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 #:	NDA 21906 21251 21226
Supplement #:	S-042 S-049 S-040
Drug Name:	Kaletra® (lopinavir/ritonavir) Once Daily 100/25 mg tablets dosed by weight
Indication(s):	Treatment of HIV-1 RNA
Applicant:	Abbvie
Date(s):	Submission Date: September 17, 2014 Primary Review Date; June 12, 2015 PDUFA Date: July 17, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
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Keywords: HIV-1 RNA, pediatric, Kaletra®, once daily, QD, Week 24, Snapshot

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1 EXECUTIVE SUMMARY

Abbvie submitted this supplemental NDA to fulfill the Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) for NDA 21906 and in support of proposed updates to the US package insert (USPI) to include additional drug interaction information with etravirine, rilpivirine and simeprevir. The following table contains information on the relevant trials contained in the submission. Penta 18 (Koncert) was the only pivotal trial for this supplement. There were approximately 85 children randomized per arm to either continue on BID regimen of Kaletra or switch to a once a day regimen (QD). The primary endpoint used to evaluate efficacy by the statistics reviewer was the FDA Snapshot algorithm using a cutoff of 50 copies/mL. The applicant stated that a non-inferiority margin of 12% was chosen to represent a clinically acceptable difference in the rate of virologic failure between the two arms, and to allow the trial to be adequately powered and feasible to conduct based on estimates of available young people followed in PENTA centers across Europe, Thailand and South America.

Summary of Pivotal Trial Design

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis
Penta 18 (Koncert)	Phase II/III Randomized Open Label Trial of Kaletra Once Daily 24 week Safety and Activity. There were 49 sites in Europe, Thailand and Argentina.	1:1 randomization (1) continued HAART regimen with Kaletra tablets taken BID (2) to continue HARRT regimen but switch to QD Kaletra tablets. N=173 subjects (approximately 85 per treatment group).	Primary Endpoint: FDA Snapshot algorithm using a cutoff of 50 copies/mL. Analysis: Risk Differences and corresponding exact 95% CI and Fisher's Exact test..

Source: Reviewer's Table

Compared to the QD regimen, a higher percentage of subjects on the BID regimen (95% vs. 85%) were classified as virologic successes for the primary efficacy endpoint using a cutoff of 50 copies/mL at the time of the Week 24 interim, according to the FDA snapshot analysis. The risk difference (QD-BID) was -11% with a 95% confidence interval (CI) ranging from -20% to -2%. This difference was statistically significant at the two-sided 0.05 level (p=0.023). A similar trend was observed using a cutoff of 400 copies/mL where the percentage of subjects classified as virologic successes was 92% for the QD regimen and 98% for the BID regimen but the difference was not statistically significant (p=0.10) at the two-sided 0.05 level.

Using 50 copies/mL as the cutoff, the percentage of virologic failures in the QD arm was observed to be 7% higher than in the BID arm (10% vs. 3%) at Week 24, although this difference was not significant with a p-value of 0.08. Using 400 copies/mL as the cutoff, the percentage of virologic failures in the QD arm was observed to be 2% higher than in the BID arm (3% vs. 1%) at Week 24 (p=0.37).

There were only a few subjects with no virologic data at Week 24 (4 subjects in the QD arm and 1 subject in the BID arm). Two subjects had missing data during the window but were still enrolled in the study, two subjects discontinued due to adverse events (AE) or death and one subject discontinued due to other reasons.

Both the reviewer's and the applicant's Week 24 efficacy analyses demonstrated that the (b) (4) Similar results were observed after adjusting for the baseline imbalance between regimens.

The 12% NI margin was too large given the high response rate of the BID regimen. A clinical NI margin of 5~6% has been used in similar settings where the control response rate was high. Despite this large NI margin, the protocol pre-specified NI criteria was not met because the lower bound for the 95% confidence interval of the risk difference was -20%, much less than -12% indicating the QD regimen could have been as much as 20% worse than the BID regimen for the snapshot responder (<50 copies/mL) endpoint. In conclusion, the QD regimen of Kaletra is not recommended for pediatric patients.

2 INTRODUCTION

This section will give some information on the drug development for this submission, the studies submitted, and those selected for the review.

2.1 Overview

Table: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
Applicant defined study number	*Phase 2/3*				*e.g., critical disease or patient characteristics*
Penta 18 (Koncert)	Phase 2/3 Randomized Open Label Trial of Kaletra Once Daily 24 week Safety and Activity. There were 49 sites in Europe, Thailand and Argentina.	Interim at 24 weeks	Patients continued to be treated for up to 48 weeks	87 continued HAART regimen with Kaletra tablets taken BID 86 to continue HARRT regimen but switch to QD Kaletra tablets.	ITT population consisting of all randomized pediatric subjects with HIV who took at least one dose of study drug

Source: Reviewer's Table

The table above contains information on the relevant trials contained in the submission. Penta 18 (Koncert) was the only pivotal trial for this supplement. There were approximately 85 subjects randomized per arm to either continue on BID regimen of Kaletra or switch to a once a day regimen. The primary endpoint used to evaluate efficacy by the statistics reviewer was the FDA Snapshot algorithm using a cutoff of 50 copies/mL. See the Appendix for the applicant's diagnosis and main criteria for inclusion.

2.2 Data Sources

Data sources include all material reviewed, e.g. applicant study reports, data sets analyzed, and literature referenced.

\\CDSESUB1\evsprod\NDA021906\0146 has the original sNDA submission
\\CDSESUB1\evsprod\NDA021906\0151\m1\us has the snapshot analysis we requested

\\CDSESUB1\evsprod\NDA021906\0151\m5\datasets\koncert-interim has the revised crfile04 dataset and snapshot dataset

\\CDSESUB1\evsprod\NDA021906\0166\m5\datasets\koncert-interim\analysis\legacy\datasets has the adeffout dataset

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Protocols and statistical analysis plans were not reviewed by a statistician. Although the sponsor appeared to have pre-specified the primary efficacy outcome in the protocol, the primary efficacy analysis was not pre-specified in protocol. Instead the sponsor listed several proposed statistical analyses. The applicant did not perform the snapshot analysis until after the sNDA was submitted.

After receiving the sNDA submission we requested the
1. FDA snapshot algorithm for the primary efficacy analysis and related snapshot dataset.
2. SAS programs for primary efficacy and for the most important secondary efficacy analyses.
3. SAS programs used to create analysis datasets.
4. Division of Antiviral Product's standardized Analysis Dataset of Efficacy Outcomes and Related Covariates (adeffout) for HIV drugs.

There were additional concerns because the primary outcome section starting on p71 of the clinical study report (CSR) appeared to be inadequate. The applicant provided only a very brief summary of the primary efficacy outcome and did not summarize the results displayed in all of their tables and figures. For example, the first two written paragraphs in Section 11.2.1.1 (Intention to Treat Analysis of Primary Efficacy Outcome) don't tell you what table numbers they were referring to. Tables 25, 26, 29-32 did not appear to be described in the text. The applicant's results are shown in the Appendix of this review.

In addition there was no pre-submission meeting for this sNDA when we would have discussed these deficiencies with the sponsor. The medical officer had numerous additional queries pertaining to grade 3 and 4 AEs and laboratory abnormalities.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

For the primary efficacy endpoint the FDA reviewer used the FDA snapshot algorithm to determine the proportion of subjects responding based on plasma HIV-1 RNA less than 50 copies per mL while 400 copies/mL was used as the cutoff for secondary efficacy analyses. (For more information about the snapshot algorithm see Appendix A of the FDA's draft HIV Guidance Document on Developing Antiretroviral Drugs for Treatment: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf)

The applicant performed cross-sectional summaries of proportion of subjects with single and confirmed HIV-1 RNA ≥ 50 copies/mL at Weeks 4, 8, 12 and 24. In addition the applicant summarized the number of patients with HIV-1 RNA ≥50 copies/mL at any of weeks 4, 8, 12 or 24.

In Section 11.2.1 of Protocol Version 1.7 (23rd April 2013) attached to the CSR, the sponsor pre-specified that the Primary Efficacy Outcome was HIV-1 RNA ≥ 50 copies/ml (confirmed) at any of weeks 4, 8, 12, 24, 36 or 48. An additional efficacy endpoint the applicant used was time to first detected HIV-1 RNA ≥50 copies/ml (confirmed) by the 24 week assessment.

3.2.2 Statistical Methodologies

The primary efficacy analysis performed by the statistics reviewer compared the percentage of virologic responders and virologic failures at Week 24 in subjects randomized to receive QD and BID dosing regimens using risk differences and their corresponding exact 95% confidence intervals. Fisher's exact test was also used by the statistics reviewer to compare QD and BID regimens. Sensitivity analyses adjusted for different potential confounding covariables were performed in order to examine the robustness of the primary efficacy analysis while interaction tests were performed by the reviewer using Zelen's exact test.

The sponsor listed several proposed statistical analyses in protocol version 1.7 including:

- Fishers exact test and logistic regression models for the analysis of binary outcome variables
- Analysis of variance and linear regression models for the analysis of continuous outcome variables, adjusting for baseline
- Log rank test and proportional hazards regression models for the analysis of time to event variables.

The applicant also used Kaplan-Meier graphs of time to first detected HIV-1 RNA ≥50 copies/ml (confirmed) by the 24 week assessment and corresponding log rank tests. The applicant claimed

that the SAP on Aug 21, 2013 changed the method of estimating CI of the difference in survival curves to the Bootstrap approach instead of using Greenwood's method.

The applicant stated that a non-inferiority margin of 12% was chosen to represent a clinically acceptable difference in the rate of virological failure between the two arms, and to allow the trial to be adequately powered and feasible to conduct based on estimates of available young people followed in PENTA centers across Europe, Thailand and South America.

Section 11.4 of the protocol that was attached to the CSR stated that the IDMC would review data from the trial approximately every 6 months and use Haybittle-Peto rule for stopping early for success ($p<0.001$) based on the primary outcome difference. In the synopsis of the CSR the applicant stated that three interim analyses were conducted by the trial statistician for review by the IDMC and that these analyses were to assess the safety of the trial. No statistical adjustments were made as a result of interim analyses for the IDMC meetings.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

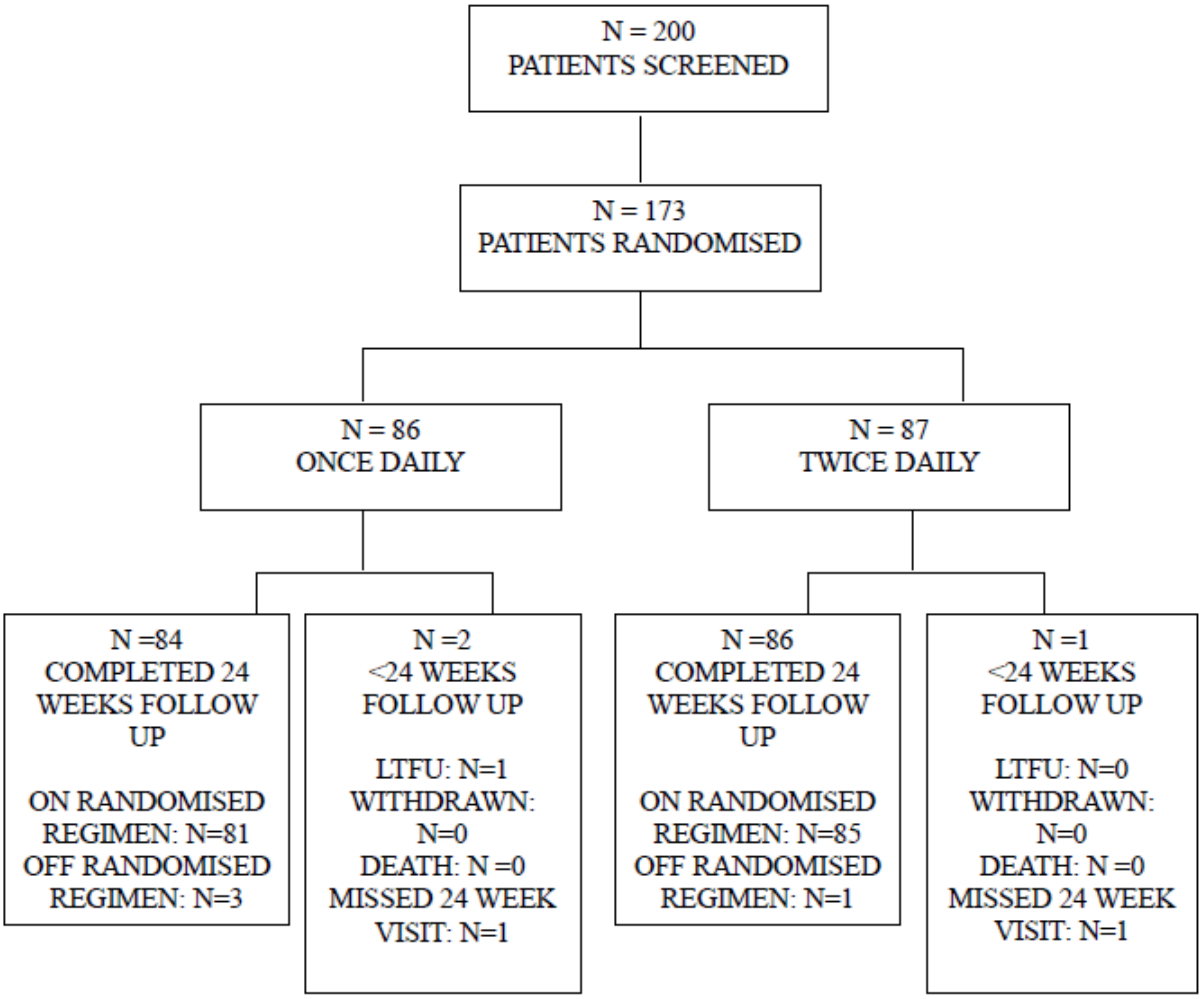


Figure 2. Disposition of patients up to the week 24 (+6 weeks) interim assessment
Source: Clinical Study Report

A total of 173 out of 200 screened patients were randomized and treated with 86 receiving the once daily regimen and 87 receiving the twice daily regimen (Figure 2).

Table 7. Enrolment by country

Country (Number of sites)		Dates of First and Last Randomisation		Number Randomised		Total
				QD	BID	
Argentina	(2)	25jun2012	18jul2012	6	1	7
Brazil	(3)	14mar2012	08aug2012	10	17	27
France	(5)	17may2011	22feb2012	2	6	8
Germany	(7)	04oct2011	23aug2012	13	11	24
Ireland	(1)	16mar2011	16mar2011	1	0	1
Italy	(3)	19jul2012	24aug2012	2	1	3
Netherlands	(2)	22jun2011	27jul2011	1	2	3
Portugal	(1)	12dec2011	12mar2012	1	1	2
Romania	(2)	22nov2011	30mar2012	2	1	3
Spain	(6)	17mar2011	27jun2012	10	6	16
Thailand	(8)	07aug2010	13jun2012	29	30	59
UK	(9)	17aug2010	06jul2012	9	11	20
Total	(49)	07aug2010	24aug2012	86	87	173

Source: Clinical Study Report

The majority of subjects came from Thailand, followed by Brazil, Germany, the UK and Spain (Table 7).

Table 8. Enrolment by stratification factors

		QD		BID		Total	
Children randomised: n		86		87		173	
		n	(%)	n	(%)	n	(%)
PK Study							
Weight:	≥15 to ≤25	8	(9)	9	(10)	17	(10)
	>25 to ≤35	8	(9)	8	(9)	16	(9)
	>35	11	(13)	11	(13)	22	(13)
Main trial only							
Weight:	≥15 to ≤25	14	(16)	15	(17)	29	(17)
	>25 to ≤35	18	(21)	16	(18)	34	(20)
	>35	27	(31)	28	(32)	55	(32)

Source: Clinical Study Report

Of the 173 subjects randomized, 46 children were enrolled in the ≥15 to ≤25 kg weight band, 50 children were enrolled in the >25 to ≤35 kg weight band and 77 children were enrolled in the >35 kg weight band (Table 8).

Table 11. Baseline characteristics: demographics

	QD		BID		Total	
Children randomised: n	86		87		173	
Sex: n (%)						
male:	41	(48)	38	(44)	79	(46)
female:	45	(52)	49	(56)	94	(54)
Age (years)						
mean (SD)	11.2	(3.4)	11.4	(3.5)	11.3	(3.5)
median (IQR)	10.8	(8.7, 14.2)	11.2	(9.0, 14.5)	11.0	(8.7, 14.3)
[range]		[4.3, 17.6]		[3.8, 17.7]		[3.8, 17.7]
n (%)						
≥3 years to <8 years	15	(17)	17	(20)	32	(18)
≥8 years to <13 years	38	(44)	36	(41)	74	(43)
≥13 years to <18 years	33	(38)	34	(39)	67	(39)
Weight (kg)						
Overall						
mean (SD)	35.5	(13.6)	35.4	(13.4)	35.5	(13.5)
median (IQR)	33.3	(24.6, 42.0)	32.2	(23.9, 43.8)	33.1	(24.6, 42.6)
[range]		[15.0, 72.5]		[15.6, 68.9]		[15.0, 72.5]
Strata 1: ≥15 to ≤25kg						
mean (SD)	20.6	(3.2)	20.6	(2.6)	20.6	(2.9)
median (IQR)	20.8	(18.1, 23.5)	20.3	(19.1, 22.8)	20.4	(19.0, 23.1)
[range]		[15.0, 24.6]		[15.6, 25.0]		[15.0, 25.0]
Strata 2: >25 to ≤35kg						
mean (SD)	30.3	(2.8)	30.2	(2.5)	30.2	(2.6)
median (IQR)	30.7	(27.5, 33.0)	30.1	(28.6, 31.5)	30.3	(28.5, 32.2)
[range]		[25.3, 34.5]		[26.0, 34.5]		[25.3, 34.5]
Strata 3: >35kg						
mean (SD)	47.8	(10.4)	47.6	(9.5)	47.7	(9.9)
median (IQR)	42.8	(39.2, 54.0)	45.5	(40.5, 57.3)	45.0	(40.0, 54.0)
[range]		[35.4, 72.5]		[35.3, 68.9]		[35.3, 72.5]
Route of infection: n (%)						
vertical	86	(100)	84	(97)	170	(98)
other/unknown	0	(0)	3	(3)	3	(2)
Ethnic origin: n (%)						
white	27	(31)	17	(20)	44	(25)
black: African or other	17	(20)	29	(33)	46	(27)
mixed black/white	5	(6)	6	(7)	11	(6)
Asian/Thai	31	(36)	30	(34)	61	(35)
other	6	(7)	5	(6)	11	(6)

Source: Clinical Study Report

Baseline demographic characteristics appeared to be balanced in the two randomization groups with the exception of ethnic origin where more black (African or other) were randomized to the BID arm (33% in the BID arm compared to 20% in the QD arm) and more white children were randomized to the QD arm than the BID arm (31% vs. 20%) (Table 11).

Table 13. Baseline characteristics: HIV related parameters

	QD		BID		Total	
Children randomised: n	86		87		173	
CDC Stage: n (%)						
N	16	(19)	14	(16)	30	(17)
A	12	(14)	25	(29)	37	(21)
B	34	(40)	22	(25)	56	(32)
C	24	(28)	26	(30)	50	(29)
missing: n	0		0		0	
CD4%						
mean (SD)	32.0	(6.5)	33.9	(8.6)	32.9	(7.7)
n (%)						
<30%	34	(40)	28	(33)	62	(36)
≥30% to <40%	42	(49)	37	(43)	79	(46)
≥40%	9	(11)	21	(24)	30	(18)
missing: n	1		1		2	
CD4 (cells/µL)						
mean (SD)	875.6	(303.2)	999.0	(395.4)	937.3	(356.7)
n (%)						
<500	4	(5)	6	(7)	10	(6)
≥500 to <1000	57	(66)	43	(50)	100	(58)
≥1000 to <1500	20	(23)	29	(34)	49	(28)
≥1500	5	(6)	8	(9)	13	(8)
missing: n	0		1		1	
CD4 z score						
mean (SD)	-1.0	(1.2)	-0.6	(1.3)	-0.8	(1.3)
n (%)						
<-4	1	(1)	2	(2)	3	(2)
≥-4 to <-3	2	(2)	2	(2)	4	(2)
≥-3 to <-2	14	(16)	9	(10)	23	(13)
≥-2	69	(80)	73	(85)	142	(83)
missing: n	0		1		1	
Viral load (HIV-1 RNA): n (%)						
<50 c/ml at randomisation	74	(86)	83	(95)	157	(91)
≥50 c/ml at randomisation*	12	(14)	4	(5)	16	(9)
missing	0		0		0	
Viral load of patients with viral load ≥50 c/ml at randomisation						
n	12		4		16	
median [range]	120	[51, 91201]	134.5	[57, 270]	120	[51, 91201]

* All <50 copies/ml at screening

Source: Clinical Study Report

There were HIV-related imbalances between the two regimens for CDC Stage A and B virus, CD4%, and viral load at baseline with a greater percentage of subjects on the QD regimen having CDC Stage B, CD4% <40%, CD4 cell counts <1000 cells/µL, and viral load ≥50 copies/mL and a greater percentage of BID subjects with CDC Stage A, CD4%≥40%, and viral load<50 copies/mL (Table 13). The applicant did not describe any of their other baseline tables; some of these tables are shown in the Appendix.

3.2.4 Results and Conclusions

Table 25. Availability of HIV-1 RNA measurements – ITT Population

Weeks Since Randomisation	HIV-1 RNA measurement	QD		BID		Total	
		n	(%)	n	(%)	n	(%)
4	available	86	(100)	84	(97)	170	(98)
	missing**	0	(0)	3	(3)	3	(2)
	LTFU before week 4	0	(0)	0	(0)	0	(0)
8	available	84	(98)	83	(95)	167	(97)
	missing**	1	(1)	4	(5)	5	(3)
	LTFU before week 8	1*	(1)	0	(0)	1*	(1)
12	available	84	(98)	83	(95)	167	(97)
	missing**	1	(1)	4	(5)	5	(3)
	LTFU before week 12	1*	(1)	0	(0)	1*	(1)
24	available	84	(98)	86	(99)	170	(98)
	missing**	1	(1)	1	(1)	2	(1)
	LTFU before week 24	1*	(1)	0	(0)	1*	(1)

*Withdrew consent

**Either missed visit or viral load was not measured – not LTFU

Source: Clinical Study Report

Of the 86 subjects randomized to the QD regimen two subjects did not have data at the Week 24 visit; one subject withdrew consent and one subject either missed a visit or their viral load was not measured (not LTFU) (Table 25). For the 87 subjects randomized to the BID regimen, one subject had missing data at the Week 24 visit; this subject either missed a visit or their viral load was not measured (not LTFU).

Snapshot Responders at Week 24 Interim

Outcome \ Cutoff	<50 copies/mL		<400 copies/mL	
	QD Kaletra N=86 n (%)	BID Kaletra N=87 n (%)	QD Kaletra N=86 n (%)	BID Kaletra N=87 n (%)
Virologic Success (<50 or <400 copies/mL)	73 (85%)	83 (95%)	79 (92%)	85 (98%)
Risk Difference and 95% CI	-11% (-20% to -2%)		-5.8% (-14% to +1%)	
Fisher's Exact p-value	0.023		0.10	

Source: Reviewer's Analysis

Compared to the QD regimen, a higher percentage of subjects on the BID regimen (95% vs. 85%) were classified as virologic successes for the primary efficacy endpoint using a cutoff of 50 copies/mL at the time of the Week 24 interim, according to the FDA snapshot analysis. This difference was statistically significant at the two-sided 0.05 level (p=0.023). A similar trend was observed using a cutoff of 400 copies/mL but the difference was not statistically significant (p=0.10) at the two-sided 0.05 level.

Virologic Failures (Snapshot Algorithm) at Week 24 Interim

Outcome\ Cutoff	<50 copies/mL		<400 copies/mL	
	QD Kaletra N=86 n (%)	BID Kaletra N=87 n (%)	QD Kaletra N=86 n (%)	BID Kaletra N=87 n (%)
Virologic Failure	9 (10%)	3 (3%)	3 (3%)	1 (1%)
Risk Difference and 95% CI	+7% (-1% to +16%)		+2% (-3% to +9%)	
Fisher's Exact p-value	0.08		0.37	
Data in window not below threshold	9 (10%)	2 (2%)	3 (3%)	0
Prior change in antiretroviral therapy	0	1 (1%)	0	1 (1%)

Source: Reviewer's Analysis

Using 50 copies/mL as the cutoff, the percentage of virologic failures in the QD arm was observed to be 7% higher than in the BID arm (10% vs. 3%) at Week 24. There was no statistically significant difference between the percentage of virologic failures in the BID and QD regimens using a cutoff of 400 copies/mL (p=0.37).

Non-Responders with No Virologic Data (Snapshot Algorithm)
Week 24 Interim

Outcome \ Cutoff	<50 copies/mL		<400 copies/mL	
	QD Kaletra N=86 n (%)	BID Kaletra N=87 n (%)	QD Kaletra N=86 n (%)	BID Kaletra N=87 n (%)
No virologic data	4 (5%)	1 (1%)	4 (5%)	1 (1%)
Missing data during window but on study	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Discontinued due to AE or Death[a]	2 (2%)	0	2 (2%)	0
Discontinued due to other reasons	1 (1%)	0	1 (1%)	0

[a] Both children had adverse events; none of the subjects discontinued due to death
Source: Reviewer's Analysis

There were only a few subjects with no virologic data at Week 24 (4 subjects in the QD arm and 1 subject in the BID arm). Two subjects had missing data during the window but were still enrolled in the study, two subjects discontinued due to AE or death and one subject discontinued due to other reasons.

Applicant's Week 24 Snapshot Analysis

	QD	BID
Randomised	86	87
HIV RNA < 50 copies/mL	73 (84.9%)	84 (96.6%)
HIV RNA ≥ 50 copies/mL	9 (10.5%)	1 (1.1%)
No virologic data at Week 24 window		
Reasons		
Discontinued study drug due to AE or death	2* (2.3%)	0
Discontinued study drug for other reasons	1** (2.3%)	1*** (1.1%)
On study, but missing data in window	1 (1.2%)	1 (1.1%)

* Both children had adverse events which led to switch from QD to BID lopinavir/r.

** Child was lost to follow up at Week 4.

*** Switched to QD lopinavir/r due to compliance issues.

Source: Applicant's Response to FDA's October 8, 2014 Information Request

The reviewer obtained 83 responders instead of 84 for the BID arm using 50 copies/mL as a cutoff because one patient had HIV RNA <100 copies/mL and was counted by the applicant as a responder. The reviewer obtained 3 virologic failures instead of only 1 in the BID arm because of that patient and another patient who had a change in ART and was classified by the applicant as discontinuing study drug for other reasons. This led to me estimating 0 subjects who discontinued study drug for other reasons in the BID arm instead of 1 by the applicant.

The applicant did not perform the required FDA Snapshot Analysis in the sNDA submission. Most of the applicant's other efficacy analyses of the primary outcome variable are shown in the Appendix.

3.3 Evaluation of Safety

See the Medical Officer's Review for an Evaluation of Safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Sensitivity Analyses for Snapshot Virologic Failures

Analysis Adjusted for:	Risk Difference (QD-BID) (95% CI)
Age Group (3-7, 8-12, 13-17)	+7% (-1% to +15%)
Gender	+7% (-0% to +15%)
Race (White, Black, Asian/Thai/Other)	+9% (+0% to +17%)
Unadjusted	+7% (-1% to +16%)

Source: Reviewer's Analysis

Similar differences between the QD and BID regimens for virologic failures were observed after adjusting for baseline age, gender, and race. There were no statistically significant interaction tests involving the three subgroups. The applicant did not perform any analyses involving gender, race, age or geographic area.

Breslow-Day Interaction Tests with QD vs. BID Treatment Comparisons

Randomization Arm	p-value
Subgroup	
Baseline Age (3-7, 8-12, 13-17)	0.21
Gender	0.60
Race (White, Black, Other)	0.80

Source: Reviewer's Analysis

4.2 Other Special/Subgroup Populations

Virologic Response rates at Baseline and Week 24

	Baseline		Week 24 (Snapshot)	
HIV RNA (copies/mL)	**QD Kaletra N=86 n (%)**	**BID Kaletra N=87 n (%)**	**QD Kaletra N=86 n (%)**	**BID Kaletra N=87 n (%)**
<50	**73 (85%)**	**83 (95%)**	**73 (85%)**	**83 (95%)**
≥50 to <400	**10 (12%)**	**4 (5%)**	**6 (7%)**	**2 (2%)**
≥400	**3* (3%)**	**0**	**3 (3%)**	**0**

*** 938, 20639 and 91201 copies/mL**

HIV-1 RNA assays used in the trial

1= Roche 1.5 (Amplicor) 2=Roche 1.5 (US)
3=Nuclisens **4=Chiron 3.0 or Bayer bDNA HIV-RNA 3.0**
5=Abbott US **6 = Cobas TaqMan 99=Other**
Source: Reviewer's Analysis

Exactly the same response rates (the percentage of subjects with HIV RNA <50 copies/mL) in the two regimens were observed at baseline and at Week 24. In order to determine how much impact the baseline imbalance had on Week 24 results, the primary efficacy analysis was performed separately for baseline viral loads <50 copies/mL and ≥50 copies/mL (see the table on the next page).

Summary of Snapshot Responders by Baseline Viral Load

Outcome	Baseline Viral Load <50 copies/mL		Baseline Viral Load ≥ 50 copies/mL	
	QD Kaletra N=73 n (%)	BID Kaletra N=83 n (%)	QD Kaletra N=13 n (%)	BID Kaletra N=4 n (%)
Snapshot Responders (<50 copies/mL)	63 (86%)	80 (96%)	10 (77%)	3 (75%)
Risk Difference and 95% CI	-10% (-21% to -1%)		+2% (-34% to +53%)	
p-value[a]	0.04		1.00	
Zelen's Interaction p-value	0.36			

[a]Fisher's Exact p-value
Source: Reviewer's Analysis

The majority of subjects (90%) had baseline viral load < 50 copies/mL. For this subgroup, the percentage of responders at Week 24 in the BID arm was still observed to be 10% higher than in the QD arm (96% vs. 86%) and the QD regimen of Kaletra was [redacted] (b) (4) to the BID regimen (p=0.04). The same trend was not apparent in the small subgroup of subjects with baseline viral load ≥50 copies/mL where approximately the same percentage of subjects in both regimens (77% of the subjects on the QD regimen and 75% of the subjects in the BID regimen) were classified as responders. The treatment by baseline viral load interaction for snapshot responders was not statistically significant (p=0.36 using Zelen's Interaction test, p=0.17 using the Breslow-Day test).

Summary of Snapshot Virologic Failures by Baseline Viral Load

Outcome	Baseline Viral Load <50 copies/mL		Baseline Viral Load ≥ 50 copies/mL	
	QD Kaletra N=73 n (%)	BID Kaletra N=83 n (%)	QD Kaletra N=13 n (%)	BID Kaletra N=4 n (%)
Virologic Failures	7 (10%)	2 (2%)	2 (15%)	1 (25%)
Risk Difference and 95% CI	+7% (-0% to +17%)		-10% (-59% to +28%)	
p-value[a]	0.08		1.00	
Zelen's Interaction p-value	0.29			

[a]Fisher's Exact p-value
Source: Reviewer's Analysis

For the subgroup of subjects with baseline viral load < 50 copies/mL the percentage of virologic failures in the QD arm was observed to be 7% higher than in the BID arm (10% vs. 2%) at Week 24. In this subgroup the QD regimen of Kaletra was trending towards being [redacted] (b) (4) to the BID regimen although the p-value (p=0.08) was not quite statistically significant at the two-sided 0.05 level. The opposite trend was observed in the small subgroup of subjects with baseline viral load ≥50 copies/mL but the treatment by baseline viral load interaction for snapshot virologic failure endpoint was not statistically significant (p=0.29 using Zelen's Interaction test).

Sensitivity Analyses for Snapshot Virologic Failures

Analysis Adjusted for:	Risk Difference (QD-BID) (95% CI)
Baseline HIV RNA (<50, ≥50 copies/mL)	+6% (-2% to +14%)
Baseline CD4 % (<30%, 30%-<40%, ≥40%)	+6% (-2% to +14%)
Baseline Weight (≥15 to ≤25, >25 to ≤35, >35 kg)	+7% (-1% to +15%)
Unadjusted	+7% (-1% to +16%)

Source: Reviewer's Analysis

Similar differences between the QD and BID regimens for virologic failures were observed after adjusting for baseline HIV RNA, baseline CD4 %, and baseline weight. The applicant did not perform any summaries within subgroups but did perform analyses adjusted for baseline randomization strata of weight (≥15 to ≤25 kg, >25 to ≤35 kg, >35 kg) and participation in the PK study (yes, no). (See Appendix for details.)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Protocols/statistical analysis plans were not reviewed by a statistician. In Section 11.2.1 of Protocol Version 1.7 (23rd April 2013) attached to the CSR, the sponsor said the Primary Efficacy Outcome was HIV-1 RNA ≥ 50 copies/ml (confirmed) at any of weeks 4, 8, 12, 24, 36 or 48.

However the primary efficacy analysis was not pre-specified in protocol. Instead the sponsor listed several proposed statistical analyses including:

- Fishers exact test and logistic regression models for the analysis of binary outcome variables
- Analysis of variance and linear regression models for the analysis of continuous outcome variables, adjusting for baseline
- Log rank test and proportional hazards regression models for the analysis of time to event variables.

The applicant did not consult with the review team prior to the sNDA submission and there was no pre-NDA meeting for this supplement. As a result there were several deficiencies in this submission. The applicant did not perform the FDA's Snapshot analysis in the original sNDA submission and did not submit the adeffout analysis dataset until several months after the sNDA submission date. Since the study was negative these deficiencies did not have an impact on labeling or the decision to approve the QD regimen.

5.2 Collective Evidence

Both the reviewer's and the applicant's Week 24 efficacy analyses demonstrated that the QD regimen was (b) (4) to the BID regimen. Similar results were observed after adjusting for the baseline imbalance between regimens. Abbvie claimed that no conclusions about NI of QD to BID could be drawn from this report since this was an interim analysis and the trial was powered for 48 week data.

5.3 Conclusions and Recommendations

The QD regimen of Kaletra (b) (4) is not recommended for pediatric patients.

5.4 Labeling Recommendations (as applicable)

Since QD regimen [redacted] (b) (4) the applicant did not propose any labeling changes to the Clinical Efficacy Results Section 14. However the applicant proposed additional labeling claims in Section 8.4 (Pediatric Use):

A prospective multicenter, randomized, open-label study evaluated the [redacted] (b) (4) efficacy, and safety of twice-daily versus once-daily dosing of KALETRA [redacted] (b) (4) dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included KALETRA, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, [redacted] (b) (4)

The last sentence was removed as there were no analyses to support the claim. A sentence was added stating that at week 24, efficacy (defined as the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL) was significantly higher in subjects receiving twice daily dosing compared to subjects receiving once daily dosing. The beginning of the Section 8.4 label also has been revised to state that Kaletra should not be administered once daily in pediatric patients. Since this was a negative trial, the results were not added to the Clinical Studies section of the label (Section 14.2 Pediatric Trials).

APPENDICES

Applicant's Diagnosis and main criteria for inclusion (Source: CSR Synopsis): Children must be aged <18 years (up to 18th birthday) with confirmed HIV-1 infection. They must weigh ≥15 kg and be able to swallow tablets. They must be stable (i.e. CD4 not declining) on a combination antiretroviral regimen that has included lopinavir/ritonavir for at least 24 weeks. They must be taking lopinavir/ritonavir dosed twice-daily and be willing at the screening visit to change to tablet formulation if not currently taking tablets and to change the lopinavir/ritonavir dose. Their most recent HIV-1 RNA viral load must be <50 copies/ml, and must have had viral suppression for the previous 24 weeks. Viral suppression is defined as HIV-1 RNA <50 copies/ml, with the exception of a single measurement ≥50 but <400 copies/ml allowed.

Children were not included if they were on an antiretroviral regimen that included a nonnucleoside reverse transcriptase inhibitor (NNRTI) or any protease inhibitor (PI) other than lopinavir/ritonavir. They were also not included if they had previously failed virologically on a PI-containing regimen (where virological failure is defined as two successive HIV-1 RNA results >1000 copies/ml (confirmed) more than 24 weeks after starting HAART, i.e. changes for toxicity are not counted as failure). People with acute illness, or with abnormal renal or liver function, were also not included. If patients were receiving concomitant therapy except for prophylaxis they were not eligible, unless the concomitant therapy was discussed and approved by a trial medical expert. Pregnant females or females at risk of pregnancy were not included.

Additional Baseline Tables

Table 18. Baseline characteristics: ART exposure excluding in utero / perinatal ART exposure

	QD		BID		Total	
Children randomised: n	86		87		173	
Number of different drugs ever received: median [range]						
All classes	5	[3, 11]	5	[3, 10]	5	[3, 11]
NRTI	3	[2, 6]	3	[2, 7]	3	[2, 7]
PI	1	[1, 4]	1	[1, 3]	1	[1, 4]
NNRTI	0	[0, 2]	1	[0, 2]	1	[0, 2]
Number of children exposed to: n (%)						
All 3 classes	41	(48)	46	(53)	87	(50)
NRTIs and PIs only	45	(52)	41	(47)	86	(50)
First ART regimen: n (%)						
Mono/dual therapy	15	(17)	18	(21)	33	(19)
HAART	71	(83)	69	(79)	140	(81)
Cumulative ART exposure (years) median [range]						
All classes	7.2	[1.0, 16.2]	7.2	[0.8, 16.3]	7.2	[0.8, 16.3]
NRTI	7.0	[1.0, 15.8]	7.0	[0.8, 16.3]	7.0	[0.8, 16.3]
PI	4.2	[1.0, 13.7]	4.0	[0.8, 14.3]	4.1	[0.8, 14.3]
NNRTI	0.0	[0.0, 11.0]	0.1	[0.0, 8.4]	0.0	[0.0, 11.0]
Baseline regimen first regimen: n (%)						
Yes	18	(21)	17	(20)	35	(20)
No	68	(79)	70	(80)	138	(80)

Source: Clinical Study Report

Table 22. Follow-up to 24 weeks

	QD		BID		Total	
Children randomised: n	86		87		173	
Seen at the following weeks: n (%)						
4	86	(100)	84	(97)	170	(98)
8	84	(98)	83	(95)	167	(97)
12	84	(98)	83	(95)	167	(97)
24	84	(98)	86	(99)	170	(98)
Weeks from randomisation to last visit						
median	24.0		24.0		24.0	
(IQR)	(23.7, 25.0)		(23.4, 24.7)		(23.6, 24.9)	
[Range]	[4.0, 29.9]		[17.0, 27.9]		[4.0, 29.9]	
mean	24.0		24.0		24.0	
Confirmed lost to follow up by week 24: n (%)	1*	(1)	0	(0)	1*	(1)

*Withdrew consent

Source: Clinical Study Report

Table 23. ART received in the first 24 weeks

	QD		BID		Total	
Children assessed for ART after randomisation: n	86		87		173	
Initiated randomised dosing schedule: n (%)	86	(100)	NA		NA	
Day started						
0	85		NA			
1	1		NA			
LPV/r dosing at 24 week ART assessment: n (%)						
twice daily	2	(2)	85	(99)	87	(51)
once daily	82	(98)	1	(1)	83	(49)
off lopinavir/ritonavir	0	(0)	0	(0)	0	(0)
Missed week 24 visit: n	2		1		3	
Number of children with known regimen at 24 weeks: n	84		86		170	
Number of children still on initial regimen at 24 weeks: n (%)*	69	(82)	81	(94)	150	(88)
Change lopinavir/ritonavir frequency per day	2	(2)	1	(1)	3	(2)
Substitution of NRTI backbone	13	(15)	4	(5)	17	(10)
Weeks after randomisation stopped taking initial regimen						
Median [range]	8.0	[3.7, 26.0]	11.6	[4.0, 25.0]	8.0	[3.7, 26.0]
Proportion of total child years at risk to last ART assessment by 24 week assessment on						
LPV/r twice-daily HAART	2		98		51	
LPV/r once-daily HAART	97		1		49	
other	0		0		0	
unknown	1		1		1	
Number of drugs ever taken during the trial by 24 week ART assessment						
median [range]						
all classes	3	[3, 5]	3	[2, 4]	3	[2, 5]
NRTI	2	[2, 4]	2	[1, 3]	2	[1, 4]
PI	1	[1, 1]	1	[1, 1]	1	[1, 1]
NNRTI	0	[0, 0]	0	[0, 0]	0	[0, 0]
Classes exposed to by 24 week ART assessment: n (%)						
NRTIs + PIs only	86	(100)	87	(100)	173	(100)
Number of known changes in ART regimen after randomisation within 24 weeks: n (%)						
0	69	(80)	82	(94)	151	(87)
1	14	(16)	5	(6)	19	(12)
2	2	(2)	0	(0)	2	(1)
3	1	(1)	0	(0)	1	(1)

*Fishers exact test p=0.035 for difference in stopping initial regimen between arms

Source: Clinical Study Report

According to the applicant, a greater proportion of children changed NRTI backbone in the QD arm than the BID arm. The applicant said this was expected, as children on once-daily treatment were allowed to switch to once-daily NRTI backbone regimens.

Table 24. Changes to ART regimen for >7 days (including lopinavir/ritonavir frequency change per day) after randomisation within the first 24 weeks

Subject	Arm	Week	Weight band	Regimen before	Regimen after	Reason	Censored for PP analysis
157	QD	1	Low: 15-25kg	ZDV 3TC LPV	ZDV 3TC LPV*	AE	Y
157	QD	4	Low: 15-25kg	ZDV 3TC LPV	-	compliance	Y
157	QD	6	Low: 15-25kg	-	ZDV 3TC LPV	return/start	Y
71	QD	3	Medium: 25-35kg	3TC LPV	3TC ABC LPV	formulation change	N
74	QD	3	Low: 15-25kg	3TC d4T LPV	3TC ABC LPV	carer request	N
88	QD	4	Low: 15-25kg	ZDV 3TC LPV	3TC ABC LPV	simplification	N
114	QD	4	High: >35kg	ZDV 3TC LPV	3TC ABC LPV	simplification	N
124	QD	4	Low: 15-25kg	ZDV 3TC LPV	3TC ABC LPV	carer request	N
5	QD	7	Medium: 25-35kg	ZDV 3TC LPV	FTC TDF LPV	simplification	N
42	QD	8	Low: 15-25kg	d4T ABC LPV	ddI ABC LPV	stop for toxicity	N
59	QD	8	Low: 15-25kg	ZDV 3TC LPV	3TC ABC LPV	carer request	N
151	QD	8	High: >35kg	ZDV ABC LPV	ZDV ABC LPV*	AE	Y
126	QD	8	High: >35kg	3TC d4T LPV	3TC ABC LPV	other	N
140	QD	12	High: >35kg	FTC TDF LPV	3TC ABC LPV	drug supply problems	N
79	QD	23	High: >35kg	ddI 3TC LPV	3TC ABC LPV	simplification	N
102	QD	22	Low: 15-25kg	ZDV 3TC LPV	3TC ABC LPV	simplification	N
170	QD	19	High: >35kg	3TC d4T LPV	-	compliance	Y
170	QD	20	High: >35kg	-	3TC d4T LPV	return/start	Y
145	QD	22	Medium: 25-35kg	ABC FTC LPV	FTC LPV	drug supply problems	N
145	QD	23	Medium: 25-35kg	FTC LPV	ABC FTC LPV	return/start	N
53	QD	26	High: >35kg	ZDV 3TC LPV	3TC ABC LPV	simplification	N
38	BID	4	Medium: 25-35kg	ZDV 3TC LPV	ZDV 3TC LPV*	other	Y
55	BID	4	Low: 15-25kg	ZDV 3TC LPV	3TC ABC LPV	switch for toxicity	N
35	BID	11	Medium: 25-35kg	ddI 3TC LPV	3TC ABC LPV	other	N
158	BID	16	High: >35kg	3TC d4T LPV	ZDV 3TC LPV	formulation change	N
112	BID	25	High: >35kg	FTC TDF LPV	3TC TDF LPV	Drug supply problems	N

*frequency change in lopinavir/ritonavir per day

Source: Clinical Study Report

Determination of Sample Size

According to Section 9.7.2 of the SCR the applicant planned to compare the proportion of children ever recording plasma HIV-1 RNA≥50 copies/mL (confirmed within 4 weeks) on once-daily Kaletra compared to BID, over 48 weeks. The applicant stated that they planned to enroll 160 young people with 80 per arm over 18 months.

The applicant assumed 10% of children in both arms experience virologic failure (confirmed HIV-1 HIV-1 RNA≥50 copies/mL by Week 48 and determined that 155 children would provide at least 80% power to exclude a difference of 12% between the two arms (i.e. to exclude failure rates of more than 22% in the once-daily arm) (one-sided alpha=0.05) (Machin, Campbell et al. 1997). The applicant also stated that 160 (80 per arm) young people were to be enrolled to allow for loss to follow-up (in previous PENTA trials loss to follow-up had been less than 3%). The applicant chose a 12% non-inferiority margin to represent what they stated in the CSR was a clinically acceptable difference in the rate of virologic failures between the two arms, and to allow the trial to be adequately powered and feasible to conduct based on estimates of available young people followed in PENTA centers across Europe, Thailand and South America.

Applicant's ITT Efficacy Analyses for the Primary Outcome

Table 26. HIV-1 RNA ≥50 copies/mL – ITT Population

Weeks since randomisation		QD		BID	
		n/N	(%)	n/N	(%)
4	single ≥50 c/ml	9/86	(10)	2/84	(2)
	confirmation test				
	≤28 days	5		2	
	>28 days	4		0	
	no test	0		0	
	confirmed≥50 copies/ml*	5	(6)	1	(1)
8	single ≥50 c/ml	10/84	(12)	3/83	(4)
	confirmation test				
	≤28 days	7		1	
	>28 days	3		2	
	no test	0		0	
	confirmed≥50 copies/ml*	4	(5)	3	(4)
12	single ≥50 c/ml	5/84	(6)	7/83	(8)
	confirmation test				
	≤28 days	3		1	
	>28 days	2		5	
	no test	0		1	
	confirmed≥50 copies/ml*	3	(4)	2	(2)
24	single ≥50 c/ml	13/84	(15)	5/86	(6)
	confirmation test				
	≤28 days	8		2	
	>28 days	2		1	
	no test	3		2	
	confirmed≥50 copies/ml*	6	(7)	0	(0)

*Cross-sectional summary – individuals still included in analysis if already confirmed>50copies/ml in the previous visit and can therefore be confirmed more than once

Source: Clinical Study Report

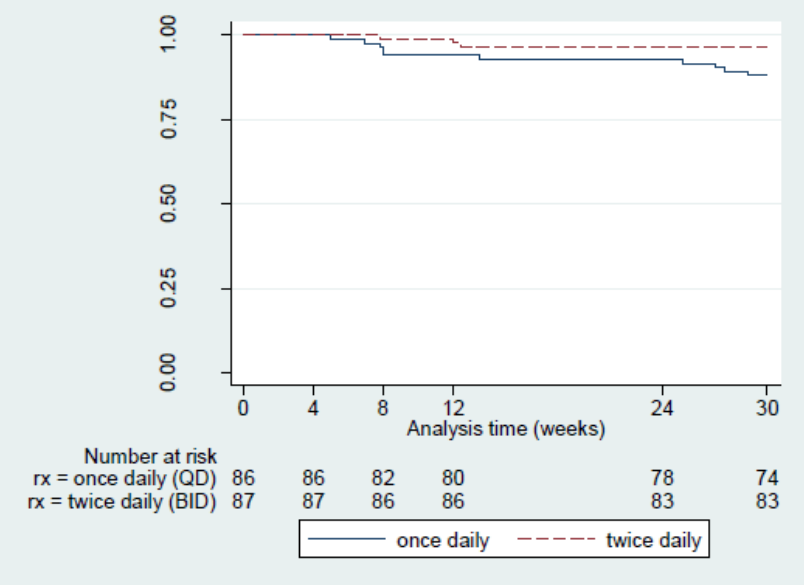
As shown in Table 26 of the CSR, virologic failure rates varied greatly depending on whether the failures were based on single unconfirmed HIV RNA values ≥50 copies/mL or confirmed tests. No matter which approach was used there were more virologic failures in the QD regimen than in the BID regimen at Week 24.

Table 27. Reported reason for confirmed HIV-1 RNA ≥50 copies/ml – ITT Population

	QD	BID
Number of patients with HIV-1 RNA ≥50 copies/ml at any of weeks 4, 8, 12, 24	10	3
Reason for HIV-1 RNA ≥50 copies/ml		
Adherence	9*	3
Resistance**	1	

*One patient had an adverse event which lead to their adherence becoming poor.
**Minor PI resistance detected in resistance FASTA file
Source: Clinical Study Report

The applicant stated in Section 11.2.1.1 of the CSR that ITT analyses showed 13 children to have HIV-1 RNA confirmed ≥50 copies/ml, 10 from the QD arm and 3 from the BID arm. This appears to match what is displayed in Table 27 of the CSR where t the applicant estimated 10 subjects in the QD regimen and 3 subjects in the BID regimen had HIV-1 RNA ≥ 50 copies/ml at any of weeks 4, 8, 12 and 24. According to the applicant, of the 13 children to fail, 12 experienced virologic failure due to poor adherence of treatment, while one child developed minor PI mutations, which the applicant stated was a possible reason for their virologic failure.



	Week 24 assessment (upper bound of week 30)			
	Number of events	Person years at risk	Estimated probability of remaining virologically suppressed	(90% CI)
BID	3	48.83	0.966	(0.913, 0.987)
QD	10	46.10	0.882	(0.809, 0.928)
	Difference (QD – BID)		-0.084	(-0.148, -0.019)
				p value*=0.040

*Log rank test

Figure 3. Kaplan-Meier graph of time to first detected HIV-1 RNA ≥50 copies/ml (confirmed) by 24 week assessment – ITT Population

Source: Clinical Study Report

In their time to event analysis comparing the time to first detected HIV-1 RNA≥50 copies/mL (confirmed) by the 24 week assessment in two regimens, the applicant found a statistically significant difference in favor of the BID regimen (p=0.040) with an unadjusted risk difference of -0.084 (Figure 3).

Table 28. Survival functions from adjusted Kaplan-Meier curve of time to first detected HIV-1 RNA≥50 copies/ml (confirmed) by 24 week assessment – ITT Population

Week 24 assessment (upper bound of week 30)		
	Estimated probability of remaining virologically suppressed	(90% CI)
BID	0.965	(0.933, 0.996)
QD	0.883	(0.826, 0.939)
Difference (QD – BID)	-0.082	(-0.147, -0.017)

Kaplan-Meier analysis adjusted for body weight band, PK study and PK study×body weight band interaction

Source: Clinical Study Report

After adjustment for baseline stratification factors, the applicant stated that the estimated difference in survival functions was -8.2% (90% CI: -14.7%, 1.7%) favoring BID treatment (Table 28). There was a statistically significant difference favoring the BID regimen over the QD regimen using Fisher's exact test (Table 29).

Table 29. Difference in proportion of patients with HIV-1 RNA confirmed ≥50 copies/ml at any of week 4, 8, 12, 24 – ITT Population

	Number of events	Estimated proportion	[90% confidence interval]	p value*
BID	3**	0.034	[0.01, 0.09]	
QD	10***	0.116	[0.06, 0.19]	
Difference (QD-BID)	0.082		[0.03, 0.13]	0.048

*Fisher's exact test

**all randomised to >35kg weight band

***5 randomised to >35kg weight band, 3 to 25-35kg weight band and 2 to 15-25kg weight band

Source: Clinical Study Report

Table 30. HIV-1 RNA confirmed ≥50 copies/ml at any of week 4, 8, 12 or 24 - ITT Population

	Number of events	(%**)	Odds Ratio	[95% Confidence Interval]	p value*
BID	3	(3.4)	1.00	-	-
QD	10	(11.6)	3.90	[1.01 15.13]	0.049

*Results from logistic model adjusted for body weight band, PK study and PK study×body weight band interaction

**Denominator is children randomised. Still included in proportion if child misses a week visit, with viral load assumed <50 copies/ml

Table 31. Hazard ratio from unadjusted Cox proportional hazards model for HIV-1 RNA confirmed ≥50 copies/ml – ITT Population

	Number of Events	Hazard Ratio	[95% Confidence Interval]	p value
BID	3	1.00	-	
QD	10	3.54	[0.97 12.84]	0.055

Table 32. Hazard ratio from adjusted Cox proportional hazards model for HIV-1 RNA confirmed ≥50 copies/ml – ITT Population

	Number of Events	Hazard Ratio	95% Confidence Interval	p value*
BID	3	1.00	-	
QD	10	3.58	[0.98 13.00]	0.053

*Cox proportional hazards model adjusted for body weight band, PK study and PK study×body weight band interaction

Source: Clinical Study Report

As shown in Tables 30-32 the BID regimen was also favored over the QD regimen using logistic regression and Cox proportional hazards analyses.

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/s/

FRASER B SMITH
05/26/2015

GUOXING SOON
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