Combined Medical Officer Clinical Review and Cross-Discipline Team Leader Review

Date	July 31, 2015
From	Prabha Viswanathan, Medical Officer
Subject	Combined Primary Clinical and Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 21652/S-019
Applicant	ViiV Healthcare
Date of Submission	November 20, 2014
PDUFA Goal Date	September 20, 2015
Proprietary Name / Established (USAN) names	Epzicom®/abacavir and lamivudine
Dosage forms / Strength	Fixed-dose combination tablet/600 mg abacavir and 300 mg lamivudine
Proposed Indication(s)	Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children weighing at least 25 kg
Recommended:	*Approval – with revisions to proposed labeling as noted*

1. Introduction

The purpose of this combined Clinical and CDTL Review is to provide an overview of the submitted clinical data, summarize the findings of the FDA multi-disciplinary team of reviewers, describe the conclusions and recommendations presented by all disciplines, and provide an overall risk-benefit assessment of once daily Epzicom use in pediatric patients.

The cornerstone of effective treatment of HIV-1 infection is combination antiretroviral therapy with at least 3 antiretroviral (ARV) medications. The need for multiple drugs often results in ARV regimens with high pill burdens and complex dosing schedules, which may lead to difficulties with optimal treatment adherence. In order to address these challenges, multiple fixed-dose combination (FDC) tablets consisting of two of more ARVs have been developed in the past 10 years. FDCs allow for simpler ARV regimens that facilitate greater adherence, thereby improving treatment outcomes.

Epzicom is a fixed-dose combination tablet comprised of abacavir (ABC) and lamivudine (3TC), which are both nucleoside reverse transcriptase inhibitors (NRTIs). These two agents are included in the list of preferred NRTI "backbone" regimens in the Department of Health and Human Services treatment guidelines for both treatment-naïve adults and pediatric patients with HIV-1 infection. [1,2] Until now, approval of the fixed-dose combination has been limited

[1] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. What to Start: Initial Combination Regimens for the Antiretroviral Naïve Patient, page 73, Table 6. Accessed July 7, 2015.

to adults; the Sponsor seeks to extend the indication to the pediatric population with the current supplemental NDA submission. The Sponsor proposes a minimum weight threshold of 25 kg and seeks a waiver for children weighing less than 25 kg.

2. Background

Both abacavir and lamivudine have been approved and marketed as single entities for more than 15 years. NDA 20564 and NDA 20596 for Epivir (lamivudine, 3TC) tablets and oral solution, respectively, received accelerated approval for twice-daily dosing on November 17, 1995 and traditional approval on April 11, 1997. Twice daily-dosing for children was approved on March 23, 1999. Approval for once-daily administration in adults was granted on June 24, 2002, which preceded PREA legislation that would require pediatric studies of once-daily dosing. NDA 20977 and NDA 20978 for Ziagen [abacavir sulfate (abacavir, ABC)] tablets and oral solution, respectively, received accelerated approval on December 17, 1998 and traditional approval on April 15, 2004. Twice-daily dosing for children was also approved on December 17, 1998.

On August 2, 2004, Epzicom was approved for the treatment of HIV-1 infection in adults, in combination with other antiretroviral agents. The approval was based on clinical data from Trial CDA30021, a randomized, double-blind, active controlled Phase 3 study which compared once-daily versus twice-daily dosing of ABC, both in combination with once-daily 3TC and efavirenz. At the time of approval, a Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) was issued to study Epzicom in children 3 months to 17 years of age (PMR 612-1). Once-daily dosing of ABC for adults was approved at the same time (also based on Trial CDA30021), which triggered issuance of a nearly identical PREA PMR for ABC [PMR Number 426-1 (NDA 020977/S-012) and PMR Number 1545-1 (NDA 020978/S-014)].

The Applicant initially planned to fulfil these PMRs with data from several pharmacokinetic studies: PENTA 15, PENTA 13, PACTG 1052 and PACTG 1018. However, in the interim, DAVP became aware of the ARROW trial through publications and presentations at scientific meetings. The ARROW trial was a large, randomized, pediatric study sponsored by the Medical Research Council (MRC) of the United Kingdom and conducted in Uganda and Zimbabwe. The Division felt that a pediatric study of this size and scope would provide valuable safety and efficacy data to complement the proposed pharmacokinetic studies. Although the study was conducted in Africa, the Division considered the ARROW data applicable to U.S. pediatric patients as HIV infection and the response to ARV treatment is similar across all populations studied to date. Hence, the Agency issued a PREA PMR Not Fulfilled letter on July 20, 2011 and requested submission of a pediatric efficacy supplement containing data and/or study reports from ARROW, PENTA 15 and PENTA13.

[2] Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. What to Start: Recommended Regimens for Initial Therapy of Antiretroviral-Naïve Children, pages 74-78, Table 8 and Table 9. Accessed July 7, 2015.

The Applicant requested a pre-NDA meeting on May 6, 2013 to discuss submission of the requested information and the meeting was held via teleconference on July 17, 2013. The content and format of the sample datasets were found to be inadequate to facilitate a substantive review; therefore, the Applicant was urged to obtain additional data from the MRC. Since the data were owned by the MRC rather than the Applicant, and additional analyses were necessary to support regulatory submission, DAVP felt that an extension was warranted to allow for more time to prepare the application for submission. Hence, a Deferral Extension Granted Letter was issued on October 4, 2013 in order to extend the Final Report Submission deadline for the PREA PMR to July 6, 2014. DAVP also requested the Applicant to stagger submission of the planned supplements such that the ABC and 3TC supplements could be reviewed and, if approved, support approval of the Epzicom supplement. Hence, the Epzicom supplement currently under review was submitted 6 months after the ABC and 3TC submissions.

In May 2014, the Applicant submitted efficacy supplements to the abacavir NDAs (20977 and 20978) and lamivudine NDAs (20564 and 20596) to support once-daily dosing of these two drugs in pediatric patients ≥ 3 months of age. As agreed, the results of the ARROW trial served as the pivotal safety and efficacy data; pharmacokinetic data from ARROW PK substudies, PENTA 15, PENTA 13, PACTG 1052 and PACTG 1018 served as supporting evidence. The ARROW results demonstrated that once daily dosing of ABC and 3TC conferred comparable efficacy to twice-daily dosing with a similar safety profile. Hence, these pediatric efficacy supplements were approved in March 2015.

Since Epzicom is a fixed-dose combination of ABC and 3TC and is bioequivalent to the individual components, approval of once-daily ABC and 3TC also supports approval of Epzicom in the applicable population. The primary focus of this review is to summarize key safety and efficacy findings from the ARROW trial and provide more focused analyses among the subpopulation of subjects who weighed > 25 kg and were therefore eligible to receive the fixed-dose combination.

3. CMC/Device

This submission did not include new product quality-related information. The ABC and 3TC formulations used in the ARROW trial were the same as the commercially available formulations marketed in the United States. The ABC/3TC fixed dose combination tablet used in the ARROW trial was also the same as the commercially available Epzicom tablet, which is marketed under the trade name Kivexa in Africa and other parts of the world.

4. Nonclinical Pharmacology/Toxicology

The nonclinical programs for ABC and 3TC were completed at the time of the NDA approvals for the individual products. No new nonclinical data were submitted with this efficacy supplement.

5. Clinical Pharmacology/Biopharmaceutics

Several pharmacokinetic (PK) studies were submitted in support of once-daily dosing of ABC and 3TC, including 2 ARROW PK sub-studies, PENTA studies 13 and 15, and PACTG studies 1052 and 1018. Overall, the PK data demonstrate mean AUC_{0-24} values are

comparable between QD and BID dosing for both ABC and 3TC. As expected, the C_{max} is higher and the C_{trough} is lower with QD dosing versus BID dosing. However, the observed values in the ARROW cohort exceeded the predicted pediatric values as well as historical adult reference values (study EPV10001). This is likely due to the slightly higher dosing recommended by the WHO in some pediatric weight bands compared to the US prescribing information.

A bioavailability trial in 25 adults was conducted to support the original approval of Epzicom tablets. This study demonstrated that 1 Epzicom tablet yielded similar AUC and C_{max} (both ABC and 3TC components) as ABC and 3TC tablets taken together.

Please refer to Dr. Su-Young Choi's clinical pharmacology review of the current Epzicom supplement as well as her review of once-daily dosing for ABC and 3TC for further details (NDA 20977/S-027 and NDA 20564/S-033, electronically archived February 13, 2015).

6. Clinical Microbiology

Logistical challenges precluded the Applicant from submitting resistance data from the ARROW study with the clinical data supporting once-daily pediatric dosing (NDA 20977/S-027 and NDA 20564/S-033). Hence, a post-marketing requirement was issued to submit ARROW resistance data with the current supplement. (b) (4)

Please refer to Dr. Lalji Mishra's clinical virology review of the current Epzicom supplement as well as his review of once-daily dosing for ABC and 3TC for further details (NDA 20977/S-027 and NDA 20564/S-033, electronically archived February 10, 2015).

7. Clinical/Statistical- Efficacy

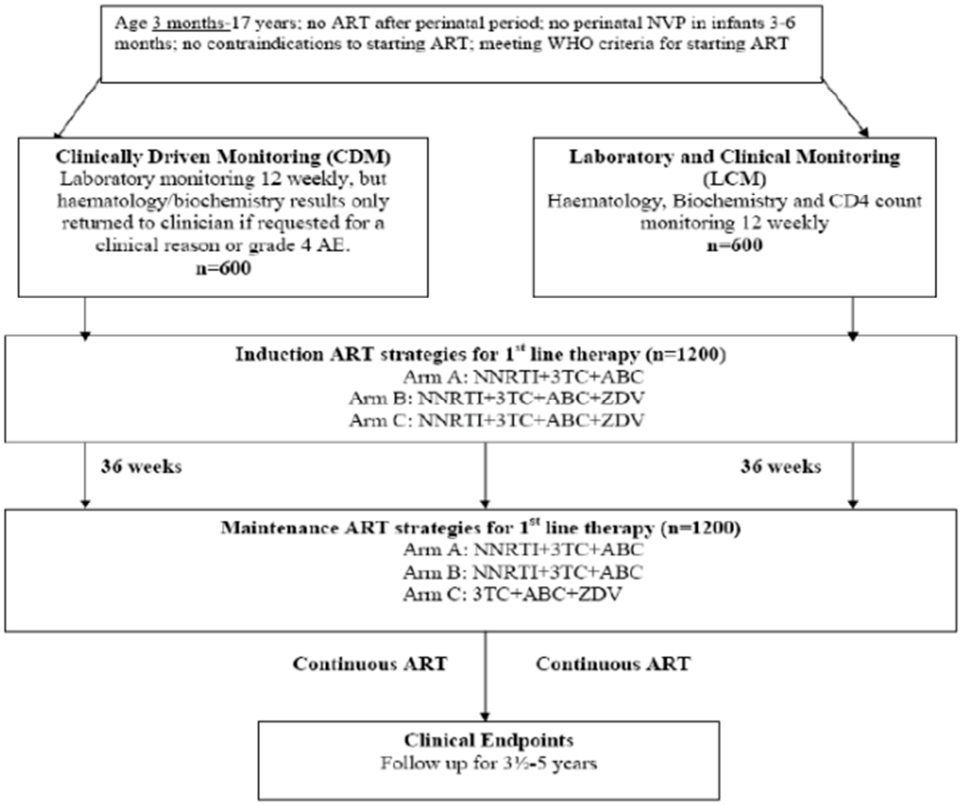
The efficacy of Epzicom in pediatric subjects weighing ≥ 25 kg is supported by the approvals of once-daily dosing of ABC and 3TC and demonstration of bioequivalence between Epzicom and the individual components. The once-daily ABC and 3TC approvals were based on the results from ARROW Randomization 3, which demonstrated that once-daily dosing is non-inferior to twice-daily dosing with ABC+3TC in children who have received at least 36 weeks of ART on a twice-daily dosing schedule. Results for the entire ARROW cohort will be summarized in this review, (b) (4) . Please refer to the clinical review conducted by Dr. Viswanathan for NDA 20977/S-027 and NDA 20564/S-033 for additional details (electronically archived February 14, 2015).

ARROW TRIAL DESIGN

The ARROW trial was an open-label randomized trial designed to evaluate various treatment strategies and develop best practices for ARV management of pediatric patients in resource-poor settings. The study was sponsored by the MRC (UK) and was not conducted for regulatory purposes. ViiV Healthcare and GSK provided study medications, but were otherwise not involved in the design, conduct, or initial data analyses for the study.

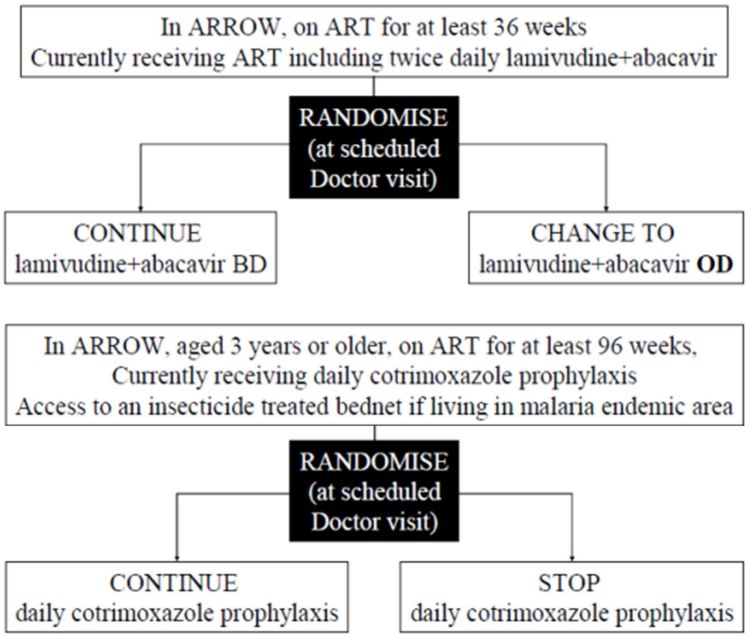
The ARROW trial enrolled HIV-1 infected, ARV-naive children ages 3 months to 17 years in Uganda and Zimbabwe who were eligible to initiate ARV based on the WHO treatment guidelines followed in those countries. Children were excluded if they exhibited symptoms of an acute infection or if the ARROW ARV regimen was contraindicated based on laboratory values or concomitant medications. There were a total of four randomizations in the study: 2 primary and 2 secondary. All subjects underwent simultaneous randomization into Randomizations 1 and 2 at study entry: Randomization 1 compared clinically driven monitoring (CDM) with laboratory plus clinical monitoring (LCM); Randomization 2 compared a 3-drug 2-class first line ARV regimen (2 NRTIs plus 1 NNRTI) with a 4-drug 2-class induction followed by maintenance with 3 drugs (1 or 2 classes). The secondary randomizations occurred after at least 36 and 96 weeks on ARV therapy (Randomization 3 and 4, respectively), to assess simplification strategies which could improve long-term ARV adherence: once versus twice daily ABC+3TC (Randomization 3) and stopping versus continuing daily cotrimoxazole prophylaxis (Randomization 4). A subset of subjects also participated in PK substudies. Figures 1 and 2 provide a visual representation of the primary and secondary randomizations, respectively.

Figure 1: ARROW Trial Schema, Primary Randomizations



Source: Figure 1, Applicant's Clinical Study Report

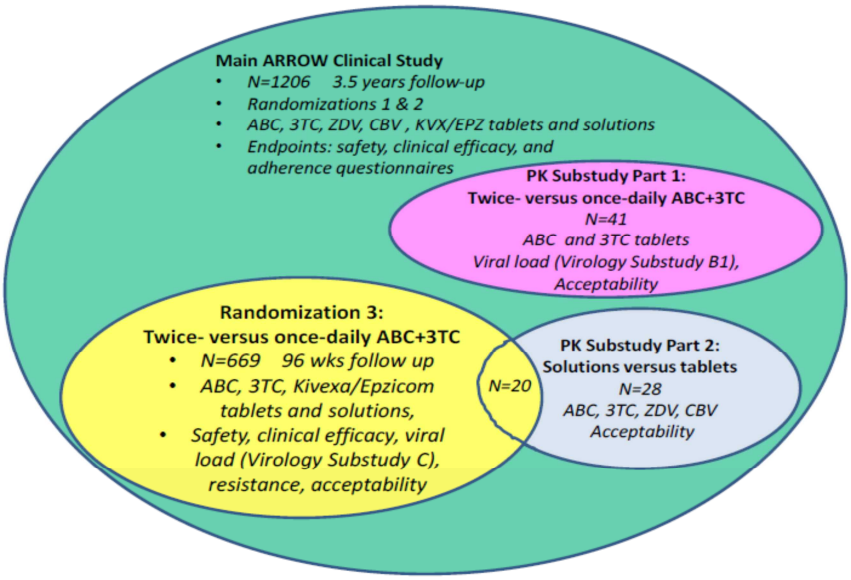
Figure 2: ARROW Trial Schema, Secondary Randomizations



Source: Figure 2, Applicant's Clinical Study Report

Randomization 3 provided pivotal safety and efficacy data for this efficacy supplement. PK Substudy Part 1, which enrolled children between 3 and 12 years of age, provided supportive PK data, though the majority of subjects who participated in the substudy were ineligible for the FDC due to young age/low weight. Figure 1 provides a graphical representation of how Randomization 3 and the PK substudies fit into the overall ARROW study design.

Figure 3: ARROW Study Populations



Source: Applicant's Clinical Overview

STUDY POPULATION AND SUBJECT DISPOSITION

A total of 1,206 subjects were enrolled in the ARROW trial, of which 669 participated in Randomization 3: 333 subjects in the BID arm and 336 subjects in the QD arm. Baseline demographic and disease characteristics were similar between the BID and QD groups (Table 1). Randomization between the two study groups was also well balanced by primary randomizations, study site, and drug formulation.

Table 1: ARROW Study Randomization 3 Baseline Demographic and Disease Characteristics

	BID Dosing (n=333)	**QD Dosing (n=336)**
Sex n (%)		
Male	161 (48)	163 (49)
Female	172 (52)	173 (51)
Median Age in Years (IQR)	5.1 (3.6 to 8.3)	5.9 (3.8 to 8.6)
Median Years Since ART Initiation (IQR)*	1.8 (1.4 to 2.3)	1.8 (1.4 to 2.1)
HIV-1 RNA PCR < 80 copies/ml	250 (76)	237 (71)
Median CD4 Percentage (IQR)	33 (27 to 39)	33 (28 to 39)
Median CD4 Count (IQR) (≥ 5 yrs)	836 (558 to 1,131)	760 (543 to 1,136)

*Reflective of time on BID ABC+3TC during the ARROW trial, prior to Randomization 3. All subjects were ART Naïve at ARROW baseline.

There was a high rate of subject retention in the trial, with all 669 subjects completing the first 48 weeks (primary endpoint) and 664 (99%) completing 96 weeks. Reasons for discontinuation prior to Week 96 included 4 deaths (3 in the BID arm and 1 in the QD arm) and one subject in the QD arm who discontinued for other reasons.

ANALYSIS OF THE PRIMARY ENDPOINT

The primary efficacy endpoint for Randomization 3 was the percentage of subjects with virologic suppression at Week 48. Virologic suppression is typically defined as HIV-1 RNA PCR < 50 copies/ml. However, due to the small sample volumes obtained in this study, samples were diluted in order to perform the assay and assay results had to be adjusted accordingly. Hence, virologic suppression is defined as HIV-1 RNA PCR < 80 copies/ml. The analysis was performed using the FDA snapshot algorithm (Table 2). Efficacy at Week 96 (a secondary endpoint) is also presented in Table 2 for the purpose of comparison. The study was powered for a pre-specified non-inferiority margin of 12%.

Table 2: ARROW Study Virologic Status at Randomization 3 Baseline, Week 48, and Week 96

Outcome	**Baseline***		**Week 48***		**Week 96***	
	BID Dosing N=333 n (%)	**QD Dosing** N=336 n (%)	**BID Dosing** N=333 n (%)	**QD Dosing** N=336 n (%)	**BID Dosing** N=333 n (%)	**QD Dosing** N=336 n (%)
Virologic Success (≤80 copies/mL)	250 (76)	237 (71)	242 (73)	233 (69)	232 (70)	226 (67)
Risk Difference (95% CI)			-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 (95% CI)			+2.1% (-5% to +9%)		+3.0% (-4% to +10%)	
Value above threshold	81 (24)	98 (29)	90 (27)	95 (28)	90 (27)	100 (30)
Prior change in ART	N/A		0	3 (1)	4 (1)	5 (1)
No virologic data			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)
Death	N/A		0	0	3 (1)	1 (<1)
D/C for other reasons	N/A		0	0	0	1 (<1)

Source: Analysis of Week 48 and Week 96 data was performed by Dr. Fraser Smith, Statistician, for review of NDA 20977/S-027 and NDA 20564/S-033. Baseline results were obtained from the Clinical Study Report.

Subjects in the QD group who weighed 25 kg at the start of Randomization 3 were treated with Epzicom tablets, whereas smaller children received the ABC and 3TC single entity products. All subjects were eligible to transition from the single entity products to Epzicom at any point during the study once they met the 25 kg weight threshold. Fourteen subjects weighed 25 kg at the onset of Randomization 3 and were treated with Epzicom for the entire 96 week study period. An additional 87 subjects reached 25kg at some point during Randomization 3 and were treated with Epzicom for some portion of the study period. Table 3 compares subjects who received Epzicom for any period of time with subjects who received single-entity products exclusively (BID or QD).

Table 3: ARROW Study Virologic Outcome at Week 48 and Week 96 by Regimen Received

Snapshot outcome category	**QD Epzicom for any portion of study period n=101**	**QD ABC+3TC as single entities exclusively N=235**	**BID ABC +3TC as single entities n=333**
Week 48			
HIV RNA <80 copies/ml	66 (65%)	170 (72%)	242 (73%)
HIV RNA >80 copies/ml	34 (34%)	60 (26%)	90 (27%)
No Virologic data	1 (1%)	5 (2%)	1 (<1%)
Week 96			
HIV RNA <80 copies/ml	66 (65%)	164 (70%)	232 (70%)
HIV RNA >80 copies/ml	34 (34%)	67 (29%)	94 (28%)
No Virologic data	1 (1%)	4 (2%)	7 (2%)

Medical Officer Comments: Epzicom is expected to confer equivalent antiviral activity to the single entity products. Interpretation of the numerically lower rates of virologic suppression among FDC recipients is complex because many variables may be at play. First, the children in the Epzicom group transitioned from single-entity products to the FDC at various time points, thereby making it difficult to truly differentiate the two QD groups. Second, the Epzicom and single entity QD groups are comprised of children of different ages, and these changes may have an independent effect on treatment success irrespective of formulation effect (i.e.: historical data documenting higher rates of medication non-adherence among adolescents compared to young children). Third, subjects in the QD arm began Randomization 3 with a lower rate of virologic suppression compared to BID subjects (71% versus 76% respectively), a difference that persisted over the study period.

Another important factor to consider is the third drug in the ARV regimen. Based on treatment assignment in Randomization 2, study participants received ABC+3TC in combination with either zidovudine (ZDV) or an NNRTI (nevirapine [NVP] or efavirenz [EFV]). Among the 101 children who received Epzicom during ARROW, 45% received ZDV as the third ARV. In contrast, only 30% of QD subjects treated exclusively with single entity ABC+3TC and 34% in the BID group received zidovudine as the third agent.

Treatment with ZDV was associated with higher rates of virologic failure. In ARROW overall, only 58% of children who were treated with a triple-NRTI regimen were virologically suppressed, compared to 77% of children on an NNRTI-based regimen. The same trend was observed among the 101 children who received Epzicom at some point during ARROW: 40% of children who were treated with a triple-NRTI regimen were virologically suppressed, compared to 86% of children on an NNRTI-based regimen. This finding is consistent with data from several other studies, and consequently triple NRTI regimens are no longer recommended as complete ARV regimens. Please see Table A1 and A2 in the Appendix for further details.

SECONDARY ENDPOINTS AND SUBGROUP ANALYSES
Secondary endpoints included HIV-1 RNA at Week 96 and change in CD4 count/percentage at Weeks 48 and 96. There were no significant differences between QD and BID treated subjects for any of these parameters. Subgroup analyses demonstrated no significant differences in efficacy between QD and BID dosing based on age group, gender, baseline HIV viral load, and weight band (US and WHO). Please see Dr. Fraser Smith's biometrics review of the current Epzicom supplement as well as his review of once-daily dosing for ABC and 3TC for further details (NDA 20977/S-027 and NDA 20564/S-033, electronically archived February 18, 2015).

8. Safety

The safety results from ARROW Randomization 3 are consistent with the findings from prior clinical trials in children and adults, as well as post-marketing experience with ABC and 3TC. QD dosing was not associated with an increase in Grade 3 or 4 AEs or laboratory abnormalities compared to BID dosing.

Similar to the efficacy section of this review, safety events will be summarized for three study groups: subjects who were randomized to receive once daily dosing and treated with Epzicom for any portion of Randomization 3; subjects randomized to receive once daily dosing and treated with the single entity formulations of ABC and 3TC exclusively throughout the trial; and subjects randomized to receive bid dosing with single-entity formulations of ABC and 3TC. All analyses presented in this section were performed by the author using JReview software.

ROUTINE CLINICAL TESTING FOR SAFETY MONITORING
Subjects underwent full physical examination and a battery of safety laboratory assessments at baseline. After randomization, subjects had follow-up visits at Weeks 2, 4, 8, and 24, and then at 12 week intervals through the study period. A full assessment was undertaken at each visit including: interval medical history to identify intercurrent illness or symptoms of HIV disease progression; assessment for adverse events and relationship to study medication; anthropometric measures; hematology and chemistry labs. As part of the objectives of Randomization 1, investigators received all laboratory results for subjects in the LCM randomization, but only Grade 4 results from subjects in the CDM randomization. Investigators could request additional results for CDM subjects if clinical signs or symptoms were suggestive of drug toxicity.

MAJOR SAFETY RESULTS
Unlike many HIV clinical trials that are performed for regulatory purposes, the ARROW study was conducted to inform best practices for treatment of HIV-1 infection in children in resource-poor settings. Hence, collection of adverse event (AE) data was focused on more severe events (Grade 3 and 4) that might limit ARV administration, and data on the occurrence of mild to moderate (Grade 1 and 2) events were not collected. Furthermore, collection of Serious Adverse Events (SAE) was limited to those events that were considered NOT directly related to HIV itself. Adverse events were graded using the Division of Acquired Immunodeficiency Syndrome (DAIDS) Toxicity Grading and Management table.

This approach was deemed acceptable by DAVP because the safety profiles of ABC and 3TC are well established. The main purpose of this safety review is to identify adverse events that may be caused by the higher maximal concentration of ABC and 3TC that result from QD versus BID dosing. Given the large sample size and comparative study design, substantive differences in the rates of severe AEs can be detected.

Deaths

Five children died during the 96-week study period: 4 in the BID arm and 1 in the QD arm. All deaths were in young children (5 to 9 years of age) and were deemed unrelated to the study or study medication. None of the deaths occurred among the 101 children exposed to Epzicom. Please refer to Dr. Viswanathan's clinical review for NDA 20977/S-027 and NDA 20564/S-033 for brief narratives of each case.

Serious Adverse Events (SAEs)

SAEs that were deemed unrelated to HIV infection were infrequent during the ARROW trial. No imbalances were noted between study groups. The events are summarized in Table 4.

Table 4: ARROW Study Serious Adverse Events during Randomization 3

Event name	QD Epzicom for any portion of study period n=101	QD ABC+3TC as single entities exclusively N=235	BID ABC +3TC as single entities n=333
P. falciparum malaria	3 (3%)	10 (4%)	13 (4%)
Anemia with clinical symptoms	2 (2%)	4 (2%)	5 (2%)
Measles	1 (1%)	0 (0%)	3 (1%)
Acute diarrhea	1 (1%)	1 (<1%)	2 (1%)

Moderate and Severe Adverse Events

All Grade 3 and 4 AEs were collected, irrespective of association with study drug or underlying HIV infection. Tables 5 and 6 summarize clinical adverse events and laboratory abnormalities, respectively.

Table 5: ARROW Study Clinical Adverse Events

Event name	QD Epzicom for any portion of study period n=101	QD ABC+3TC as single entities exclusively N=235	BID ABC +3TC as single entities n=333
P. falciparum malaria	2 (2%)	10 (4%)	13 (4%)
Symptomatic anemia	2 (2%)	4 (2%)	5 (2%)
Measles	1 (1%)	0 (0%)	3 (1%)
Cataract	1 (1%)	0 (0%)	0 (0%)
Acute diarrhea	1 (1%)	1 (<1%)	2 (1%)

Table 6: ARROW Study Grade 3 and 4 Laboratory Events

Parameter and Toxicity Grade	QD Epzicom for any portion of study period n=101	QD ABC+3TC as single entities exclusively N=235	BID ABC +3TC as single entities n=333
Hemoglobin Decreased			
3	2 (2%)	3 (1%)	8 (2%)
4	2 (2%)	2 (1%)	3 (1%)
Neutrophils Decreased			
3	11 (11%)	9 (4%)	15 (5%)
4	2 (2%)	1 (<1%)	0 (0%)
Platelets Decreased			
3	3 (3%)	5 (2%)	4 (1%)
4	4 (4%)	3 (1%)	4 (1%)
AST Elevated			
3	1 (1%)	2 (1%)	5 (2%)
4	0	6 (3%)	2 (1%)
ALT Elevated			
3	2 (2%)	3 (1%)	7 (2%)
4	0	4 (2%)	4 (1%)

Medical Officer Comments: The rate of adverse events and laboratory abnormalities is comparable between the QD and BID treatment groups. As discussed in the efficacy section of this review, comparisons between the QD Epzicom group and the QD ABC + 3TC group should be made with caution, as the majority of the 101 children received single entities for at least some portion of the 96 week study period. With this limitation in mind, it is worth noting that the rate of P. falciparum malaria appears to be lower among the Epzicom cohort, which is likely related to the older age of this cohort. The lower rate of Grade 4 hepatic transaminase elevations among Epzicom subjects is also related to the lower incidence of malaria in this cohort. The Epzicom cohort also had a notably higher rate of neutropenia and thrombocytopenia, which is likely related to higher zidovudine exposure in this cohort relative to the others.

9. Advisory Committee Meeting

An advisory committee meeting will not be convened.

10. Pediatrics

Extension of the current indication to pediatric subjects weighing 25 kg or more is supported by:

- Clinical safety and efficacy data from the ARROW trial, which supported approval of once daily dosing of ABC and 3TC in pediatric subjects (May 2015)
- Pharmacokinetic studies (PENTA 13, PACTG 1018 and 1052, and ARROW PK Substudy 1) which demonstrate that pediatric exposures are comparable to adult exposures with once-daily dosing

- Trial CDA30021, which supported approval of Epzicom in adults (August 2004)
- Demonstration of bioequivalence between the Epzicom tablet and the individual ABC and 3TC tablets

At the time of Epzicom' s original marketing approval, a Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) was issued to study Epzicom in children 3 months to 17 years of age (PMR 612-1). The Sponsor has requested a waiver for children weighing less than 25 kg, citing the availability of ABC and 3TC in age-appropriate formulations as the justification. In adjudicating whether such a waiver was appropriate, the Division considered how much of the pediatric population would be eligible to receive Epzicom with a minimum weight threshold of 25 kg. The following table from the ARROW trial, provided in the Sponsor's NDA package, was used as a reference.

Table 7: Summary of FDC Starting Weight Band and Age Categories in the ARROW Trial

		FDC Starting Age (years)			
Category	n	Mean	Median	SD	Range
All subjects	104	10.4	10.1	1.55	7.6-16.9
Subjects by Weight at FDC start[a]					
20-<25 kg	2	10.1	10.1	0.89	9.5-10.7
25-<30 kg	88	10.1	10.0	1.39	7.6-13.9
30-<35 kg	11	11.3	11.0	1.24	9.3-13.7
35-<40 kg	3	13.6	12.1	2.88	11.7-16.9
Subjects by Age at FDC start					
3-6 years	0	-	-	-	-
7 years	4	7.8	7.8	0.17	7.6-8.0
8 years	13	8.5	8.5	0.26	8.0-8.8
9 years	31	9.6	9.6	0.29	9.0-10.0
10 years	24	10.4	10.4	0.29	10.0-10.9
11 years	19	11.5	11.5	0.27	11.0-12.0
12 years	8	12.5	12.4	0.37	12.1-13.0
13 years	4	13.6	13.6	0.27	13.3-13.9
14 years	0	-	-	-	-
15+ years	1	16.9	16.9	-	16.9-16.9

Table 7 demonstrates that a substantial number of children were able to transition to the FDC formulation at 9 years of age, with a few children able to transition before their 9th birthday. American children would be expected to reach 25 kg weight at an even earlier age than this cohort of children from Uganda and Zimbabwe. Considering that the average American child is unable to swallow tablets until roughly 6 years of age, the Division felt that a minimum weight of 25 kg enabled use of the FDC in a significant proportion of the pediatric population that is developmentally able to swallow tablets. Furthermore, the Division felt that development of a reduced-strength FDC formulation is unnecessary due to the small number of subjects in the United States that would benefit.

On July 15, 2015, the Division presented this justification for granting the applicant's request for a partial waiver to the Pediatric Review Committee at FDA, who agreed with the proposal. Hence, a partial waiver will be issued to study subjects less than 6 years of age or weighing less than 25kg. As a result of this approval, Epzicom will be considered appropriately labeled for patients weighing 25 kg or more.

11. Other Relevant Regulatory Issues

Financial disclosures were reviewed with the once-daily dosing efficacy supplements for ABC and 3TC. Please refer to Dr. Viswanathan's clinical review for NDA 20977/S-027 and NDA 20564/S-033 for the full Clinical Investigator Financial Disclosure Template.

12. Labeling

Labeling discussions were ongoing at the time this review was finalized. Hence, draft language is presented in this section may be altered. Please refer to Victoria Tyson's RPM review for the final labeling.

Section 2. DOSAGE AND ADMINISTRATION

2.2 Pediatric Patients

The recommended oral dose of EPZICOM for pediatric patients weighing at least 25 kg is one tablet daily in combination with other antiretroviral agents *[see Clinical Studies (14.2)]*. Before prescribing EPZICOM tablets, pediatric patients should be assessed for the ability to swallow tablets.

Section 6. ADVERSE REACTIONS

6.2 Clinical Trials Experience in Pediatric Subjects

The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as EPZICOM, was assessed in the ARROW trial (n=336). Primary safety assessment in the ARROW trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator. No additional safety issues were identified in pediatric subjects receiving abacavir and lamivudine once-daily compared with historical data in adults *[see Adverse Reactions (6.1)]*.

Section 14. CLINICAL STUDIES

14.2 Pediatric Subjects

ARROW (COL105677) was a 5-year, randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric subjects. HIV-1–infected, treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first-line regimen containing abacavir and lamivudine, dosed twice daily according to World Health Organization recommendations. After a minimum of 36 weeks of treatment, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once-daily dosing with twice-daily dosing of abacavir and lamivudine, in combination with a third antiretroviral drug, for an additional 96 weeks. Virologic suppression was not a requirement for participation at baseline for Randomization 3. At baseline for Randomization 3 (following a minimum of 36 weeks of twice-daily treatment), 75% of subjects in the twice-daily cohort were virologically suppressed, compared to 71% of subjects in the once-daily cohort.

Of the 1,206 original 697 ARROW subjects, 669 participated in Randomization 3. Subjects randomized to receive once-daily dosing (n = 336) and who weighed at least 25 kg received abacavir 600 mg and lamivudine 300 mg, as either the single entities or as EPZICOM.

The proportions of subjects with HIV-1 RNA less than 80 copies per mL through 96 weeks are shown in Table 11. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 11. Virologic Outcome of Randomized Treatment at Week 96[a] (ARROW Randomization 3)

Outcome	Abacavir plus Lamivudine Twice-daily Dosing (n = 333)	Abacavir plus Lamivudine Once-daily Dosing (n = 336)
HIV-1 RNA <80 copies/mL[b]	70%	67%
HIV-1 RNA ≥80 copies/mL[c]	28%	31%
No virologic data		
Discontinued due to adverse event or death	1%	<1%
Discontinued study for other reasons[d]	0%	<1%
Missing data during window but on study	1%	1%

[a]Analyses were based on the last observed viral load data within the Week 96 window.
[b]Predicted difference (95% CI) of response rate is -4.5% (-11% to 2%) at Week 96.
[c]Includes subjects who discontinued due to lack or loss of efficacy or for reasons other than an adverse event or death, and had a viral load value of greater than or equal to 80 copies per mL, or subjects who had a switch in background regimen that was not permitted by the protocol.
[d]Other includes reasons such as withdrew consent, loss to follow-up, etc. and the last available HIV-1 RNA less than 80 copies per mL (or missing).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  I recommend approval of this efficacy supplement to expand the age range for use of Epzicom to pediatric patients weighing 25 kg or more. This recommendation reflects the conclusions of the entire review team.

- Risk Benefit Assessment
  Treatment with Epzicom confers the benefit of reduced pill burden with no additional risk beyond that conferred by administration of the individual components separately. The overall risk-benefit assessment for once-daily versus twice-daily dosing of ABC and 3TC in pediatric patients was determined to be favorable during the review of the once daily dosing supplemental NDAs for the individual products. When given in combination with other antiretroviral drugs, both drugs are effective in suppressing HIV-1 viral replication and have acceptable safety and tolerability profiles in pediatric patients. Hence, there is a clear benefit. To ascertain the possibility of increased risk associated with once-daily dosing, the safety review focused on the following: 1) possible toxicity due to higher peak concentrations resulting from once-daily dosing; 2) potential virologic failure due to a longer interval between doses resulting from once-

daily dosing; and 3) difficulties with adherence or medication tolerance due to a larger volume of drug administered at one time in once-daily dosing. Results from the ARROW study demonstrate that none of these three issues are significant concerns. Thus, we concluded that there is no increased risk of drug-related toxicity from once-daily dosing compared to twice-daily dosing. Expanding the indication for Epzicom use to include pediatric patients provides an effective, easy to administer backbone regimen that can be combined with other ARVs given once daily.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  Postmarketing REMS are not required for this product and indication.

- Recommendation for other Postmarketing Requirements and Commitments
  Postmarketing Requirements and Commitments are not required.

- Recommended Comments to Applicant
  No additional comments.

14. Appendix

The tables below summarize treatment outcomes by background regimen.

Table A1: Primary Efficacy Outcome by Randomization 2 Assignment in the ARROW Trial

HIV-1 RNA PCR < 80 copies/ml	**Week 48**		**Week 96**	
	BID Dosing N=333 % (n)	**QD Dosing** N=336 % (n)	**BID Dosing** N=333 % (n)	**QD Dosing** N=336 % (n)
Arm A (standard, ABC+3TC+NNRTI)	79% (83/105)	74% (78/105)	76% (80/105)	73% (73/105)
Arm B (induction maintenance, ABC+3TC+NNRTI)	75% (88/118)	82% (98/120)	76% (90/118)	80% (96/120)
Arm C: (induction maintenance, ABC+3TC+ZDV)	65% (71/110)	51% (57/111)	56% (62/110)	48% (53/111)

Table A2: ARROW Trial Week 48 Outcome by Third Antiretroviral Drug among Subjects Treated with Epzicom

Snapshot outcome HIV-1 PCR <80 copies/mL N (%)	**EFV n=27**	**NVP n=29**	**ZDV n=45**	**Total n=101**
HIV RNA <80 copies/mL	23 (85%)	25 (86%)	18 (40%)	66 (65%)
Virologic failure	4 (15%)	4 (14%)	26 (58%)	34 (34%)
No Virologic data	0 (0%)	0 (0%)	1 (2%)	1 (<1%)

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/s/

PRABHA VISWANATHAN
08/14/2015

LINDA L LEWIS
08/14/2015

I concur with the analyses, conclusions, and risk-benefit assessment described in Dr. Viswanathan's combined clinical and cross-discipline team leader review and recommend approval of this supplement.