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 #:	21652
Supplement #:	S-019
Drug Name:	Epzicom® (abacavir sulfate and lamivudine) tablets
Indication(s):	Once daily dosing for treatment of HIV-1 infection in pediatric patients weighing at least 25 kg
Applicant:	ViiV Healthcare Company
Date(s):	Submission Date: November 20, 2014
	Primary Review Due Date: August 11, 2015
	PDUFA Date: September 20, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Fraser Smith, Ph.D.
Concurring Reviewers:	Greg Soon, Ph.D.
Medical Division:	Division of Antiviral Products.
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Keywords: HIV-1 infection, pediatrics, Epzicom®, abacavir sulfate, lamivudine, ARROW, switch trial

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1 EXECUTIVE SUMMARY

This Supplemental New Drug Application (sNDA) fulfilled the Pediatric Research Equity Act (PREA) Post-Marketing Requirement (PMR) for Epzicom® [abacavir sulfate (ABC) and lamivudine (3TC)] tablets. The statistics review of Epzicom was based upon efficacy results of the ARROW trial. However unlike the abacavir and lamivudine pediatric indications, the indication for Epzicom is for pediatric patients weighing at least 25 kg. The ARROW clinical study report and data were submitted in the Ziagen® (abacavir sulfate) NDA 020977/S-027 and NDA 020978/S-031 and Epivir® (lamivudine) NDA 20564/S-033 and NDA 20596/S-032 (submitted 23 May 2014 and subsequent submissions).

At baseline, 75% and 71% of the subjects in BID and QD arms had HIV-1 RNA viral loads that were suppressed below 80 copies/mL prior to randomization; the risk difference was -4.5% (95% CI: -11% to +2%). At Week 48, 73% and 69% of the subjects were responders in BID and QD arms with a risk difference of -3.3% (95% CI: -10% to +4%). At Week 96 response rates decreased to 70% and 67% in the BID and QD arms with a risk difference of -2.4% (95% CI: -9% to +5%).

There were very few subjects who discontinued since to be eligible for the twice versus once daily lamivudine and abacavir randomization children must have been on antiretroviral therapy (ART) for at least 36 weeks and they must have been taking twice daily 3TC and ABC. There were very few subjects who discontinued since to be eligible for the twice versus once daily lamivudine (3TC) and abacavir (ABC) randomization children must have been on ART for at least 36 weeks and must have been taking twice daily 3TC and ABC.

The applicant declared that since the NI margin was 12% that non-inferiority (NI) was demonstrated. Note that the 12% NI margin was not justified by the applicant and may have been too large for a switch trial where subjects were initially virologically suppressed, did not have problems with compliance, and did not experience many AEs leading to discontinuation. In adult switch trials, NI margins using the appropriate amount of discounting are typically 6-8%. However since response rates were lower (around 70% in the ARROW trial instead of 90% in switch trials for other NDAs) the larger margin was of less concern. The statistics reviewer also found that most of difference between response rates in the QD and BID arms disappeared after adjusting for the baseline HIV RNA imbalance. Therefore the statistics reviewer agrees with the applicant's conclusion that the QD regimen was NI to the BID regimen.

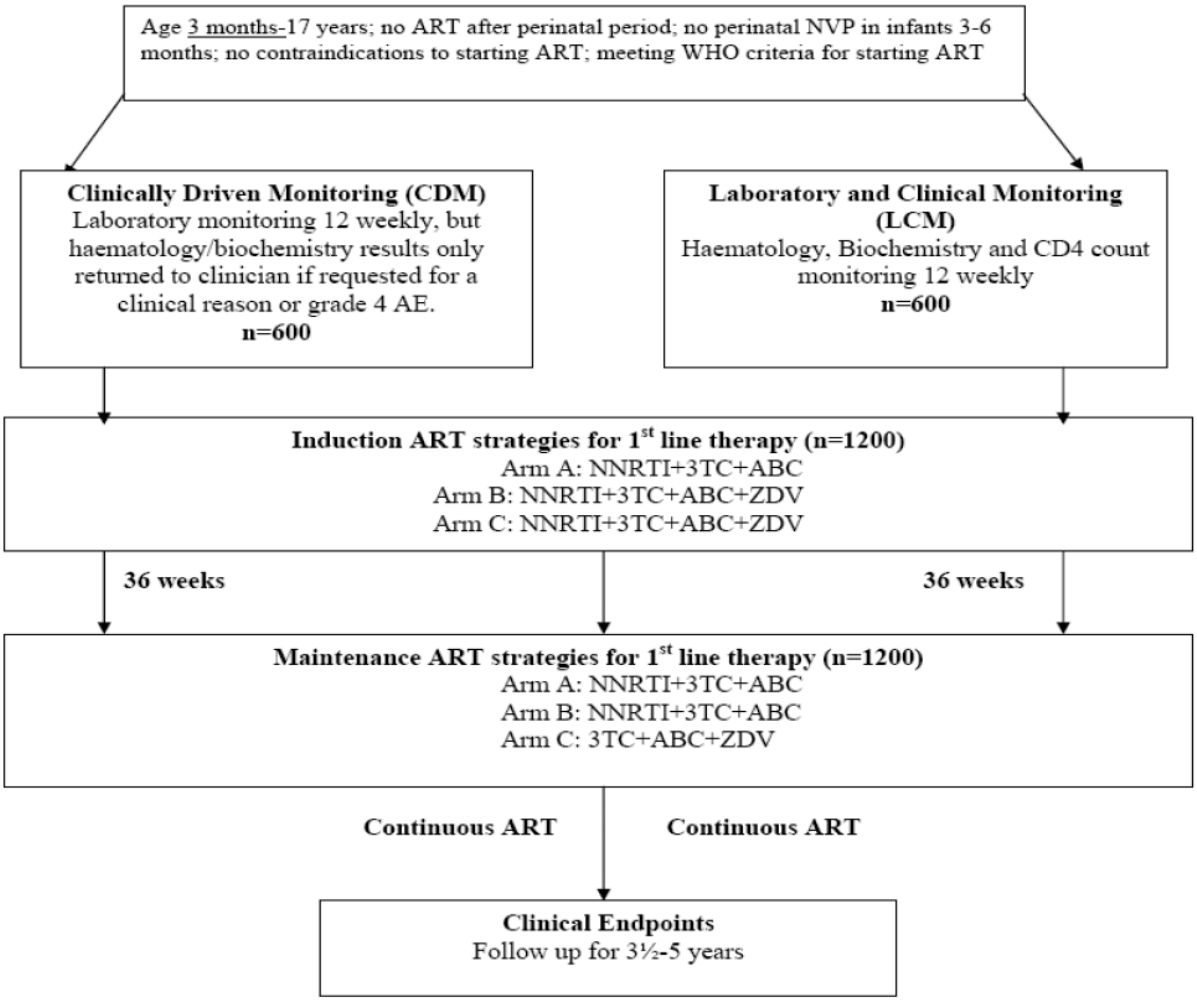
2 INTRODUCTION

2.1 Overview

List of all studies included in analysis

	Phase and Design	Study Population
ARROW (AntiRetroviral Research fOr Watoto)	Phase IV randomized trial of monitoring practice and induction maintenance drug regimens in the management of antiretroviral therapy in treatment-naïve HIV-1 infected children	African children aged 3 months to 17 years with a confirmed documented diagnosis of HIV-1 infection. These children were ART-naïve (except for exposure to perinatal ART for the prevention of mother-to-child HIV transmission) and met the criteria for requiring ART according to the WHO stage and CD4 percent or count.

Figure 1 ARROW Trial Schema



Source: Clinical Study Report

Randomization 1: Subjects were randomized to Clinically Driven Monitoring versus Laboratory plus Clinical Monitoring

Randomization 2: Subjects were randomized to receive standard antiretroviral therapy (3 drugs) versus Induction Maintenance (4 drug induction for 36 weeks, followed by 3 drug maintenance). (See Figure 1 for Randomization 1 and 2 and Table 1 for Randomization 2.)

At ARROW enrollment approximately 1200 children were randomized to either a control arm or one of two induction-maintenance arms for first line ART, to be taken once or twice daily (depending on age and regimen):

Arm A (standard):	NNRTI + ABC +3TC continuously
Arm B (induction maintenance):	NNRTI + ZDV + ABC + 3TC for 36 weeks, then NNRTI + ABC +3TC (drop ZDV – same as Arm A) Arm
Arm C (induction maintenance):	NNRTI + ZDV + ABC + 3TC for 36 weeks, then ZDV + ABC + 3TC (drop NNRTI)

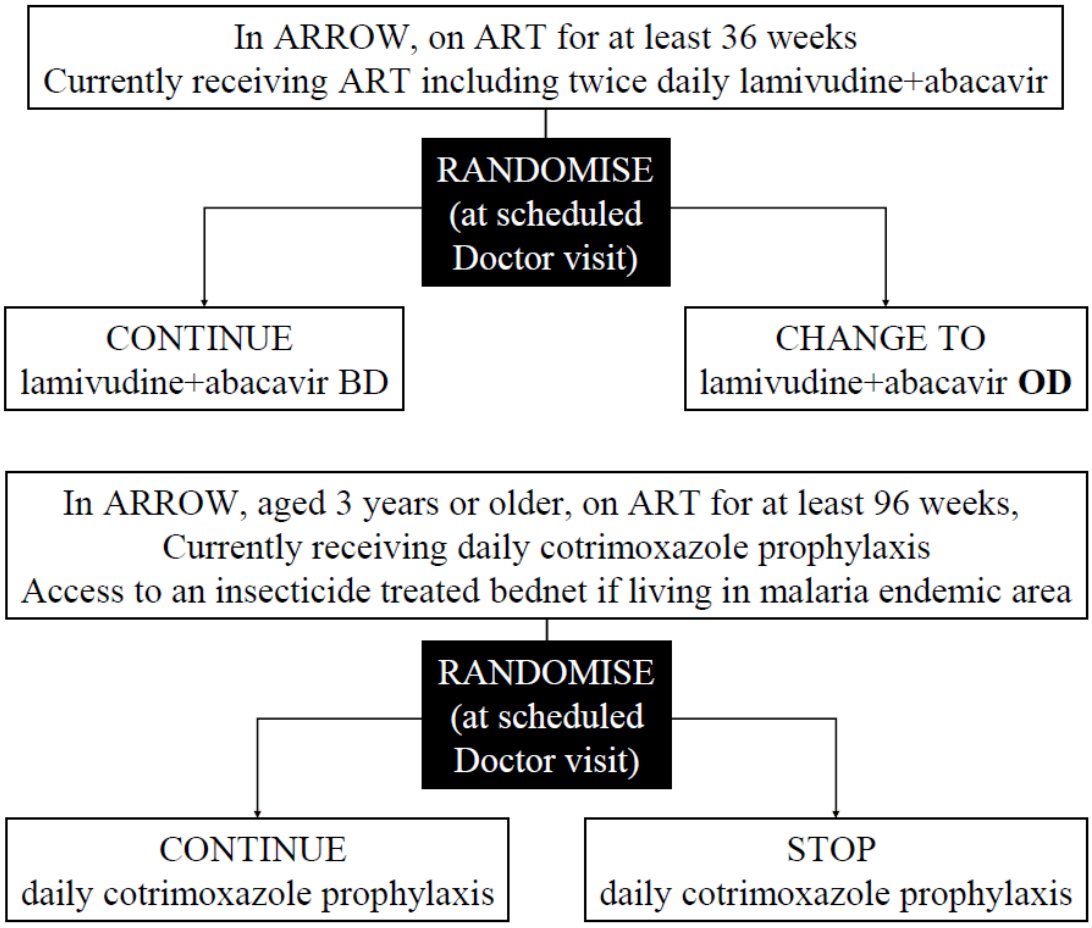
Table 1 First and second-line drug regimens for ARROW

First-line treatment (up to 36 weeks)	First-line treatment (after 36 weeks)	Second-line treatment
NNRTI + ABC+3TC	NNRTI + ABC+3TC	2 NRTIs + boosted PI[a]
NNRTI + ZDV+ ABC+3TC	NNRTI + ABC+3TC	2 NRTIs + boosted PI[a]
NNRTI + ZDV+ ABC+3TC	ZDV+ ABC+3TC	2 NRTIs + boosted PI[a] or NNRTI + boosted PI[a]

a. Lopinavir/ritonavir

Source: Clinical Study Report

Figure 2 Secondary Randomisations: Simplification of Long-Term ART



Source: Clinical Study Report

Randomization 3: After 36 Weeks of treatment in Randomizations 1 and 2, subjects were randomized to continue twice-daily abacavir and lamivudine or transition to once-daily abacavir and lamivudine (See Figure 2).

Randomization 4: After 96 Weeks of antiretroviral therapy (ART), subjects were randomized to continue or stop daily cotrimoxazole prophylaxis (See Figure 2).

Data from Randomization 3 form the basis for this pediatric efficacy supplement. The applicant states in their cover letter that pediatric subjects weighing ≥25 kg received total daily doses of 600 mg ABC+ 300 mg 3TC and could choose to receive their once-daily doses as Kivexa® (the brand name for Epzicom in markets outside the United States). For further details, see the Statistics Review of abacavir NDA 20977 S-027.

2.2 Data Sources

The application was submitted electronically and can be found on the following FDA network drive: \\CDSESUB1\evsprod\NDA021652\0092. The applicant stated in their cover letter that as agreed with the Division in the Type C Meeting (Written Responses), reports and data for the pediatric clinical studies and the population pharmacokinetic modeling included in Ziagen NDA 020977/S-027 (submitted 23 May 2014 and subsequent submissions) were incorporated into this Epzicom pediatric sNDA by cross-reference.

The application for Ziagen sNDA was submitted electronically and can be found on the following FDA network drive: \\CDSESUB1\evsprod\NDA020977\0105. For further details, see the Statistics Review of the abacavir NDA 20977 S-027.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

See the Statistics Review of the abacavir NDA 20977 S-027 for details.

3.2 Evaluation of Efficacy

Primary Objective (Type of Hypothesis to be Tested/Primary Endpoint/Definition of the Primary Endpoint if necessary):
The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA <80 copies/mL 48 weeks after Week 36 when subjects were randomized to either Switch to QD treatment or Continue BID treatment.

3.2.1 Study Design and Endpoints

Brief summary of COL105677 AntiRetroviral Research fOr Watoto (ARROW)

Design	**Treatment arms/Sample size**	**Primary endpoint/Analysis**
Phase IV randomized trial of monitoring practice and induction maintenance drug regimens in the management of antiretroviral therapy in treatment-naïve HIV-1 infected children 3 months to 17 years in Africa: **Proposed Indication:** Once daily dosing for treatment of HIV-1 infection in children ≥ 3 months of age*	After 36 weeks of BID ABC+LAM treatment, subjects were **Randomized to:** Continue BID Dosing (n=333) Transition to QD Dosing (n=336) **Randomized and Treated with:** Twice Daily n=331 Once Daily n=335	Proportion of Subjects with Plasma HIV-1 RNA<80 copies/mL at Week 48 using FDA Snapshot Algorithm (Week 0=time of Randomization 3)

* The current indication is for pediatric patients weighing at least 25 kg

Trial Specification:

Trial Phase: IV
Region: Africa

Multicenter: Yes (4 clinical centers)

Blinding: Unblinded

Control: Active

Randomization: Yes
Method: not stated

Stratification: No

Treatment Arms:
Experimental Treatment: switch from ABC+3TC twice daily after 36 weeks of ABC+3TC once daily

Control: continue ABC+3TC twice daily

Allocation Ratio: 1:1

Sample Size Per Treatment Group: **N**=333 to BID, 336 to switch from BID to QD arm
Statistic = Risk Difference, Δ=0 (70% response rate in both groups),
α =2-sided 0.05, **1 - β = 90%** **NI Margin** =12% (originally (b)(4)% but increased to 12% due to slow recruitment),

For further details, see the Statistics Review of the abacavir NDA 20977 S-027.

3.2.2 Statistical Methodologies

Original Analysis of Viral Load
The applicant did not perform the snapshot analysis in the clinical study report. Subjects with missing data were not included in the applicant's original analysis of the primary endpoint. Snapshot results were conducted after finalization of the clinical study report and were presented in the ISE.

The statistics reviewer carried out sensitivity analyses adjusting for different potential confounding covariables in order to examine the robustness of the applicant's findings. The statistics reviewer also performed Breslow-Day interaction tests for selected baseline covariates using the snapshot efficacy analysis. The applicant also performed numerous subgroup analyses of responders using cutoff values of 80 and 400 copies/mL.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

See the Statistics Review of the abacavir NDA 20977 S-027.

3.2.4 Results and Conclusions

Summary of Primary Efficacy Analysis: Snapshot Outcomes (≤80 copies/mL)

Outcome	Baseline*		Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Virologic Success (≤80 copies/mL)	250 (75)	237 (71)	242 (73)	233 (69)	232 (70)	226 (67)
Risk Difference and 95% CI	-4.5% (-11% to +2%)		-3.3% (-10% to +4%)		-2.4% (-9% to +5%)	
Virologic Failure (>80 copies/mL)	81 (24)	98 (29)	90 (27)	98 (29)	94 (28)	105 (31)
Risk Difference and 95% CI	+4.8% (-2% to +12%)		+2.1% (-5% to +9%)		+3.0% (-4% to +10%)	
Data in window not below threshold	81 (24)	98 (29)	90 (27)	95 (28)	90 (27)	100 (30)
Prior change in antiretroviral therapy	N/A	N/A	0	3 (1)	4 (1)	5 (1)
No virologic data	2 (1)	1 (<1)	1 (<1)	5 (1)	7 (2)	5 (1)
Missing data during window but on study	2 (1)	1 (<1)	1 (<1)	5 (1)	4 (1)	3 (1)
Discontinued due to AE or Death[c]	N/A	N/A	0	0	3 (1)	1 (<1)
Discontinued due to other reasons	N/A	N/A	0	0	0	1 (<1)

* Baseline=beginning of Randomization 3 and is equivalent to Week 0
[a] Week 48 study days ranged from 255-424 with median of 336
[b] Week 96 study days ranged from 553-757 with median of 672
[c] Deaths only; none of the subjects discontinued due to AEs
Source: Reviewer's analysis

At baseline, 75% and 71% of the subjects in BID and QD arms had HIV-1 RNA viral loads that were suppressed below 80 copies/mL prior to randomization; the risk difference was -4.5% (95% CI: -11% to +2%). At Week 48, 73% and 69% of the subjects were responders in BID and QD arms with a risk difference of -3.3% (95% CI: -10% to +4%). At Week 96 response rates decreased to 70% and 67% in the BID and QD arms with a risk difference of -2.4% (95% CI: -

9% to +5%). See the Statistics Review of the abacavir NDA 20977 S-027 for the applicant's analyses.

3.3 Evaluation of Safety

For the evaluation of safety see the medical review by Dr. Prabha Viswanathan.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

See the Statistics Review of Abacavir NDA 20977 S-027 for subgroup analyses involving gender, race, age and geographic region.

4.2 Other Special/Subgroup Populations

Breslow-Day Interaction Tests with BID vs. QD Treatment (Randomization 3)

Randomization Arm	Week 48 p-value	Week 96 p-value
Monitoring Arm (Randomization 1)	0.57	0.40
ART strategies for first-line therapy (Randomization 2)	0.07	0.39
Subgroup		
Baseline Viral Load (≤80 copies/mL, >80 copies/mL)	0.29	0.14
US Weight Band (<14, 14 to 21, >21 to <30, 30+)	0.33	0.47
WHO Weight Band (<14, 14 to <20, 20 to <25, 25+)	0.31	0.18

Source: Reviewer's analysis

The statistics reviewer did not find any statistically significant interactions between treatment group and other special subgroup populations of interest. However the Breslow-Day test of interaction for treatment by ART strategies for first-line therapy (Randomization 2) at Week 48 was close to reaching statistical significance (p=0.07).

Sensitivity Analyses of Risk Differences and 95% CI for Primary Efficacy Analysis of Snapshot Responders (≤80 copies/mL)

Outcome	Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Virologic Success (≤80 copies/mL)	242 (73)	233 (69)	232 (70)	226 (67)
	Risk Difference (95% CI)[a]			
Adjusted for				
Center	-3.4% (-10% to +3%)		-2.4% (-9% to +5%)	
Baseline Age (≤3, 4 6, 7+)	-3.1% (-10% to +4%)		-2.0 (-9.0% to +5.0%)	
Center and Baseline Age (≤3, 4 6, 7+)	-3.5% (-10% to +3%)		-2.4% (-9% to +5%)	
Gender	-3.3% (-10% to +4%)		-2.4% (-9% to +5%)	
Baseline HIV viral load (≤80, >80 copies/mL)	-0.8% (-6% to +5%)		-0.3% (-5% to +6%)	
US Weight Band (<14, 14 to 21, >21 to <30, 30+)	-3.5% (-10% to +3%)		-2.6% (-10% to +4%)	
WHO Weight Band (<14, 14 to <20, 20 to <25, 25+)	-3.6% (-10% to +3%)		-2.7% (-10% to +4%)	
Unadjusted	-3.3% (-10% to +4%)		-2.4% (-9% to +5%)	

[a]MH Risk Difference and 95% CI
Source: Reviewer's analysis

The statistics reviewer obtained results that were similar to the unadjusted primary efficacy analysis after adjusting for center, baseline age, gender and US and WHO weight bands. However treatment effects appeared to be confounded by baseline HIV viral load and after adjustment there were much smaller risk differences (-1 at Week 48 and -0.3 at Week 96 and the lower bounds of the 95% CI were only -6% and -5% at Weeks 48 and 96). (For further details see the statistics review of the abacavir NDA 20977 S-027.)

Summary of Primary Efficacy Analysis by US Weight Band at Baseline

Outcome	Baseline		Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Baseline Weight <14 kg						
Snapshot Responders (≤80 copies/mL)	68% (54/79)	60% (43/72)	62% (49/79)	67% (48/72)	59% (47/79)	65% (47/72)
Risk Difference and 95% CI	-8.6% (-24% to +7%)		+4.6% (-11% to +20%)		+5.8% (-10% to +21%)	
p-value[a]	0.31		0.61		0.50	
Baseline Weight 14-<20 kg						
Snapshot Responders (≤80 copies/mL)	82% (117/142)	74% (103/140)	79% (112/142)	72% (101/140)	76% (108/142)	69% (96/140)
Risk Difference and 95% CI	-8.8% (-19% to +1%)		-6.7% (-17% to +3%)		-7.5% (-18% to +3%)	
p-value[a]	0.08		0.21		0.18	
Baseline Weight 20-<25 kg						
Snapshot Responders (≤80 copies/mL)	73% (53/73)	78% (68/87)	73% (53/73)	74% (64/87)	70% (51/73)	75% (65/87)
Risk Difference and 95% CI	+5.6% (-9% to +19%)		+1.0% (-13% to +15%)		+4.9% (-10% to +19%)	
p-value[a]	0.46		1.00		0.59	
Baseline Weight ≥25 kg						
Snapshot Responders (≤80 copies/mL)	67% (26/39)	62% (23/37)	72% (28/39)	54% (20/37)	67% (26/39)	49% (18/37)
Risk Difference and 95% CI	-4.5% (-26% to +18%)		-18% (-39% to +5%)		-18% (-39% to +5%)	
p-value[a]	0.81		0.15		0.16	

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

Since the indication for Epzicom is for pediatric patients weighing at least 25 kg, the statistics reviewer performed additional subgroup analyses by baseline weight categories that were not

performed for the abacavir review. Although post-baseline response rates for the BID regimen were higher than for the QD dose in pediatric subjects with baseline weight of at least 25 kg, the differences were not statistically significant. In addition, this trend was not consistent across the four different baseline weight categories; for example, in the next highest weight category (20-<25 kg) there was a trend favoring the QD regimen over the BID regimen at Week 96. See the Statistics Review of the abacavir NDA 20977 S-027 for additional subgroup analyses.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Brief summary of COL105677 AntiRetroviral Research fOr Watoto (ARROW)

Design	**Treatment arms/Sample size**	**Primary endpoint/Analysis**
Phase IV randomized trial of monitoring practice and induction maintenance drug regimens in the management of antiretroviral therapy in treatment-naïve HIV-1 infected children 3 months to 17 years in Africa: **Proposed Indication:** Once daily dosing for treatment of HIV-1 infection in children ≥ 3 months of age*	After 36 weeks of BID ABC+LAM treatment, subjects were **Randomized to:** Continue BID Dosing (n=333) Transition to QD Dosing (n=336) **Randomized and Treated with:** Twice Daily n=331 Once Daily n=335	Proportion of Subjects with Plasma HIV-1 RNA<80 copies/mL at Week 48 using FDA Snapshot Algorithm (Week 0=time of Randomization 3)

* The current indication is for pediatric patients weighing at least 25 kg

Section 4.7.3 of the Clinical Study Report in the abacavir sNDA stated that data from the once daily versus twice daily ABC+3TC part of the study were reviewed twice by the independent DMC as part of their annual reviews of ARROW data (May 2010, June 2011). However the applicant used 95% CI without any adjustment for multiplicity, although the typical 0.001 penalties would not change the conclusions. DSMB minutes and data are not available and the protocol was not reviewed by a statistician.

The applicant used a 12% margin to determine whether the QD regimen was NI to the BID regimen. Note that the 12% non-inferiority margin was not justified by the applicant and may have been too large for a switch trial where subjects were initially virologically suppressed, did not have problems with compliance, and did not experience many AEs leading to discontinuation. In adult switch trials, NI margins using the appropriate amount of discounting are typically 6-8%.

5.2 Collective Evidence

Summary of Primary Efficacy Analysis: Snapshot Outcomes (≤80 copies/mL)

Outcome	Baseline*		Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Virologic Success (≤80 copies/mL)	250 (75)	237 (71)	242 (73)	233 (69)	232 (70)	226 (67)
Risk Difference and 95% CI	-4.5% (-11% to +2%)		-3.3% (-10% to +4%)		-2.4% (-9% to +5%)	
Virologic Failure (>80 copies/mL)	81 (24)	98 (29)	90 (27)	98 (29)	94 (28)	105 (31)
Risk Difference and 95% CI	+4.8% (-2% to +12%)		+2.1% (-5% to +9%)		+3.0% (-4% to +10%)	
Data in window not below threshold	81 (24)	98 (29)	90 (27)	95 (28)	90 (27)	100 (30)
Prior change in antiretroviral therapy	N/A	N/A	0	3 (1)	4 (1)	5 (1)
No virologic data	2 (1)	1 (<1)	1 (<1)	5 (1)	7 (2)	5 (1)
Missing data during window but on study	2 (1)	1 (<1)	1 (<1)	5 (1)	4 (1)	3 (1)
Discontinued due to AE or Death[a]	N/A	N/A	0	0	3 (1)	1 (<1)
Discontinued due to other reasons	N/A	N/A	0	0	0	1 (<1)

* Baseline=beginning of Randomization 3 and is equivalent to Week 0
[a] Deaths only; none of the subjects discontinued due to AEs
Source: Reviewer's analysis

At baseline, 75% and 71% of the subjects in BID and QD arms had HIV-1 RNA viral loads that were suppressed below 80 copies/mL prior to randomization; the risk difference was -4.5% (95% CI: -11% to +2%). At Week 48, 73% and 69% of the subjects were responders in BID and QD arms with a risk difference of -3.3% (95% CI: -10% to +4%). . At Week 96 response rates decreased to 70% and 67% in the BID and QD arms with a risk difference of -2.4% (95% CI: -9% to +5%). There were very few subjects who discontinued since to be eligible for the twice versus once daily lamivudine (3TC) and abacavir (ABC) randomization children must have been on ART for at least 36 weeks and they must have been taking twice daily 3TC and ABC.

5.3 Conclusions and Recommendations

The applicant declared that since the NI margin was 12% that NI was demonstrated. As noted in Section 5.1, typically 12% NI margins for switch trials may be too large. However since response rates were lower (around 70% instead of 90% in switch trials for other NDAs) the larger margin was of less concern.

In addition, the lower bound of the 95% confidence intervals for treatment differences at Weeks 48 and 96 was also ≥-10%. The statistics reviewer also found that most of difference between response rates in the QD and BID arms disappeared after adjusting for the baseline HIV RNA imbalance. Therefore the statistics reviewer agrees with the applicant's conclusion that the QD regimen is NI to the BID regimen.

5.4 Labeling Recommendations (as applicable)

The draft label has efficacy results from the ARROW trial in Section 14.2 (see below) including correct responder rates at Week 96. However it still needs to display the correct snapshot sub-categories like Discontinuations due to AEs and Discontinuations due to Other Reasons.

The sentence above should be modified to state that the differences between virologic outcomes between BID and QD treatment arms were comparable across gender and age. An additional sentence should be added stating that 75% (n=250) of the 333 subjects randomized to the BID arm had HIV-1 RNA<80 copies/mL at baseline compared to 71% (237) of the 336 subjects randomized to the QD arm. As in the abacavir and lamivudine labels there should be a table of snapshot virologic outcomes at Week 96.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRASER B SMITH
07/30/2015

GUOXING SOON
08/19/2015