75% (9/12)	78% (7/9)	50% (2/4)	75% (6/8)	83% (10/12)	0% (0/1)
TE							
% of subjects with HIV RNA < 50 c/mL	50% (4/8)	57% (4/7)	80% (4/5)	62% (8/13)	20% (1/5)	71% (5/7)	n/a
% of subjects with HIV RNA < 400 c/mL	63% (5/8)	71% (5/7)	100% (5/5)	69% (9/13)	40% (2/5)	71% (5/7)	n/a

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 old. The 48-week ATV powder treatment phase has completed in the PRINCE I study but was ongoing in the PRINCE II study. In this submission, the applicant included the final and interim study reports for the 48 weeks of ATV powder treatment for the PRINCE I and II studies, respectively. This report focuses on reviewing the efficacy of the 48 weeks of ATV powder treatment in the two studies. Table 2 below briefly summarizes the key elements in the study design for the two studies.

Table 2: List of Studies Included in Review Report

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 consists of two stages. In the first stage, AZT powder (50 mg/sachet) boosted with Ritonavir (RTV) liquid with an optimized NRTI background therapy for up to 48 weeks. The AZT 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 AZT 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 consists of two stages. In the first stage, the subjects received AZT powder (50 mg/sachet) boosted with Ritonavir (RTV) with an optimized NRTI background therapy for up to 48 weeks. The AZT 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 AZT 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 and half 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 was still enrolling subjects and planned to include 95 subjects treated with ATV powder. As of the data cutoff date for the interim clinical study report, 117 subjects had been enrolled and 78 had been treated.

2.2 Data Sources

The data submitted are located in \\CDSESUB1\evsprod\NDA206352\0000. During the review course, the review team requested the applicant to clarify some issues and provide additional analyses related to the efficacy endpoints of HIV viral load and CD4. The applicant's responses are located in \\CDSESUB1\evsprod\NDA206352\0004. Finally, the proposed label discussed in Section 5.4 is located in \\CDSESUB1\evsprod\NDA206352\0003.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The efficacy datasets for the PRINCE I study were well defined and clear. The PRINCE II study was ongoing and its interim study report was included in the submission. In the initial

submission, the applicant did not have a flag variable in the efficacy datasets to indicate the subset for the Week 48 analysis in the study. During the review course, the reviewer sent the comments to the applicant to clarify. The issue got resolved after the applicant responded the reviewer's comments.

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 2 and Figure 3 in Appendix 6 displays the study design for the two studies. Both studies were Phase 3b prospective, international, multicenter, non-randomized trials. The primary objective in the two studies were 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.

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 received 150 mg ATV and a minimum 6 of subjects received 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 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 as follows:

1) The PRINCE I study enrolled the pediatric patients from ≥ 3 months to < 5 and half 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 weight ≥ 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 Patient Disposition, Demographics and Baseline Characteristics

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

Table 3 shows the patient disposition for the PRINCE I and II studies. The PRINCE I study has completed the 48 weeks of ATV powder treatment. In the study, 56 subjects were treated. Approximately 82% of the all treated subjects 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 expect for the two subjects who had switched to the ATV capsule before Week 48.

The PRINCE II study was still enrolling subjects, and the 48-week powder treatment phase was ongoing. The study planned to enroll 95 subjects. Up to the database lock for this interim study report, the study recruited and treated 78 subjects, accounting for approximately 82% of the planned enrollment. Among all treated subjects, 53% of the subjects completed the 48-week ATV powder treatment; 22% were still receiving the ATV powder; and 26% discontinued the treatment. Since the PRINCE II study was still ongoing, the criteria for the Week 48 ATV powder cohort not only requested the subjects who did not switch to ATV capsule before Week 48 but also required that the subjects had initiated treatment at least 49 weeks (i.e.,. 343 days, the protocol specified upper bound for Week 48 visit) prior to the date for the data cutoff of the submitted interim clinical study report. This would ensure that all subjects in this cohort would have had the opportunity to be followed up for 48 weeks. As the result, the Week 48 powder cohort only included approximately 64% of the 78 treated subjects and 53% of the planned sample size of 95 subjects.

Table 4 and Table 5 in Appendix 6 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 approximately 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 (61%). The overall median HIV RNA was approximately 5 $\log_{10}$ copies/mL, and 57% of the subjects had HIV RNA > 100,000 copies/mL. The overall median absolute CD4 count was 1004 cells/mm^3, and the median CD4 percent was 24%. In the PRINCE II study, the mean age for all treated subjects was approximately 42.5 (SD=27) months. Slightly more than half of the subjects were female (53%). The majority of the subjects were from Africa (62%). Half the subjects were treatment-naïve. The overall median HIV RNA was approximately 5 $\log_{10}$ copies/mL, and approximately 49% of the subjects had HIV RNA > 100,000 copies/mL. The median absolute CD4 count was 2235 cells/mm^3, and the median CD4 percent was 25%.

Table 3: Patient Disposition in PRINCE I and PRINCE II

	PRINCE I				PRINCE II				
	All	**baseline weight (kg) 5 – < 10**	**baseline weight (kg) 10 – < 15**	**baseline weight (kg) 15 – < 25**	**All**	**baseline weight (kg) 5 – < 10**	**baseline weight (kg) 10 - <15**	**baseline weight (kg) 15 – < 25**	**baseline weight (kg) 25 – < 35**
Treated	56 (100%)	21 (100%)	19 (100%)	16 (100%)	78 (100%)	23 (100%)	20 (100%)	34 (100%)	1 (100%)
Completed 48-wk ATV powder treatment[1]	46 (82%)	17 (81%)	14 (74%)	15 (94%)	41 (53%)	12 (52%)	11 (55%)	18 (53%)	0
Ongoing 48-wk ATV powder treatment	0	0	0	0	17 (22%)	4 (17%)	4 (20%)	9 (27%)	0
Did not complete 48-wk ATV powder treatment	10 (18%)	4 (19%)	5 (26%)	1 (6%)	20 (26%)	7 (30%)	5 (25%)	7 (21%)	1 (100%)
Adverse event	5 (9%)	4 (19%)	1 (5%)	0	3 (4%)	0	2 (10%)	1 (3%)	0
Lack of efficacy	2 (4%)	0	2 (11%)	0	8 (10%)	3 (13%)	3 (15%)	1 (3%)	1 (100%)
No longer meets study criteria	0	0	0	0	2 (3%)	1 (4%)	0	1 (3%)	0
Poor/non-compliance	2 (4%)	0	2 (11%)	0	2 (3%)	0	0	2 (6%)	0
Consent withdrawn	1 (2%)	0	0	1 (6%)	2 (3%)	1 (4%)	0	1 (3%)	0
Lost to follow-up	0	0	0	0	1 (1%)	1 (4%)	0	0	0
Other	0	0	0	0	2 (3%)	1 (4%)	0	1 (3%)	0
Week 48 powder cohort	54 (96%)	21 (100%)	19 (100%)	14 (88%)	50 (64%)	17 (74%)	13 (65%)	19 (56%)	1 (100%)

[1]including two subjects in PRINCE I and one in PRINCE II switched to ATV capsule.

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

	PRINCE I				PRINCE II				
	All (N=56)	**baseline weight 5 - < 10 kg (N=21)**	**baseline weight 10 - <15 kg (N=19)**	**baseline weight 15 - <25 kg (N=16)**	**All (N=78)**	**baseline weight 5 - < 10 kg (N=23)**	**baseline weight 10 - <15 kg (N=20)**	**baseline weight 15 - <25 kg (N=34)**	**baseline weight 25 - <35 kg (N=1)**
Age (month)									
n	56	21	19	16	78	23	20	34	1
Mean (SD)	30 (20)	7 (4)	35 (12)	52 (10)	42 (27)	8 (6)	37 (13)	66 (15)	79
Median	28.5	6	35	55	42.5	5	35.5	67	79
Gender									
Male	28 (50%)	11 (52%)	7 (37%)	10 (62.5%)	37 (47%)	11 (48%)	9 (45%)	16 (47%)	1 (100%)
Female	28 (50%)	10 (48%)	12 (63%)	6 (37.5%)	41 (53%)	12 (52%)	11 (55%)	18 (53%)	0
Race									
White	11 (20%)	2 (9.5%)	3 (16%)	6 (37.5%)	27 (35%)	2 (9%)	11 (55%)	13 (38%)	1 (100%)
Black / African American	32 (57%)	13 (62%)	12 (63%)	7 (44%)	46 (59%)	19 (83%)	7 (35%)	20 (59%)	0
Asian	1 (2%)	0	1 (5%)	0	0	0	0	0	0
Other	12 (21%)	6 (29%)	3 (16%)	3 (19%)	5 (6%)	2 (9%)	2 (10%)	1 (3%)	0
Ethnicity									
Hispanic/Latino	0	0	0	0	3 (4%)	0	2 (10%)	1 (3%)	0
Not Hispanic/Latino	1 (2%)	0	0	1 (6%)	3 (4%)	1 (4%)	1 (5%)	1 (3%)	0
Not reported	55 (98%)	21 (100%)	19 (100%)	15 (94%)	72 (92%)	22 (96%)	17 (85%)	32 (94%)	1 (100%)
Region									
Africa	38 (68%)	17 (81%)	13 (68%)	8 (50%)	48 (61.5%)	20 (87%)	8 (40%)	20 (59%)	0
Asia	1 (2%)	0	1 (5%)	0	4 (5%)	0	1 (5%)	3 (9%)	0
Europe	0	0	0	0	4 (5%)	0	1 (5%)	3 (9%)	0
North America	9 (16%)	2 (9.5%)	3 (16%)	4 (25%)	15 (19%)	2 (9%)	9 (45%)	4 (12%)	0
South America	8 (14%)	2 (9.5%)	2 (10.5%)	4 (25%)	7 (9%)	1 (4%)	1 (5%)	4 (12%)	1 (100%)

Sources: Table 5.3.1 in Final Clinical Study Report for PRINCE I (Study AI424397) and Interim Clinical Study Report for PRINCE II (Study AI424451)

Table 5: Baseline HIV Disease Characteristics in PRINCE I and PRINCE II (All Treated)

	PRINCE I				PRINCE II				
	All (N=56)	**baseline weight 5 - < 10 kg (N=21)**	**baseline weight 10 - <15 kg (N=19)**	**baseline weight 15 - <25 kg (N=16)**	**All (N=78)**	**baseline weight 5 - < 10 kg (N=23)**	**baseline weight 10 - <15 kg (N=20)**	**baseline weight 15 - <25 kg (N=34)**	**baseline weight 25 - <35 kg (N=1)**
HIV RNA (log_{10} copies/mL)									
n	56	21	19	16	78	23	20	34	1
Mean (SD)	4.6 (0.6)	4.8 (0.6)	4.8 (0.3)	4.2 (0.7)	4.8 (0.6)	4.6 (0.9)	4.9 (0.5)	4.8 (0.4)	5.0
Median	5.0	5.0	5.0	4.3	5.0	5.0	5.0	4.8	5.0
< 30,000 copies/mL	14 (25%)	3 (14%)	2 (10.5%)	9 (56%)	21 (27%)	6 (26%)	5 (25%)	10 (29%)	0
30,000 – 100,000 copies/mL	10 (18%)	0	7 (37%)	3 (19%)	19 (24%)	5 (22%)	2 (10%)	11 (32%)	1 (100%)
> 100,000 copies/mL	32 (57%)	18 (86%)	10 (53%)	4 (25%)	38 (49%)	12 (52%)	13 (65%)	13 (38%)	0
CD4 count (cells/mm^3)									
n	39	16	13	10	59	20	12	26	1
Mean (SD)	1193 (784)	1594 (897)	1107 (643)	661 (303)	1262 (1041)	2245 (1233)	814 (499)	738 (277)	615
Median	1004	1814.5	1002	668.5	912	2234.5	768.5	730	615
CD4 percent									
n	41	16	14	11	65	21	14	29	1
Mean (SD)	25 (11)	25 (12)	22 (9)	27.5 (10)	25 (11)	29 (11)	21 (11)	25 (10)	21
Median	24	23.5	22	27	25	29	21	25	21
Prior ARV use									
ARV naïve	34 (61%)	13 (62%)	12 (63%)	9 (56%)	39 (50%)	5 (22%)	14 (70%)	19 (56%)	1 (100%)
ARV experienced	22 (39%)	8 (38%)	7 (37%)	7 (44%)	39 (50%)	18 (78%)	6 (30%)	15 (44%)	0

Sources: Table 5.3.2 in Final Clinical Study Report for PRINCE I (Study AI424397) and Interim Clinical Study Report for PRINCE II (Study AI424451)

3.2.3 Statistical Methodologies

The efficacy analysis for Week 48 was performed in the powder cohort at Week 48. The powder cohort in the PRINCE I study included all subjects who received at least one dose of ATV powder and did not switch to ATV capsule at or before Week 48. Meanwhile, since the PRINCE II study was still ongoing, the powder cohort in the study had an additional criteria which was that subjects must have initiated treatment at least 49 weeks (i.e.,. 343 days, the protocol specified upper bound for Week 48 visit) prior to the date for the data cutoff of the submitted interim clinical study report. 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 Week 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 11 in Appendix 6.

The CD4 cell counts and percent were assessed at each visit 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. The last observation carried forward (LOCF) and baseline observation carried forward (BOCF) approaches were also used to summarize the CD4 cell counts and change from baseline at each visit. 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 BOCF, missing values were replaced with the baseline value. For both 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.

3.2.4 Results and Conclusions

A. HIV RNA

Table 6, Table 7 and Figure 1 summarize the applicant's outcomes for the proportion of HIV RNA < 50 copies/mL and < 400 copies/mL at Week 48 in the Week 48 Powder cohort using the snapshot algorithm. The reviewer carried out the separate analyses and got the same results as the applicant's.

In the PRINCE I study, 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 Week 48 increased with the higher baseline weight band.

In the PRINCE II study, 52% of the subjects had HIV RNA < 50 copies/mL and 68% had HIV RNA < 400 copies/mL at Week 48. The response rates for the groups of the subjects with the baseline body weight of 5 to less 10 kg and 15 to less than 25 kg were fairly consistent with what were observed in the PRINCE I study. However, in the baseline body weight of 10 to less than 15 kg group, the proportion of subjects with HIV RNA < 50 copies/mL was more than 50% lower than that observed in the PRINCE I study (i.e., 68% in the PRINCE I study and 31% in the PRINCE II study). During the course of the review, the review team requested the applicant to perform further analyses to investigate the reasons for the difference. The applicant's additional analyses showed that there were no differences in the baseline characteristics for the weight groups in the two studies. In the applicant's view, approximately half of the nonresponders just had temporary "viral blips" since their viral load was below 50 copies/mL before Week 48 and was between > 50 copies/mL and < 400 copies/mL at Week 48. The applicant's explanation was acceptable. In addition, the PRINCE II study was ongoing. Up to when the database was locked for the interim clinical study report, the study enrolled approximately 82% of the planned sample size of 95 subjects in the protocol. Also, only 64% of the treated subjects who had started their treatment at least 49 weeks prior to the database lock for the report were included in the analysis. Therefore, the study results were inconclusive.

Table 8 and Table 9 display the proportions of subjects with HIV RNA < 50 copies/mL and < 400 copies/mL at each visit in the two studies, respectively. These results are also presented in Figure 4 and Figure 5 in Appendix 6. In general, the response rates increased with the duration of treatment. Response rates may have improved over time due to a training effect that could have led to better adherence.

Table 6: Applicant's Snapshot Outcomes for Proportion of Subjects with HIV RNA <50 copies/mL at Week 48 for ALL Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I				PRINCE II				
	All	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	All	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	baseline weight 25 - <35 kg
Number of subjects in powder cohort	54	21	19	14	50	17	13	19	1
Virologic success - HIV RNA <50 c/mL	61% (33)	48% (10)	68% (13)	71% (10)	52% (26)	47% (8)	31% (4)	74% (14)	0% (0)
Virologic failure[1]	30% (16)	33% (7)	26 % (5)	29% (4)	40% (20)	47% (8)	54% (7)	21% (4)	100% (1)
No virologic data in analysis week window	9% (5)	19% (4)	5% (1)	0	8% (4)	6% (1)	15% (2)	5% (1)	0% (0)
Discontinued due to AE or death	9% (5)	19% (4)	5% (1)	0	6% (3)	0	15% (2)	5% (1)	0% (0)
Discontinued due to other reason	0	0	0	0	2% (1)	6% (1)	0	0	0% (0)
Missing data in window but on treatment	0	0	0	0	0	0	0	0	0% (0)

Sources: Table 7.3.1-1 in Final Clinical Study Report for PRINCE I (Study AI424397) and Interim Clinical Study Report for PRINCE II (Study AI424451)
[1]including HIV RNA ≥ 50 copies/mL, discontinued due to virologic failure, and discontinued due to other reasons and HIV RNA ≥ 50 copies/mL at time of discontinuation

Table 7: Applicant's Snapshot Outcomes for Proportion of Subjects with HIV RNA <400 copies/mL at Week 48 for ALL Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I				PRINCE II				
	All	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	All	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	baseline weight 25 - <35 kg
Number of subjects in powder cohort	54	21	19	14	50	17	13	19	1
Virologic success - HIV RNA <400 c/mL	74% (40)	67% (14)	74% (14)	86% (12)	68% (34)	65% (11)	62% (8)	79% (15)	0% (0)
Virologic failure[1]	17% (9)	14% (3)	21% (4)	14% (2)	24% (12)	29% (5)	23% (3)	16% (3)	100% (1)
No virologic data in analysis week window	9% (5)	19% (4)	5% (1)	0	8% (4)	6% (1)	15% (2)	5% (1)	0% (0)
Discontinued due to AE or death	9% (5)	19% (4)	5% (1)	0	6% (3)	0	15% (2)	5% (1)	0% (0)
Discontinued due to other reason	0	0	0	0	2% (1)	6% (1)	0	0	0% (0)
Missing data in window but on treatment	0	0	0	0	0	0	0	0	0% (0)

Sources: Table 7.3.1-1 in Final Clinical Study Report for PRINCE I (Study AI424397) and Interim Clinical Study Report for PRINCE II (Study AI424451)
[1]including HIV RNA ≥ 400 copies/mL, discontinued due to virologic failure, and discontinued due to other reasons and HIV RNA ≥ 400 copies/mL at time of discontinuation

Figure 1: Applicant's Results for HIV Viral Load at Week 48 for All Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

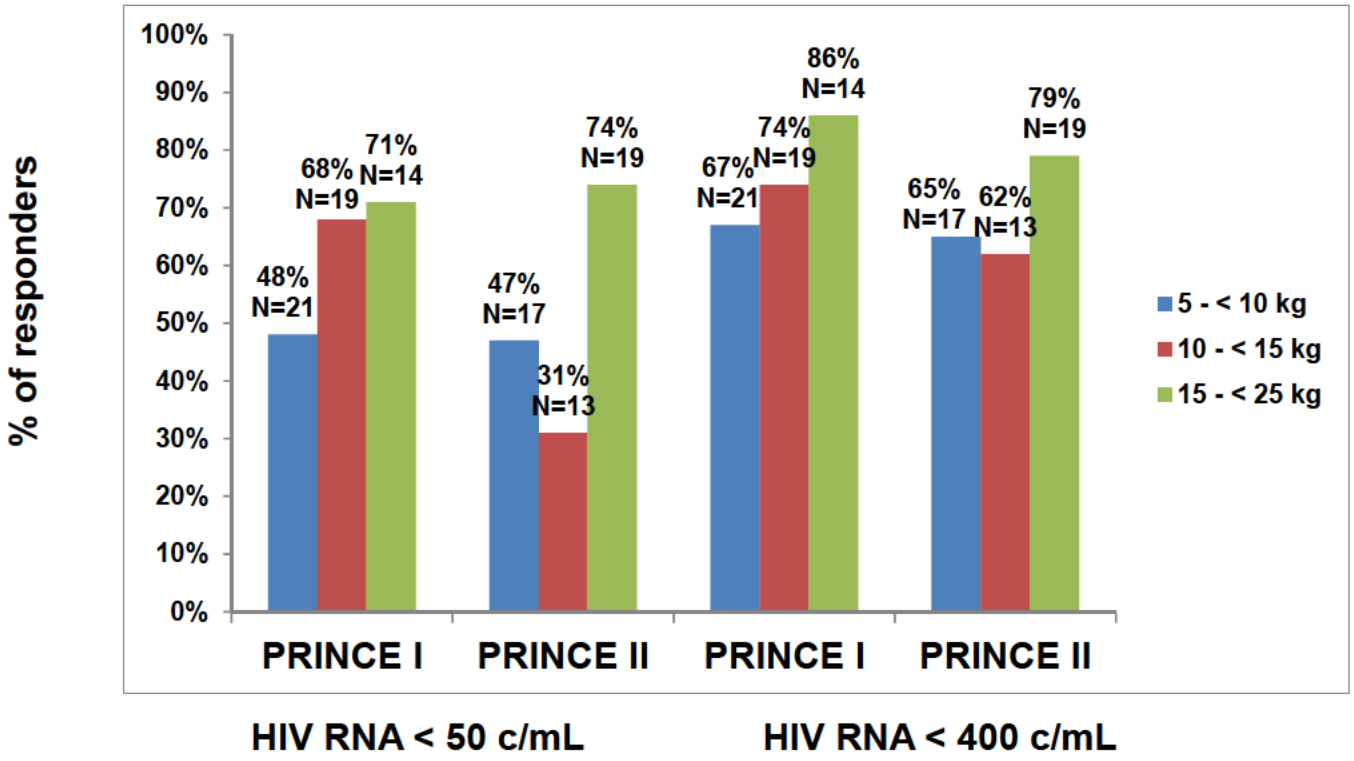


Table 8: Applicant's Proportion and 95% CI of Subjects with HIV RNA <50 copies/mL at Each Visit for All Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I				PRINCE II				
% (# of responders) (95% CI)	**All N=54**	**baseline weight 5 - < 10 kg N=21**	**baseline weight 10 - < 15 kg N=19**	**baseline weight 15 - < 25 kg N=14**	**All N=50**	**baseline weight 5 - < 10 kg N=17**	**baseline weight 10 - < 15 kg N=13**	**baseline weight 15 - < 25 kg N=19**	**baseline weight 25 - < 35 kg N=1**
Week 4	9% (5) (3%, 20%)	0% (0) (0%, 16%)	16% (3) (3%, 40%)	14% (2) (2%, 43%)	4% (2) (0.5%, 14%)	6% (1) (0%, 29%)	0% (0) (0%, 25%)	5% (1) (0%, 26%)	0% (0) (0%, 97.5%)
Week 8	19% (10) (9%, 31%)	5% (1) (0%, 24%)	16% (3) (3%, 40%)	43% (6) (18%, 71%)	20% (10) (10%, 34%)	12% (2) (1%, 36%)	15% (2) (2%, 45%)	32% (6) (13%, 57%)	0% (0) (0%, 97.5%)
Week 12	33% (18) (21%, 48%)	10% (2) (1%, 30%)	42% (8) (20%, 67%)	57% (8) (29%, 82%)	32% (16) (20%, 47%)	12% (2) (1%, 36%)	31% (4) (9%, 61%)	53% (10) (29%, 76%)	0% (0) (0%, 97.5%)
Week 16	39% (21) (26%, 53%)	10% (2) (1%, 30%)	58% (11) (33%, 80%)	57% (8) (29%, 82%)	44% (22) (30%, 59%)	29% (5) (10%, 56%)	38% (5) (14%, 68%)	63% (12) (38%, 84%)	0% (0) (0%, 97.5%)
Week 24	46% (25) (33%, 60%)	33% (7) (15%, 57%)	53% (10) (29%, 76%)	57% (8) (29%, 82%)	52% (26) (37%, 66%)	41% (7) (18%, 67%)	54% (7) (25%, 81%)	63% (12) (38%, 84%)	0% (0) (0%, 97.5%)
Week 32	56% (30) (41%, 69%)	43% (9) (22%, 66%)	68% (13) (43%, 87%)	57% (8) (29%, 82%)	56% (28) (41%, 70%)	47% (8) (23%, 72%)	38% (5) (14%, 68%)	79% (15) (54%, 94%)	0% (0) (0%, 97.5%)
Week 40	57% (31) (43%, 71%)	38% (8) (18%, 62%)	63% (12) (38%, 84%)	79% (11) (49%, 95%)	54% (27) (39%, 68%)	47% (8) (23%, 72%)	46% (6) (19%, 75%)	68% (13) (43%, 87%)	0% (0) (0%, 97.5%)
Week 48	61% (33) (47%, 74%)	48% (10) (26%, 70%)	68% (13) (43%, 87%)	71% (10) (42%, 92%)	52% (26) (37%, 66%)	47% (8) (23%, 72%)	31% (4) (9%, 61%)	74% (14) (49%, 91%)	0% (0) (0%, 97.5%)

Sources: Appendix 5.1A in Final Clinical Study Report for PRINCE I (Study AI424397) and Interim Clinical Study Report for PRINCE II (Study AI424451)

Table 9: Applicant's Proportion and 95% CI of Subjects with HIV RNA <400 copies/mL at Each Visit for All Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I				PRINCE II				
% (# of responders) (95% CI)	**All N=54**	**baseline weight 5 - < 10 kg N=21**	**baseline weight 10 - < 15 kg N=19**	**baseline weight 15 - < 25 kg N=14**	**All N=50**	**baseline weight 5 - < 10 kg N=17**	**baseline weight 10 - < 15 kg N=13**	**baseline weight 15 - < 25 kg N=19**	**baseline weight 25 - < 35 kg N=1**
Week 4	28% (15) (16.5%, 42%)	10% (2) (1%, 30%)	42% (8) (20%, 67%)	36% (5) (13%, 65%)	4% (2) (0.5%, 14%)	12% (2) (1%, 36%)	23% (3) (5%, 54%)	37% (7) (16%, 62%)	0% (0) (0%, 97.5%)
Week 8	44% (24) (31%, 59%)	14% (3) (3%, 36%)	58% (11) (33%, 80%)	71% (10) (42%, 92%)	44% (22) (30%, 59%)	35% (6) (14%, 62%)	38% (5) (14%, 68%)	58% (11) (33%, 80%)	0% (0) (0%, 97.5%)
Week 12	57% (31) (43%, 71%)	33% (7) (15%, 57%)	79% (15) (54%, 94%)	71% (10) (42%, 92%)	66% (33) (51%, 79%)	47% (8) (23%, 72%)	69% (9) (39%, 91%)	84% (16) (60%, 97%)	0% (0) (0%, 97.5%)
Week 16	70% (38) (56%, 82%)	62% (13) (38%, 82%)	79% (15) (54%, 94%)	71% (10) (42%, 92%)	66% (33) (51%, 79%)	59% (10) (33%, 82%)	62% (8) (32%, 86%)	79% (15) (54%, 94%)	0% (0) (0%, 97.5%)
Week 24	68.5% (37) (54%, 80.5%)	57% (12) (34%, 78%)	79% (15) (54%, 94%)	71% (10) (42%, 92%)	66% (33) (51%, 79%)	65% (11) (38%, 86%)	62% (8) (32%, 86%)	74% (14) (49%, 91%)	0% (0) (0%, 97.5%)
Week 32	74% (40) (60%, 85%)	71% (15) (48%, 89%)	74% (14) (49%, 91%)	79% (11) (49%, 95%)	68% (34) (53%, 80.5%)	53% (9) (28%, 77%)	69% (9) (39%, 91%)	84% (16) (60%, 97%)	0% (0) (0%, 97.5%)
Week 40	72% (39) (58%, 83.5%)	62% (13) (38%, 82%)	74% (14) (49%, 91%)	86% (12) (57%, 98%)	58% (29) (43%, 72%)	53% (9) (28%, 77%)	54% (7) (25%, 81%)	68% (13) (43%, 87%)	0% (0) (0%, 97.5%)
Week 48 .	74% (40) (60%, 85%)	67% (14) (43%, 85%)	74% (14) (49%, 91%)	86% (12) (57%, 98%)	68% (34) (53%, 80.5%)	65% (11) (38%, 86%)	62% (8) (32%, 86%)	79% (15) (54%, 94%)	0% (0) (0%, 97.5%)

Sources: Appendix 5.1A in Final Clinical Study Report for PRINCE I (Study AI424397) and Interim Clinical Study Report for PRINCE (Study AI424451)

B. CD4

Table 10 summarizes the applicant's results for change from baseline in CD4 count and percent at Week 48, using either observed values without imputing any missing data (i.e.,Observed case) or LOCF approach to impute the missing data which is defined in Section 3.2.3 above. Approximately 30% of the subjects in both studies missed the baseline CD4 data. The mean and median change from baseline in absolute CD4 count at Week in the subgroup of baseline weight 5 to less than 10 kg was inconsistent in the two studies. The mean change was positive in the PRINCE I study but negative in the PRINCE II study. This could be due to the fact that the mean baseline CD4 count in the PRINCE II study was higher than that in the PRINCE I study. On the other hand, the mean change from baseline in CD4 percent was positive in both studies although the PRINCE II study had lower value than the PRINCE I study possibly due to a higher baseline CD4 percent in the PRINCE II study.

Table 10: Applicant's Results for Change from Baseline in CD4 Count and Percent at Week 48 in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I			**PRINCE II**		
	baseline weight 5 - < 10 kg N=21	**baseline weight 10 - <15 kg N=19**	**baseline weight 15 - <25 kg N=14**	**baseline weight 5 - < 10 kg N=17**	**baseline weight 10 - <15 kg N=13**	**baseline weight 15 - <25 kg N=19**
Baseline absolute CD4 count						
n	16	13	10	14	7	14
mean (SD)	1594 (897)	1107 (643)	661 (303)	2484.5 (1241)	709 (445)	829 (293)
median	1814.5	1002	668.5	2308.5	619	798
Change from baseline in absolute CD4 count						
Observed case[1]						
n	13	11	5	9	6	10
mean (SE)	550 (285)	225 (198)	374 (69)	-532 (470)	557 (158)	362 (169)
median	491	274	363	-423	394	156
Last observation carried forward (LOCF)[2]						
n	16	13	10	14	7	14
mean (SE)	507 (233)	216 (168)	235.5 (63)	-336 (320)	250 (122)	255 (132)
median	389	274	228	-309.5	175	115
Baseline CD4 percent						
n	16	14	11	15	8	16
mean (SE)	25 (12)	22 (9)	27.5 (10)	31.5 (10)	20 (13)	27 (10)
median	23.5	22	27	33	16.5	26.5
Change from baseline in CD4 percent						
Observed case[1]						
n	14	12	6	10	6	13
mean (SE)	6 (2)	7 (2)	9 (1)	2 (3)	12 (2)	8 (3)
median	6	7.5	9.5	2.5	13	11

to be continued

Table 10: Applicant's Results for Change from Baseline in CD4 Count and Percent at Week 48 in PRICE I and PRICE II (Week 48 Powder Cohort) (continued)

	PRINCE I			PRINCE II		
	baseline weight 5 - < 10 N=21	baseline weight 10 - <15 kg N=19	baseline weight 15 - <25 kg N=14	baseline weight 5 - < 10 kg N=17	baseline weight 10 - <15 kg N=13	baseline weight 15 - <25 kg N=19
LOCF[2]						
n	16	14	11	15	8	16
mean (SE)	6 (1)	6 (2)	6 (1)	3 (3)	5.5 (3)	6 (2)
median	4.5	5.5	5	2	4	6.5

[1]The results for Study AI424397 were obtained from Appendix 5.3A, 5.3E in final clinical study report. The results for Study AI424451 were generated by statistical reviewer based on sponsor's program.
[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 other LOCF results displayed in the table were obtained from the sponsor's responses to the FDA's comments submitted on Feb. 21, 2014.

3.3 Evaluation of Safety

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes the subgroup analyses for the two efficacy endpoints: proportions of the subjects with HIV RNA < 50 copies/mL and < 400 copies/mL at Week 48. Some of the analyses were performed by the applicant, and some were by the reviewer.

4.1 Gender, Race, Age, and Geographic Region

Table 12 and Table 13 show the reviewer's subgroup analyses by gender (male, female), race (Black/African American, non Black/African American) and geographic region (African, non African). In the PRINCE I study, overall male subjects had numerically lower response rates than the females. However, this trend was not obvious in the PRINCE II study. In both studies, the Black/African Americans had slightly higher response rates than the non-Black/African Americans. For the subgroup analysis by region, the sample sizes for the regions of non-Africa were too small to be conclusive. 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 Subgroup Populations by Previous HIV Treatment History

The previous HIV treatment history (i.e., TN versus TE) is expected to affect the virologic response rate. Also, the applicant (b) (4) . Therefore, the applicant and the reviewer performed subgroup analyses by the previous HIV treatment history. The applicant's analyses combined all weight groups while the reviewer's analyses were for each weight group. Table 14 to Table 17, Figure 6 and Figure 7 in Appendix 6 summarize the reviewer's results. The proposed indication was for

the children with the body weight (b) (4) to less than 25 kg. The subgroup analyses show that, compared with the PRINCE I study, TE subjects in the PRINCE II study had lower response rates in the group with baseline weight of 10 to less than 15 kg. This is similar to what was seen in the pooled analysis (i.e., combining TN and TE) as discussed in Section 3.2.4.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There is no statistical issue. The reviewer confirmed the applicant's efficacy results at Week 48.

5.2 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 confirmed the recommended ATV powder dosage for the pediatric patients with weight of 10 to less than 25 kg. However, the studies cannot confirm the ATV powder dose for pediatric patients with 25 to less than 35 kg since there was only one subject in that weight group in the studies.

5.3 Labeling Recommendations

Section 14.3 Pediatric Patients in the label are provided in the following sections and is relevant to the efficacy results in the two phase 3 studies reviewed in this report.

14.2 Pediatric Patients

(b) (4)

The reviewer has the following comments.

1) The results for the change from baseline in absolute CD4 count at 48 weeks of therapy proposed by the applicant were based on observed case. The observed approach did not impute any missing data. Based on the observed approach, the median change was 412 cell/mm^3 (n=20) for the treatment-naïve children and 228 cell/mm^3 (n=10) for the treatment-experienced children. Since the CD4 counts usually are maintained for a while after the

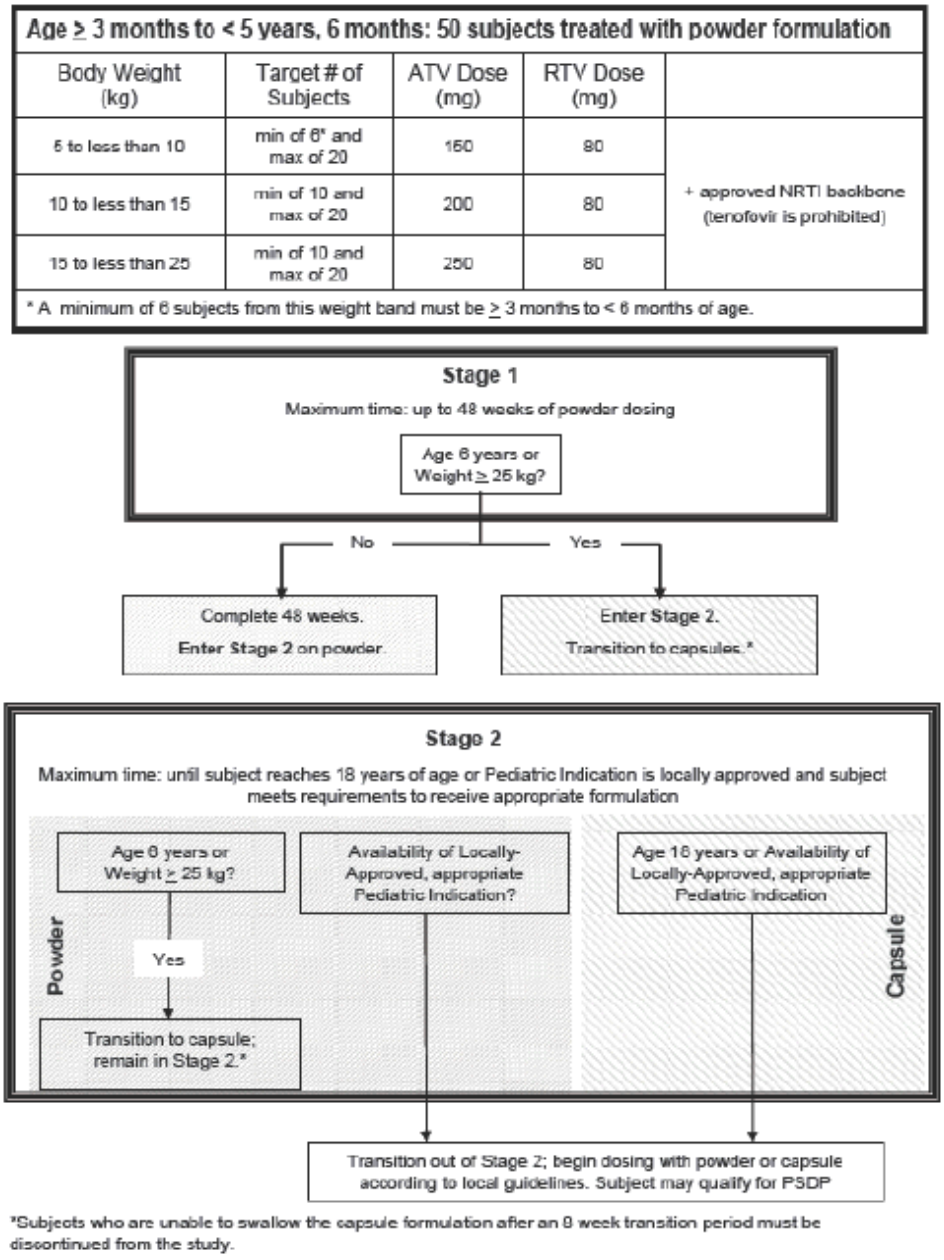
treatment, the LOCF approach is usually used to analyze the change from baseline in CD4 in the adult studies and results using the LOCF approach are presented in the label. The median change from baseline in absolute CD4 count at Week 48 using LOCF approach was 175 cells/mm^3 (n=27) for the treatment-naïve patients and 134 cells/mm^3 (n=17) for the treatment-experienced patients.

2) 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 be presented in the label. In fact, this information was presented in the pediatric section in the raltegravir label. Using the observed approach, the median change in CD4 percent was 10.5% (n=22) for the treatment-naïve patients and 6% (n=12) for the treatment-experienced patients. Using the LOCF approach, the median change in CD4 percent was 8% (n=29) for the treatment-naïve patients and 3% (n=20) for the treatment-experienced patients.

Of note, to be consistent with what presented for ATV capsule in the label, the clinical review team decided to present the observed case results for the changes from baseline in absolute CD4 count and percent at Week 48 for ATV powder in the label.

6 APPENDIX

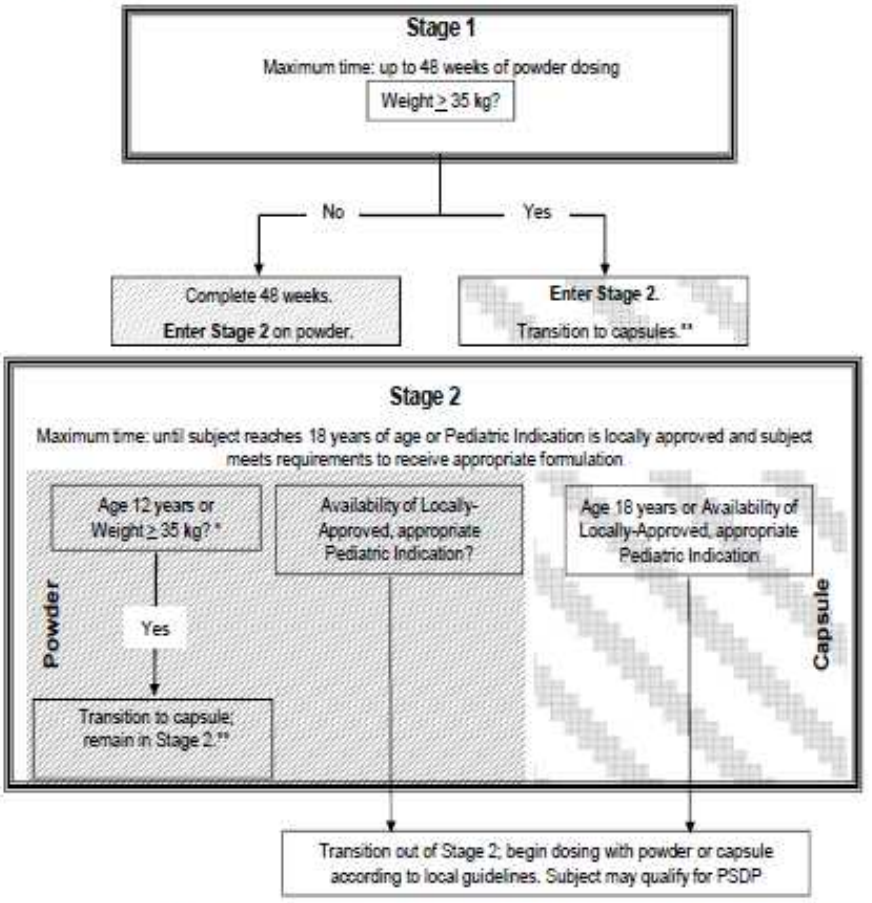
Figure 2: Study Schema in PRINCE I



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

Figure 3: 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 11: 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 4: Applicant's Results for Proportion (95% CI) of HIV RNA < 50 copies/mL at Each Visit in PRINCE I and PRINCE II (Week 48 Powder Cohort)

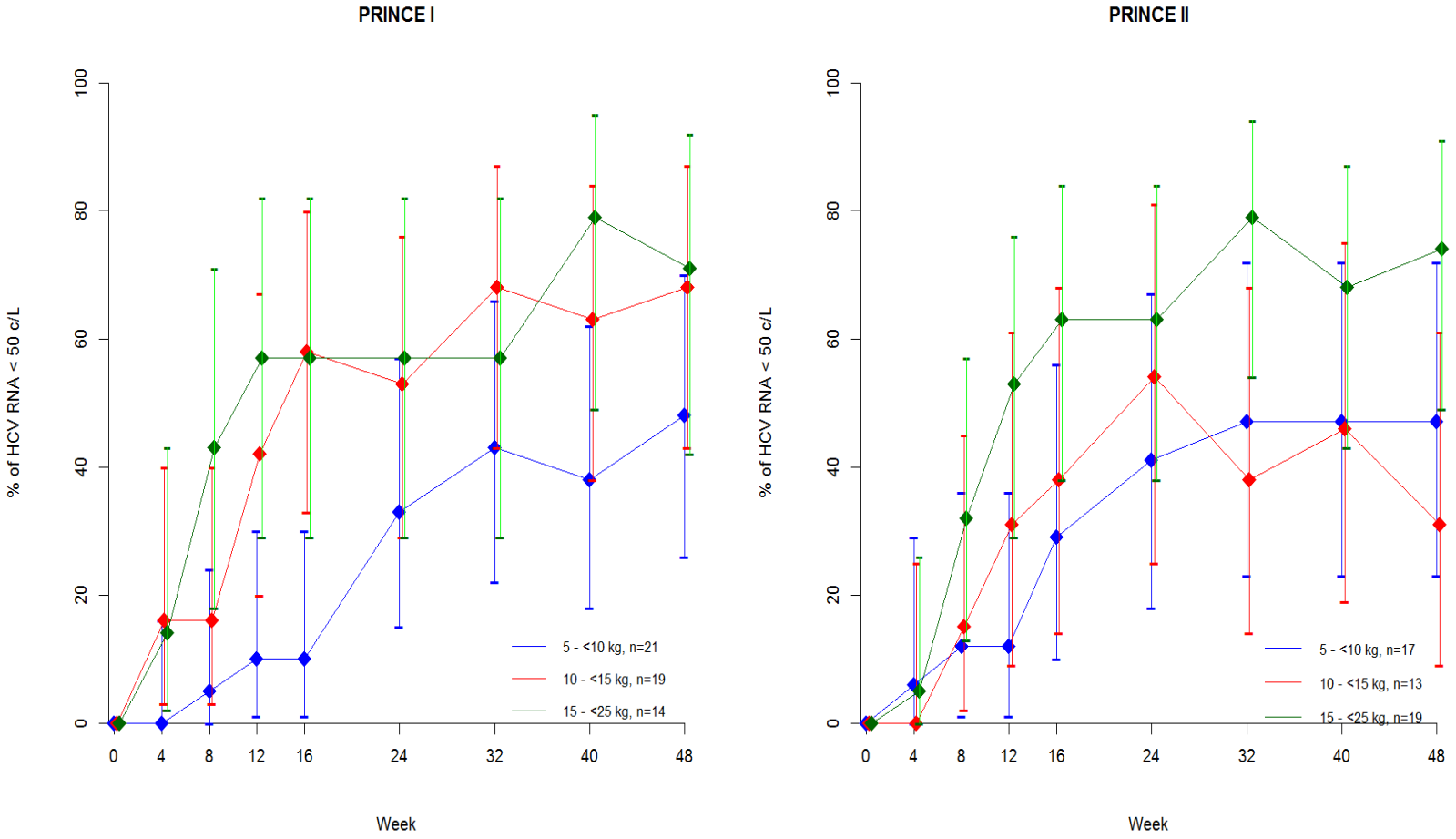


Figure 5: Applicant's Results for Proportion (95% CI) of HIV RNA < 400 copies/mL at Each Visit in PRINCE I and PRINCE II (Week 48 Powder Cohort)

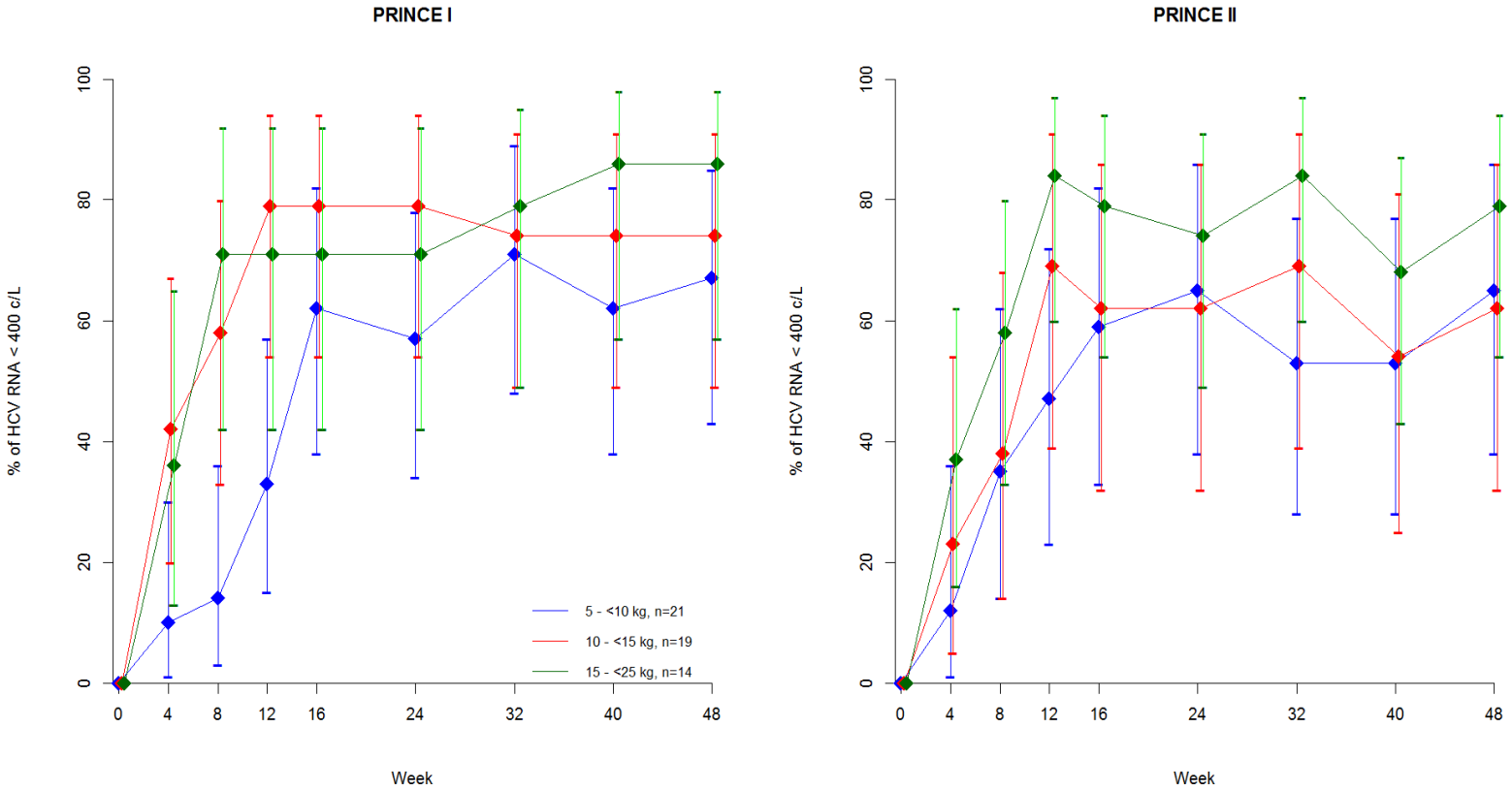


Table 12: Reviewer's Subgroup Analysis for Proportion of Subjects with HIV RNA < 50 copies/mL by Gender, Race and Region in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	All (N=54)	**baseline weight 5 - < 10 kg (N=21)**	**baseline weight 10 - <15 kg (N=19)**	**baseline weight 15 - <25 kg (N=14)**	**All (N=50)**	**baseline weight 5 - < 10 kg (N=17)**	**baseline weight 10 - <15 kg (N=13)**	**baseline weight 15 - <25 kg (N=19)**
Gender								
Male	48% (13/27)	36% (4/11)	43% (3/7)	67% (6/9)	52% (12/23)	50% (4/8)	40% (2/5)	67% (6/9)
Female	74% (20/27)	60% (6/10)	83% (10/12)	80% (4/5)	52% (14/27)	44% (4/9)	25% (2/8)	80% (8/10)
Race								
Black/African American	69% (22/32)	62% (8/13)	75% (9/12)	71% (5/7)	55% (18/33)	53% (8/15)	0% (0/5)	77% (10/13)
Other	50% (11/22)	25% (2/8)	57% (4/7)	71% (5/7)	47% (8/17)	0% (0/2)	50% (4/8)	67% (4/6)
Region								
Africa	66% (25/38)	59% (10/17)	69% (9/13)	75% (6/8)	58% (19/33)	50% (8/16)	20% (1/5)	83% (10/12)
Asia	100% (1/1)	0	100% (1/1)	0	0	0	0	0
Europe	0	0	0	0	25% (1/4)	0	0% (0/1)	33% (1/3)
North America	29% (2/7)	0% (0/2)	33% (1/3)	50% (1/2)	56% (5/9)	0	43% (3/7)	100% (2/2)
South America	62.5% (5/8)	0% (0/2)	100% (2/2)	75% (3/4)	25% (1/4)	0% (0/1)	0	50% (1/2)

Table 13: Reviewer's Subgroup Analysis for Proportion of Subjects with HIV RNA < 400 copies/mL by Gender, Race and Region in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	All (N=54)	**baseline weight 5 - < 10 kg (N=21)**	**baseline weight 10 - <15 kg (N=19)**	**baseline weight 15 - <25 kg (N=14)**	**All (N=50)**	**baseline weight 5 - < 10 kg (N=17)**	**baseline weight 10 - <15 kg (N=13)**	**baseline weight 15 - <25 kg (N=19)**
Gender								
Male	63% (17/27)	55% (6/11)	43% (3/7)	89% (8/9)	70% (16/23)	87.5% (7/8)	60% (3/5)	67% (6/9)
Female	85% (23/27)	80% (8/10)	92% (11/12)	80% (4/5)	67% (18/27)	44% (4/9)	62.5% (5/8)	90% (9/10)
Race								
Black/African American	75% (24/32)	69% (9/13)	75% (9/12)	86% (6/7)	70% (23/33)	73% (11/15)	20% (1/5)	85% (11/13)
Other	73% (16/22)	62.5% (5/8)	71% (5/7)	86% (6/7)	65% (11/17)	0% (0/2)	87.5% (7/8)	67% (4/6)
Region								
Africa	79% (30/38)	76% (13/17)	77% (10/13)	87.5% (7/8)	70% (23/33)	69% (11/16)	40% (2/5)	83% (10/12)
Asia	100% (1/1)	0	100% (1/1)	0	0	0	0	0
Europe	0	0	0	0	50% (2/4)	0	0% (0/1)	67% (2/3)
North America	43% (3/7)	50% (1/2)	33% (1/3)	50% (1/2)	89% (8/9)	0	86% (6/7)	100% (2/2)
South America	75% (6/8)	0% (0/2)	100% (2/2)	100% (4/4)	25% (1/4)	0% (0/1)	0	50% (1/2)

Table 14: Reviewer's Snapshot Outcomes for Proportion of Subjects with HIV RNA <50 copies/mL at Week 48 for TN Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I (Study AI424397)				PRINCE II (Study AI424451)			
	Overall	**baseline weight 5 - < 10 kg**	**baseline weight 10 - <15 kg**	**baseline weight 15 - <25 kg**	**Overall**	**baseline weight 5 - < 10 kg**	**baseline weight 10 - <15 kg**	**baseline weight 15 - <25 kg**
Number of subjects in powder cohort	34	13	12	9	24	4	8	12
Virologic success - HIV RNA <50 c/mL	21 (62%)	6 (46%)	9 (75%)	6 (67%)	12 (50%)	0	3 (38%)	9 (75%)
Virologic failure[1]	11 (32%)	6 (46%)	2 (17%)	3 (33%)	10 (42%)	4 (100%)	4 (50%)	2 (17%)
No virologic data in analysis week window	2 (6%)	1 (8%)	1 (8%)	0	2 (8%)	0	1 (13%)	1 (8%)
Discontinued due to AE or death	2 (6%)	1 (8%)	1 (8%)	0	2 (8%)	0	1 (13%)	1 (8%)
Discontinued due to other reason	0	0	0	0	0	0	0	0
Missing data in window but on treatment	0	0	0	0	0	0	0	0

[1]including HIV RNA ≥ 50 copies/mL, discontinued due to virologic failure, and discontinued due to other reasons and HIV RNA ≥ 50 copies/mL at time of discontinuation

Table 15: Reviewer's Snapshot Outcomes for Proportion of Subjects with HIV RNA <50 copies/mL at Week 48 for TE Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I (Study AI424397)				PRINCE II (Study AI424451)			
	Overall	**baseline weight 5 - < 10 kg**	**baseline weight 10 - <15 kg**	**baseline weight 15 - <25 kg**	**Overall**	**baseline weight 5 - < 10 kg**	**baseline weight 10 - <15 kg**	**baseline weight 15 - <25 kg**
Number of subjects in powder cohort	20	8	7	5	25	13	5	7
Virologic success - HIV RNA <50 c/mL	12 (60%)	4 (50%)	4 (57%)	4 (80%)	14 (56%)	8 (62%)	1 (20%)	5 (71%)
Virologic failure[1]	5 (25%)	1 (13%)	3 (43%)	1 (20%)	9 (36%)	4 (31%)	3 (60%)	2 (29%)
No virologic data in analysis week window	3 (15%)	3 (38%)	0	0	2 (8%)	1 (8%)	1 (20%)	0
Discontinued due to AE or death	3 (15%)	3 (38%)	0	0	1 (4%)	0	1 (20%)	0
Discontinued due to other reason	0	0	0	0	1 (4%)	1 (8%)	0	0
Missing data in window but on treatment	0	0	0	0	0	0	0	0

[1]including HIV RNA ≥ 50 copies/mL, discontinued due to virologic failure, and discontinued due to other reasons and HIV RNA ≥ 50 copies/mL at time of discontinuation

Table 16: Reviewer's Snapshot Outcomes for Proportion of Subjects with HIV RNA <400 copies/mL at Week 48 for TN Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I (Study AI424397)				PRINCE II (Study AI424451)			
	Overall	**baseline weight 5 - < 10 kg**	**baseline weight 10 - <15 kg**	**baseline weight 15 - <25 kg**	**Overall**	**baseline weight 5 - < 10 kg**	**baseline weight 10 - <15 kg**	**baseline weight 15 - <25 kg**
Number of subjects in powder cohort	34	13	12	9	24	4	8	12
Virologic success - HIV RNA <400 c/mL	25 (74%)	9 (69%)	9 (75%)	7 (78%)	18 (75%)	2 (50%)	6 (75%)	10 (83%)
Virologic failure[1]	7 (21%)	3 (23%)	2 (17%)	2 (22%)	4 (17%)	2 (50%)	1 (13%)	1 (4%)
No virologic data in analysis week window	2 (6%)	1 (8%)	1 (8%)	0	2 (8%)	0	1 (13%)	1 (4%)
Discontinued due to AE or death	2 (6%)	1 (8%)	1 (8%)	0	2 (8%)	0	1 (13%)	1 (4%)
Discontinued due to other reason	0	0	0	0	0	0	0	
Missing data in window but on treatment	0	0	0	0	0	0	0	

[1]including HIV RNA ≥ 400 copies/mL, discontinued due to virologic failure, and discontinued due to other reasons and HIV RNA ≥ 400 copies/mL at time of discontinuation

Table 17: Reviewer's Snapshot Outcomes for Proportion of Subjects with HIV RNA <400 copies/mL at Week 48 for TE Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

	PRINCE I (Study AI424397)				PRINCE II (Study AI424451)			
	Overall	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg	Overall	baseline weight 5 - < 10 kg	baseline weight 10 - <15 kg	baseline weight 15 - <25 kg
Number of subjects in powder cohort	20	8	7	5	25	13	5	7
Virologic success - HIV RNA <400 c/mL	15 (75%)	5 (63%)	5 (71%)	5 (100%)	16 (64%)	9 (69%)	2 (40%)	5 (71%)
Virologic failure[1]	2 (10%)	0	2 (29%)	0	7 (28%)	3 (23%)	2 (40%)	2 (29%)
No virologic data in analysis week window	3 (15%)	3 (38%)	0	0	2 (8%)	1 (8%)	1 (20%)	0
Discontinued due to AE or death	3 (15%)	3 (38%)	0	0	1 (4%)	0	1 (20%)	0
Discontinued due to other reason	0	0	0	0	1 (4%)	1 (8%)	0	0
Missing data in window but on treatment	0	0	0	0	0	0	0	0

[1]including HIV RNA ≥ 400 copies/mL, discontinued due to virologic failure, and discontinued due to other reasons and HIV RNA ≥ 400 copies/mL at time of discontinuation

Figure 6: Reviewer's Results for HIV Viral Load at Week 48 for TN Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)

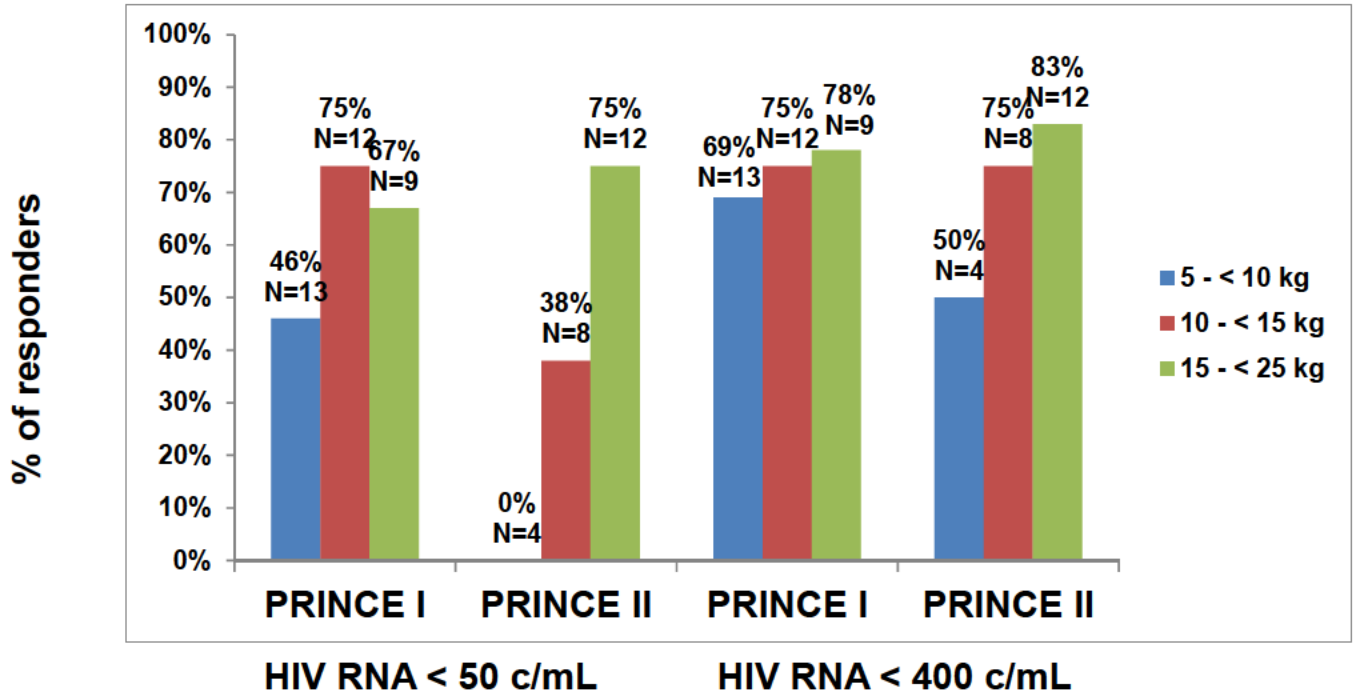
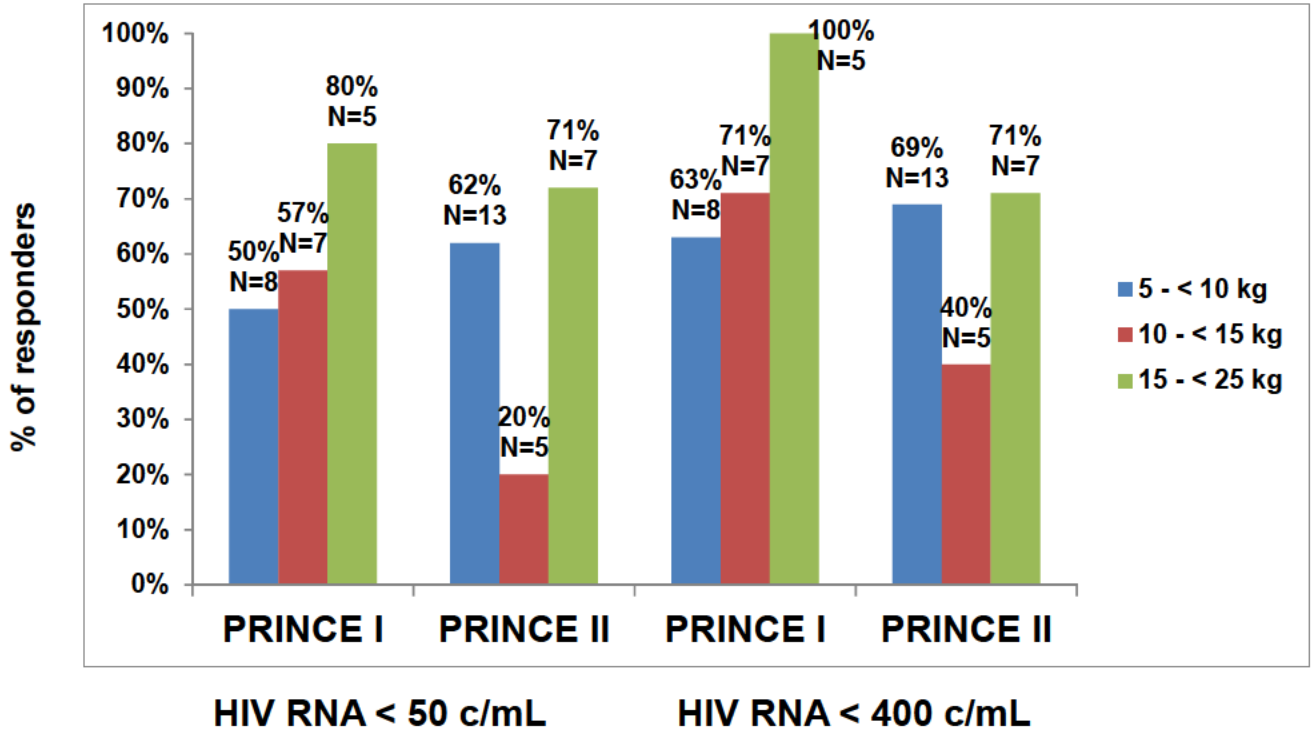


Figure 7: Reviewer's Results for HIV Viral Load at Week 48 for TE Subjects in PRINCE I and PRINCE II (Week 48 Powder Cohort)



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/s/

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05/09/2014

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