CLINICAL REVIEW

Application Type	Pediatric Efficacy Supplement
Application Number(s)	20977/S-027, 20978/S-031, 20564-S-033, 20596/S-032
Priority or Standard	Standard
Submit Date(s)	May 23, 2014
Received Date(s)	May 23, 2014
PDUFA Goal Date	March 23, 2015
Division / Office	DAVP/OAP
Reviewer Name(s)	Prabha Viswanathan, MD
Review Completion Date	February 13, 2015
Established Name	Abacavir, Lamivudine
Trade Name	Ziagen, Epivir
Therapeutic Class	Nucleoside Reverse Transcriptase Inhibitor
Applicant	ViiV Healthcare
Formulation(s)	(b) (4) and Tablet
Dosing Regimen	Weight-based dosing, once daily
Indication(s)	Treatment of HIV-1 infection
Intended Population(s)	Children 3 months to 17 years of age

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of once-daily dosing of abacavir and lamivudine in pediatric patients at least 3 months of age is supported by 1) safety and efficacy results from Randomization 3 of the AntiRetroviral Research fOr Watoto (ARROW) trial; and 2) pharmacokinetic data which demonstrate similar abacavir and lamivudine exposures between adults and children, thereby supporting extrapolation of efficacy from adult studies. In concert, the ARROW and pharmacokinetic data support both initiation of antiretroviral treatment with once-daily abacavir and lamivudine, as well as transition from twice-daily to once-daily dosing for treatment maintenance in children.

1.2 Risk Benefit Assessment

The overall risk-benefit assessment for once-daily dosing of abacavir (ABC) and lamivudine (3TC) is similar to the risk-benefit assessment for twice-daily dosing of these drugs, which is the current standard of care. When given in combination with other antiretroviral drugs, both drugs are effective in suppressing HIV-1 viral replication and are well-tolerated by pediatric patients. Hence, this review focused on evaluating key differences between once-daily and twice-daily dosing, including 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 no significant differences in efficacy or safety between once-daily dosing and twice-daily dosing. Hence, these findings, in conjunction with the results of the supportive pharmacokinetic studies, suggest that none of these three issues are significant concerns.

While not directly related to the risk-benefit assessment of once-daily versus twice-daily dosing, one noteworthy finding is a lower percentage of subjects who achieve virologic suppression with liquid formulations of ABC and 3TC compared to those who were treated with a tablet formulation: 55% versus 74%, respectively. The difference in response rate was established during the primary randomizations of the ARROW study (during which all subjects received twice-daily dosing), and maintained during Randomization 3; the finding is therefore independent of once-daily versus twice-daily dosing. There is no clear explanation for why children dosed with oral solutions had a lower rate of virologic suppression, but pharmacokinetic data demonstrate lower 3TC exposures among subjects dosed with the oral solution. Previous studies have also demonstrated 3TC AUCs similar to adult AUCs after dosing with tablets but lower AUCs

after dosing with 3TC solution. The clinical significance of this finding was not apparent in the past, but the ARROW results suggest that the lower exposures may contribute to less favorable treatment response. Correlation with virologic data may help clarify this issue, but these data will not be available during the current review cycle. Hence, at present, there is concern that the 3TC oral solution dose may need to be adjusted, but there are insufficient data to identify and verify an alternative dose. This does not affect the approvability of the current submission, because this observation is independent of the dosing interval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

A postmarketing requirement will be issued to obtain complete virologic data from the ARROW trial, including resistance information. These data were not available during the current review cycle due to logistical challenges.

At the time this review was finalized, the review team was considering (b) (4)

2 Introduction and Regulatory Background

2.1 Product Information

ABC and 3TC belong to the nucleoside reverse transcriptase inhibitor (NRTI) class of antiretroviral drugs. Both drugs have been approved and marketed as single drug entities for over 15 years in the United States and around the world and have been used extensively for the treatment of adults and children with HIV-1 infection. ABC and 3TC are also available in the fixed-dose combination tablet EPZICOM, which is approved and marketed for the treatment of HIV-1 infection in adults. Pediatric formulations of EPZICOM have not been developed.

The Department of Health and Human Services HIV Treatment Guidelines include both ABC and 3TC as first-line treatment options for pediatric patients, in combination with other antiretroviral medications [1]. Both drugs are considered safe and well-tolerated across all pediatric populations. Of note, 3TC has a low barrier to resistance, so optimal dosing is critical to treatment success.

2.2 Tables of Currently Available Treatments for Proposed Indications

Many antiretroviral medications are available for pediatric use, though not all drugs are indicated for the entire pediatric age range. The currently approved drugs are listed in Table 1, organized by antiretroviral (ARV) drug class.

Table 1: ARVs Approved for Pediatric Use in the United States

Brand Name	Generic Name	Pediatric Use Labeling
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Combivir	ZDV and 3TC	**> 12 yr**
Emtriva	emtricitabine (FTC)	**≥ 0-3 months:**
Epivir	lamivudine (3TC)	**≥ 3 months**
Retrovir	zidovudine (ZDV), azidothymidine (AZT)	**Birth**
Truvada	TDF and 3TC	**>12 years**
Videx EC	didanosine (ddI)	**≥ 6 years**
Videx	didanosine (ddI)	**≥ 2 weeks**
Viread	tenofovir disoproxil fumarate (TDF)	**≥ 2 years**
Zerit	stavudine (d4T)	**Birth**
Ziagen	abacavir (ABC)	**≥ 3 months**
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Intelence	etravirine (ETV)	**≥ 3 years**
Sustiva	efavirenz (EFV)	**>3 months**
Viramune	nevirapine (NVP)	**≥ 15 days**
Viramune XR	nevirapine (NVP extended release)	**≥ 6 years**
Protease Inhibitors (PIs)		
Aptivus	tipranavir (TPV)	**≥ 2 years**
Kaletra	lopinavir and ritonavir (LPV/r)	**≥ 14 days**
Lexiva	fosamprenavir (FPV)	**≥ 4 Weeks**
Norvir	ritonavir (RTV)	**>1 month**
Prezista	darunavir (DRV)	**≥ 3 years**
Reyataz	atazanavir (ATV)	**≥ 3 months**
Viracept	nelfinavir (NFV)	**≥ 2 years**
Fusion Inhibitors		
Fuzeon	enfuvirtide, T-20 (ENF)	**≥ 6 years**
HIV integrase strand transfer inhibitors (INSTI)		
Isentress	raltegravir (RAL)	**≥ 4 weeks**

Tivicay	dolutegravir (DTG)	**≥ 12 years**
Fixed Dose Combinations Providing Complete Regimen		
Atripla	EFV, FTC, and TDF	**≥ 12 years**

2.3 Availability of Proposed Active Ingredient in the United States

Both ABC and 3TC are readily available in solid (tablet) and liquid (solution) dosage forms in the United States. ABC and 3TC are also co-formulated and marketed as EPZICOM in the United States. This fixed-dose combination tablet is also marketed under the name KIVEXA.

2.4 Important Safety Issues With Consideration to Related Drugs

The prescribing information for nucleoside analogues includes a boxed warning for lactic acidosis and severe hepatomegaly with steatosis. Sudden discontinuation of NRTIs that are active against Hepatitis B Virus (HBV), including lamivudine, may lead to exacerbations of CHB in HIV/HBV co-infected patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

NDA 20564 and NDA 20596 for EPIVIR (lamivudine, 3TC) tablets and oral solution, respectively, received accelerated approval on November 17, 1995, traditional approval on April 11, 1997, and approval for once-daily administration in adults on June 24, 2002. NDA 020977 and NDA 020978 for ZIAGEN [abacavir sulfate (abacavir, ABC)] tablets and oral solution, respectively, received accelerated approval on December 17, 1998, traditional approval on April 15, 2004, and approval for once-daily administration in adults on August 2, 2004. The approval of once-daily dosing of ABC in adults resulted in issuance of Pediatric Research Equity Act (PREA) Post-Marketing Requirements (PMR) for a deferred pediatric study for the treatment of HIV-1 infection in pediatric patients ages 3 months to 17 years [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 several pharmacokinetic studies. However, DAVP became aware of the ARROW study, which was sponsored by the Medical Research Council, through publications and presentations at scientific meetings. Though the ARROW study was not being conducted for regulatory purposes, the Division felt that this large pediatric study would provide valuable safety and efficacy data to complement the pharmacokinetic studies. Hence, the Agency issued a PREA PMR Not Fulfilled letter on July 20, 2011 and requested submission of a pediatric efficacy supplement containing the following:

- Pharmacokinetic, safety and activity data, in the format appropriate for FDA review, from the ARROW Study
- Final study report for PENTA 15

- Inclusion of the results from PENTA 13 in the labeling
- Abacavir and lamivudine population pharmacokinetic analysis data evaluating once daily dosing in the appropriate formats to enable the FDA to recreate the modeling and simulation

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 formatting 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 Medical Research Council (MRC). Since the data were owned by the MRC rather than the Applicant, and because 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 and allow more time for the Applicant to compile a complete, reviewable sNDA submission.

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submission were adequate. From a clinical review perspective, the submission was well organized and reasonable to navigate.

3.2 Compliance with Good Clinical Practices

The ARROW study was conducted in accordance with recognized international scientific and ethical standards, including, but not limited to, the International Conference on Harmonization guideline for Good Clinical Practice and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 and the European Community Directive 2001/20/EC.

An independent Data Monitoring Committee (DMC) was established and monitored all aspects of the trial, including all 4 randomizations. The DMC reported to the ARROW Trial Steering Committee and to the Ethics Committee in each country.

3.3 Financial Disclosures

(b

Three primary studies were submitted in support of this efficacy supplement, none of which were sponsored or conducted by ViiV Healthcare or GlaxoSmithKline (GSK). The ARROW study (COL105677) was sponsored by the Medical Research Council Clinical Trials Unit. PENTA-13 (EPV40002) and PENTA-15 (COL104929) were sponsored by the Paediatric European Network for the Treatment of AIDS (PENTA). ViiV and GSK relied upon questionnaires to collect financial interest information from the study investigators.

None of the investigators received significant payments of other sorts [21 CFR 54.4(a) (3) (ii), 54.2(f)], had a proprietary interest in the tested product (21 CFR 54.4(a) (3) (iii), 54.2(c)), received compensation potentially affected by the outcome of the covered study (21CFR 54.4(a)(3)(i),54.2(a)), or served as current or former ViiV/GSK employees. Please see Section 9.4 for full investigator financial disclosure information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This submission did not include CMC-related issues. The ABC and 3TC formulations used in this trial were the same as the commercially available formulations marketed in the United States.

4.2 Clinical Microbiology

The Applicant was unable to obtain resistance data for the ARROW study during the current review cycle. In a communication dated June 11, 2014, ViiV reported that the ARROW sponsor (MRC) had 202 sequences and 16 failures from subjects treated at sites in Uganda. They indicated that there were 92 additional sequences from Uganda that may or may not be available due to limited sample volumes. In addition, there were 76 samples from subjects treated at the site in Zimbabwe. These samples had to be shipped to Uganda for analysis due to lack of accreditation of the local lab. The Applicant anticipates that the samples will be run and the data analyzed by Spring 2015. A post-marketing requirement will be issued to request submission of resistance data.

Please see Dr. Lalji Mishra's review for further details.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical data were not submitted with this efficacy supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

ABC and 3TC are nucleoside analogues that exert antiviral activity by inhibiting HIV-1 reverse transcriptase. The drugs are incorporated into the growing viral DNA strand, thereby leading to premature chain termination.

4.4.2 Pharmacodynamics

Pharmacodynamic studies were not performed for this efficacy supplement.

4.4.3 Pharmacokinetics

Several pharmacokinetic (PK) studies were included in this application, including 2 ARROW PK substudies and PENTA studies 13 and 15. Analysis of the ARROW study data demonstrates mean AUC_{0-24} values that 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 in WHO weight bands compared to the US prescribing information.

The most notable finding in both the ARROW PK study and PENTA-13 was lower 3TC exposure among young subjects who received the solution formulation. This finding was not entirely surprising, as prior studies have also demonstrated that treatment with 3TC solution yielded lower AUC than treatment with tablets, which generates an AUC comparable to adults. The clinical implications of this finding will be discussed in Sections 6.1.7 and 6.1.8 of this review. Please see Dr. Su-Young Choi's clinical pharmacology review for further details regarding pharmacokinetic analyses, and Dr. Fang Li's review for pharmacometric analyses.

5 Sources of Clinical Data

Randomization 3 of the ARROW study provided pivotal efficacy data for this submission. The ARROW PK substudies, PENTA-13, and PENTA-15 provided supportive PK data. Study reports from 2 PACTG studies were also submitted as supportive pharmacokinetic evidence for ABC.

5.1 Tables of Studies/Clinical Trials

Table 2: Summary of Studies

Study Identifier	Study Objective	Study Design	Study Population	Treatment Regimen	Total Subjects
Pivotal Safety and Efficacy for ABC and 3TC					
ARROW, Randomization 3 (COL105677)	To determine whether changing from twice-daily (BID) ABC+3TC to once-daily (QD) ABC+3TC after 36 weeks on ART will have a similar outcome in terms of virologic suppression.	Open label, multicenter, randomized, parallel group with 2 randomizations at enrollment and 2 randomizations after enrollment	Age 3 months to ≤ 17 years; HIV-infected, ART-naïve at ARROW enrollment but with a minimum of 36 weeks of ART in the ARROW study	ABC: Solution: 8 mg/kg BID or 16 mg/kg QD Tablet: Per WHO weight band dosing guidelines 3TC: Solution: 4 mg/kg BID or 8 mg/kg QD Tablet: Per WHO weight band dosing guidelines	BID: 333 randomized 326 completed QD: 336 randomized 331 completed
Supportive Pharmacokinetic Studies for ABC and 3TC					
ARROW PK Substudy Part 1 (COL105677)	To describe and compare plasma PK of BID vs. QD dosing of ABC and 3TC scored tablets in HIV-infected children	Single sequence, 2 period, open label PK on last day of BID dosing and 4 weeks after switch to QD dosing	Children ages 3 years to ≤ 12 years who are participating in ARROW	Dosing per ARROW protocol	41 entered and completed Evaluable: ABC: 36 3TC: 35
ARROW PK Substudy Part 2 (COL105677)	To describe the plasma PK of 3TC and ABC when used as liquids vs. scored tablets in young HIV infected children	Single sequence, 2 period, open label crossover. PK on last day of solution dosing and 4 weeks after switch to solid formulation	Children weighing 12 to 15 kg who began dosing with solution and are transitioning to tablet	Dosing per ARROW protocol	28 entered and completed Evaluable: ABC: 19 3TC: 19
PENTA 13 (EPV40002)	Comparison of the PK of BID vs. QD 3TC and ABC as part of combination ART in children with HIV infection	Single sequence, 2 period, open label, crossover. PK on last day of BID dosing and 4 weeks after switch to QD dosing	HIV-infected children ages 2 to <13 years	ABC: 8 mg/kg BID or 16 mg/kg QD (max total daily dose 600 mg) 3TC: 4 mg/kg BID or 8 mg/kg QD (max total daily	24 entered and completed Evaluable: ABC: 14 3TC: 19

				dose 300 mg)	
PENTA 15 (COL 104929)	To compare plasma PK parameters of QD vs. BID dosing of ABC in HIV-1 infected infants and children aged 3 months to <36 months	Single sequence, 2 period, open label, crossover. PK on last day of BID dosing and 4 weeks after switch to QD dosing	HIV-infected children ages 3 to <36 months	ABC: 8 mg/kg BID or 16 mg/kg QD (max total daily dose 600 mg) 3TC: 4 mg/kg BID or 8 mg/kg QD (max total daily dose 300 mg)	23 entered and completed Evaluable: ABC: 18 3TC: 17
Supportive Pharmacokinetic Studies for ABC					
PACTG 1052	Determine ABC PK parameters in HIV-infected adolescents and young adults	Single sequence, 1 period, open label, parallel	HIV–infected children and young adults ages 13 to 25 years	Single dose of 300mg ABC tablet	30 entered and completed
PACTG 1018	Describe PK parameters of ABC given as single oral dose to children and adolescents stratified based on Tanner Stage	Single dose, 1 period, open label, parallel	HIV-infected children ages 9 to 18 years, stratified by Tanner stage	Single dose of ABC oral solution, 8 mg/kg (max 600 mg)	25 entered and completed

5.2 Review Strategy

The clinical review for this efficacy supplement was focused on data from Randomization 3 of the ARROW study. All safety analyses presented in Section 7 of this review were performed by the clinical reviewer using JReview and/or JMP 9.0 software. The datasets from PENTA 13 and PENTA 15 were reviewed, but due to the small size and limited safety and efficacy data from these studies, the results were not integrated with the ARROW data and will not be presented in this review. The efficacy review was conducted in collaboration with Dr. Fraser Smith, the primary statistical reviewer.

5.3 Discussion of Individual Studies/Clinical Trials

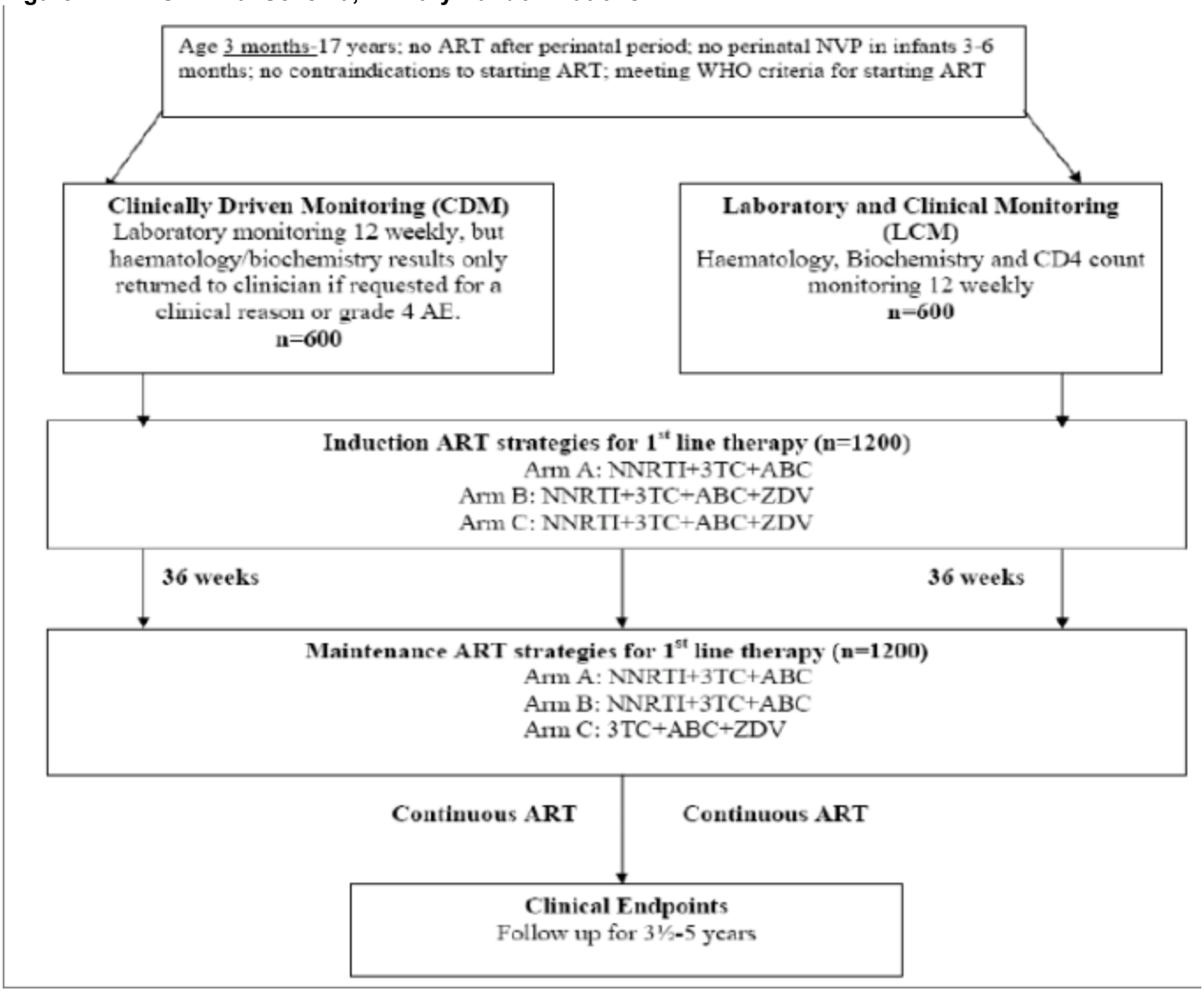
AntiRetroviral Research fOr Watoto (ARROW):
Randomization 3 of the ARROW study provides pivotal safety and efficacy data for this efficacy supplement. The study was sponsored by the Medical Research Council (UK) and was not conducted for regulatory purposes, but rather to help develop best practices for antiretroviral (ARV) management in resource-poor settings. ViiV Healthcare and GSK provided study medications, but were otherwise not involved in the design, conduct, or initial data analyses for the study.

ARROW was designed as a pediatric corollary to the Development of AntiRetroviral Therapy in Africa (DART) study, which was conducted to determine whether antiretroviral therapy (ART) could be given safely with clinical monitoring alone, in the absence of regular CD4 measurements and laboratory monitoring for toxicity. The DART study enrolled 3,316 subjects at 3 sites in Uganda and Zimbabwe between 2003 and 2009. DART found no benefits from routine toxicity monitoring on any outcome, and a small, but significant benefit from routine CD4 monitoring on 5 year survival (87% without versus 90% with CD4 monitoring. DART therefore demonstrated that ART could be safely implemented in lower level health centers [2].

The primary goals of the ARROW study were to determine whether a similar streamlined approach to treatment and monitoring could be safely performed in the pediatric population. ARROW was an open-label randomized trial primarily evaluating two strategic approaches for management of ART. The first strategy (Randomization 1) compares clinically driven monitoring (CDM) with laboratory plus clinical monitoring (LCM). The second approach (Randomization 2) compares a 3-drug 2-class first line ART regimen comprised of 2 NRTIs plus 1 NNRTI with an induction-maintenance approach that begins with a 4-drug 2-class regimen followed by maintenance with 3 drugs (1 or 2 classes). After at least 36 and 96 weeks on ART respectively, two further randomizations assess simplification strategies which could improve long-term ART adherence: once versus twice daily ABC+3TC (Randomization 3) and stopping versus continuing daily cotrimoxazole prophylaxis (Randomization 4).

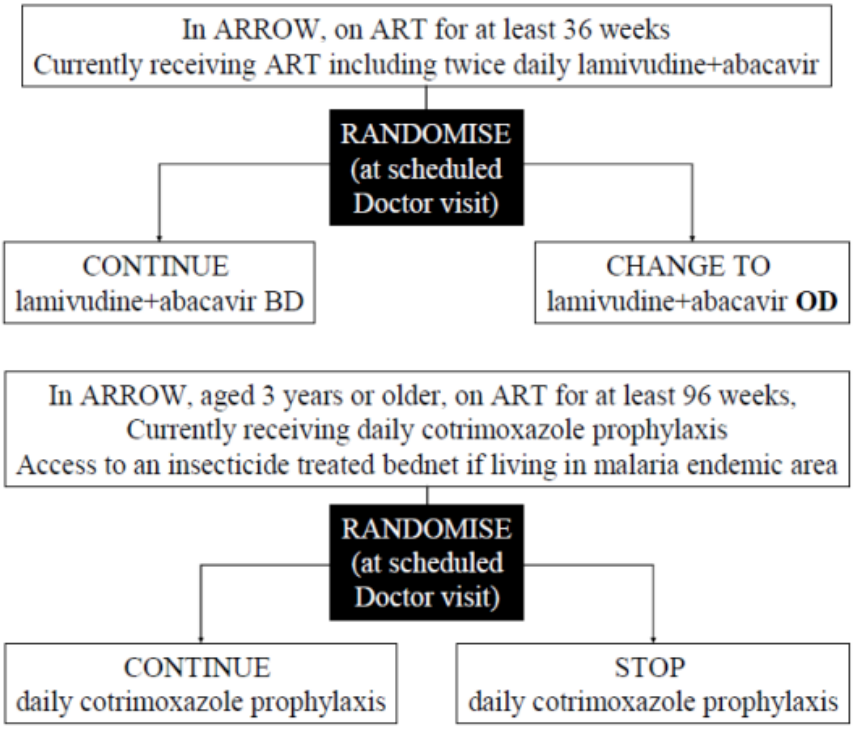
The study design is summarized in Figures 1 and 2.

Figure 1: ARROW Trial Schema, Primary Randomizations



Source: Figure 1, Clinical Study Report

Figure 2: ARROW Trial Schema, Secondary Randomizations



Source: Figure 2, Clinical Study Report

Key inclusion criteria for the ARROW study were: 1) age 3 months to 17 years; 2) confirmed documented diagnosis of HIV-1 infection; 3) ART-naïve (excluding perinatal ARV exposure for prevention of mother-to-child transmission); 4) eligible for ART according to WHO stage and CD4 percent or count. Many children were cared for by an adult who was participating or had participated in the DART trial, but this was not a requirement.

Key exclusion criteria for the ARROW study were: 1) being unable or unlikely to attend clinical appointments regularly or likely to have poor adherence; 2) presence of an acute infection; 3) receiving medication contraindicated by ART; 4) laboratory abnormalities which were a contraindication for ART; 5) pregnant or breastfeeding an infant; and 6) perinatal exposure to NVP (children aged 3 - 6 months only).

As indicated in Figures 1 and 2, all subjects underwent simultaneous randomization into Randomizations 1 and 2 at study entry. After a minimum of 36 weeks of ART, subjects were eligible to participate in Randomization 3, in which they were randomized to continue on twice-daily (BID) ABC+3TC or transition to once-daily (QD) ABC+3TC, in combination with either ZDV or an NNRTI (per Randomization 2). The third drug

continued to be dosed at the same frequency after randomization, regardless of whether the subject was receiving BID or QD ABC+3TC (e.g.: ZDV and NVP were dosed BID and EFV was dosed QD). Virologic suppression was not a requirement for participation in Randomization 3.

> **Medical Officer Comment:** ARROW Randomization 3 was designed as a "switch study," which means that all subjects begin on the same ART regimen and are subsequently randomized to continue on the initial regimen or transition to a new regimen (different drugs, dosing interval etc.). DAVP typically recommends that all subjects in a switch study are virologically suppressed at the time of the switch, especially when evaluating transitions to less intensive regimens. This strategy was not followed in ARROW Randomization 3, but since the study was designed and conducted at a time when there was less regulatory guidance for switch studies, it is acceptable for this submission.

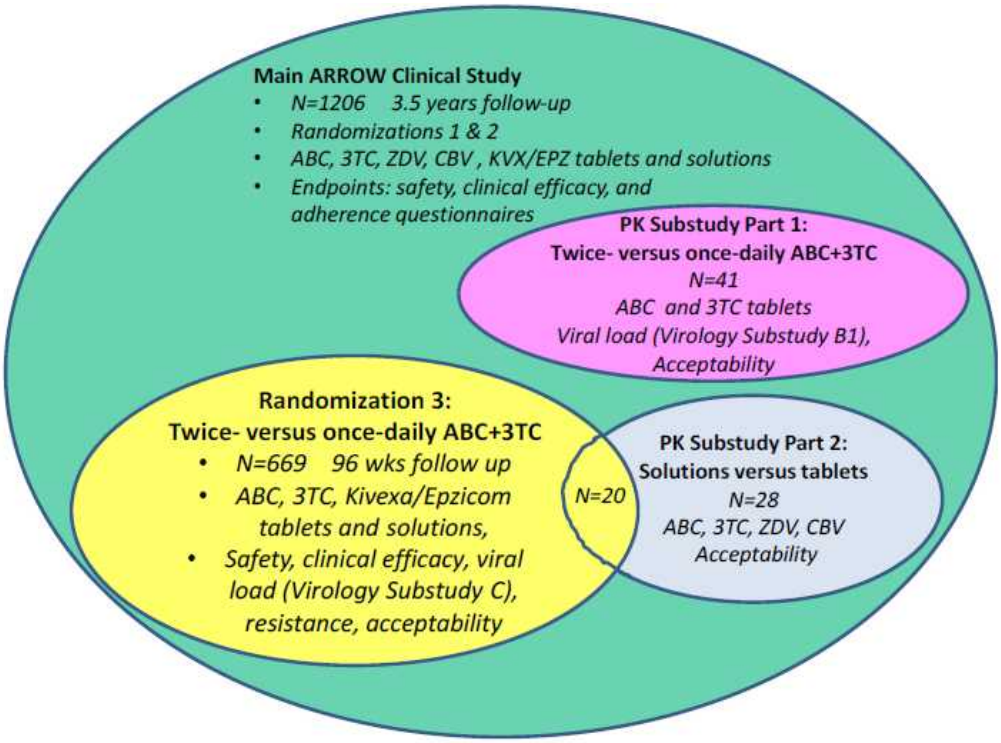
The data from Randomization 3 are the focus of this review. For the remainder of this review, the beginning of Randomization 3 will be referred to as "baseline" or "Week 0." The primary efficacy endpoint was HIV-1 viral load at 48 weeks post randomization 3 baseline, which is referred to as "Week 48." Samples collected at Weeks 0, 48 and 96 were assayed retrospectively in the Virology Substudy (Part C). As such, no plasma HIV-1 RNA was assayed in real-time. The primary safety endpoint was the occurrence of Grade 3 or 4 adverse events that were not considered solely HIV-related and definitely, probably or uncertainly related to ABC or 3TC.

ARROW Pharmacokinetic Substudy 1 (PK1): PK1 was a crossover study that compared the PK parameters of BID and QD dosing of ABC+3TC scored tablets in children 3 to 12 years of age. Two samples were collected. The first sample was obtained from subjects on the last day of BID dosing, and the second sample was obtained 4 weeks after transitioning to QD dosing. In addition, as part of the Virology Substudy (Part B1), plasma samples from PK 1 participants were assayed for viral load at Week 0, Week 12 and Week 48 after switching to QD dosing. Subjects who participated in this study were NOT participating in Randomization 3.

ARROW Pharmacokinetic Substudy 2 (PK2): PK2 was a crossover study that compared the PK parameters of solution and tablet formulations of ABC, 3TC, and ZDV in children weighing 12-15 kg who were ready to transition from the liquid to solid formulation. All subjects received BID dosing with both solution and tablet formulations. The first sample was obtained from subjects on the last day of dosing with solution and the second sample was obtained 4 weeks after transitioning to tablets. Participation in Randomization 3 was permitted but not required.

A graphical representation of the relationship between these 3 components of the ARROW study is provided in Figure 3.

Figure 3: ARROW Study Populations



3TC = lamivudine; ABC = abacavir sulfate; ARROW = AntiRetroviral Research fOr Watoto; CBV = COMBIVIR; KVX/EPZ = KIVEXA or EPZICOM; PK = pharmacokinetic; wks = weeks; ZDV = zidovudine.
Note: Subjects in the PK Substudy Part 1 were permitted to remain on once-daily dosing after the second PK day.
Note: The other 3 fully powered randomizations included comparisons of strategies for monitoring, 4- versus 3-drug induction maintenance medication regimens, and continued versus stopping cotrimoxazole prophylaxis.

Source: Module 2.5 Clinical Overview, Page 10

PENTA 13 was reviewed in 2005 by Dr. Andreas Pikis, Medical Officer, and both **PENTA 13 and 15** were reviewed during this review cycle by Dr. Su-Young Choi, Clinical Pharmacology Reviewer. Please see their respective reviews for a description of the studies.

6 Review of Efficacy

Efficacy Summary

The results from ARROW Randomization 3 demonstrate 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. No differences in efficacy were observed between once-daily and twice-daily dosing among various subgroups based on demographic factors or primary ARROW randomization.

Subjects who were treated with solution had lower rates of virologic success compared to those who were treated with tablets. This finding is independent of QD versus BID dosing because the difference in response rate had already occurred at the beginning of Randomization 3 and did not change during the 96 week study period. A lower 3TC exposure was also observed in children treated with solutions, but a direct causative relationship between lower 3TC exposure and lower rates of virologic success cannot be established.

6.1 Indication

ABC and 3TC are currently approved for twice-daily dosing for the treatment of HIV-1 infection in children. With this supplement, the Sponsor proposes to change the dosing regimen to permit once daily or twice daily dosing, with no change to the total daily dose.

6.1.1 Methods

The primary efficacy analyses are based upon efficacy data from Randomization 3 of the ARROW study and were analyzed by the clinical reviewer using JReview software. All children who were randomized and received at least one dose of study medication were included in the ITT population. Overall efficacy was confirmed by Dr. Fraser Smith, and additional analyses are available in his biometrics review.

6.1.2 Demographics

A total of 1,206 subjects were enrolled and treated in the ARROW study in Randomizations 1 and 2, of which 732 were eligible to participate in Randomization 3. Of those, 669 subjects consented to participate and were randomized: 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 at baseline for Randomization 3 (Table 3). Randomization between the two

study groups was also well balanced by primary randomizations, study site, and drug formulation.

Table 3: Demographic and Disease Characteristics at Baseline for Randomization 3

	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) (Subjects ≥ 5 yrs of age)		
	836 (558 to 1,131)	760 (543 to 1,136)
Randomization 1: Monitoring Group n (%)		
Laboratory and Clinical Monitoring (LCM)	159 (24)	163 (24)
Clinically Driven Monitoring (CDM)	174 (26)	173 (26)
Randomization 2: Initial ART Regimen n (%)		
Arm A: ABC+3TC+NNRTI	105 (16)	105 (16)
Arm B: ABC+3TC+NNRTI+ZDV x 36 wks → ABC+3TC+NNRTI	118 (18)	120 (18)
Arm C: ABC+3TC+NNRTI+ZDV x 36 wks → ABC+3TC+ZDV	110 (16)	111 (17)
NNRTI n (%)		
Nevirapine	171 (51)	148 (44)

Efavirenz	49 (15)	73 (22)
Study Site n (%)		
Entebbe	65 (10)	65 (10)
JCRC	74 (11)	77 (12)
Harare	87 (13)	87 (13)
PIDC	107 (16)	107 (16)
Drug Formulation n (%)		
Any Liquid	26 (8)	30 (9)
All Tablets	307 (92)	306 (91)

Source: Clinical Study Report, Section 5.4

Medical Officer Comment: The two treatment groups are reasonably well balanced with respect to baseline characteristics. However, there was some imbalance with respect to the NNRTI received, with more subjects in the BID arm receiving nevirapine and more subjects in the QD arm receiving efavirenz. Data regarding disease characteristics at ARROW baseline are limited, but seem to be balanced at the initiation of Randomization 3.

6.1.3 Subject Disposition

There was a high rate of subject retention in the study, with all 669 subjects completing study through the first 48 weeks (primary endpoint). This trend continued well beyond the first 48 weeks, with 664/669 subjects (99%) continuing at Week 96. Reasons for discontinuation by Week 96 are summarized in Table 4.

Table 4: Subject Disposition at Week 96

	BID Dosing(n=333) N (%)	**QD (n=336)** N (%)
Remained on Study	330 (99)	334 (99)
Discontinued	3 (1)	2 (< 1)
Death	3 (1)	1 (< 1)
Other Reasons	0 (0)	1 (<1)

6.1.4 Analysis of Primary Endpoint(s)

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. Hence, virologic suppression is defined as HIV-1 RNA PCR < 80 copies/ml. The analysis was performed using the FDA snapshot algorithm (Table 5). Efficacy at Week 96 (a secondary endpoint) is also presented in Table 5 for the purpose of comparison. The study was powered for a pre-specified non-inferiority margin of 12%.

Table 5: Virologic Status at 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 and 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 and 95% CI			+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 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)
Discontinued due to other reasons	N/A		0	0	0	1 (<1)

Source: Analysis of Week 48 and Week 96 data was performed by Dr. Fraser Smith. Baseline results were obtained from the Clinical Study Report.

*Baseline= beginning of Randomization 3 and is equivalent to Week 0. Weeks 48 and Weeks 96 are counted from Randomization 3 baseline.

Medical Officer Comment: The results demonstrate that QD dosing is non-inferior to BID dosing using the pre-specified 12% NI margin. This finding is also consistent with the results from the adult studies of QD 3TC and ABC.

6.1.5 Analysis of Secondary Endpoints(s)

Two secondary efficacy endpoints were assessed:
1. HIV RNA viral load at 96 weeks after randomization (measured retrospectively):

The percentage of subjects who were virologically suppressed at Week 96 post-randomization was similar between the BID and QD groups, as demonstrated in Table 5. Both groups saw modest declines in efficacy over time at similar rates.

2. Change in CD4 percentage and cell counts at 48 and 96 weeks after randomization:

   The BID and QD groups experienced modest increases in CD4 percentage at Week 48 and Week 96. Relative to baseline, the BID group gained 1.3% at Week 48 and 2.5% at Week 96, while the QD group gained 0.9% at Week 48 at 1.6% at Week 96. The difference between groups was not statistically significant. Change in CD4 cell count was only assessed in subjects 5 years and older, as the absolute cell count is not informative in younger children. Subjects in the BID cohort had a mean loss of 3 cells at Week 48 and mean gain of 60 cells at Week 96. Subjects in the QD cohort had a mean gain of 4 cells at Week 48 and a mean loss of 26 cells at Week 96. The difference between groups was not statistically significant.

   Medical Officer Comment: The results of the secondary endpoint analyses are as expected. At the onset of Randomization 3, subjects had already received a median 1.8 years of ART and experienced substantial gains in CD4 percentage during that period of time, such that the median CD4 percentage and cell counts were in the normal range at Randomization 3 baseline: 33%, 836 cells in the BID group and 33%, 760 cells in the QD group.

6.1.6 Other Endpoints

Additional efficacy endpoints were not assessed.

6.1.7 Subpopulations

A number of subgroup analyses were performed on the primary efficacy endpoint to identify differences in response rates between the BID and QD dosing cohorts based on demographic factors and primary ARROW trial randomizations. No significant differences in response rates were identified between BID and QD dosing for any factor. Table 6 provides a summary of risk differences between the 2 dosing cohorts at 48 and 96 weeks when adjusted for various demographic factors. Table 7 summarizes the results based on primary ARROW randomizations.

Table 6: Sensitivity Analyses of Risk Differences Based on Demographic Factors

Outcome	Week 48		Week 96	
	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)	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%)	
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 (kg) (<14, 14 to 21, >21 to <30, 30+)	-3.5% (-10% to +3%)		-2.6% (-10% to +4%)	
WHO Weight Band (kg) (<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%)	

Source: Statistics Review by Dr. Fraser Smith
[a]MH Risk Difference and 95% CI

Table 7: Primary Efficacy Outcome by Primary ARROW Randomizations

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)
Randomization 1				
Laboratory + Clinical Monitoring	73% (116/159)	72% (118/163)	69% (110/159)	71% (115/163)
Clinically Driven Monitoring	72% (126/174)	68% (118/173)	71% (124/174)	66% (115/173)
Randomization 2				
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)

Medical Officer Comment: Subgroup analyses demonstrate similar rates of efficacy between BID and QD groups in nearly every population considered. The only exception is Randomization 2, Cohort C, in which the response rates in the QD group are notably lower than the BID group. The overall response rate in this group is lower, which is consistent with data from other studies. Hence, triple NRTI regimens are no longer recommended in any region of the world.

The study cohort was racially homogenous, so differences in racial groups could not be assessed. Response rates based on HIV viral load at ART initiation could also not be assessed because these data were unavailable, but response based on viral load at Randomization 3 baseline revealed no difference between the QD and BID cohorts.

Age

Populations that are not well represented in Randomization 3 are infants and adolescents. Infants as young as 3 months were recruited into the primary ARROW randomizations, but given the minimum duration of 36 weeks of ART for Randomization 3 eligibility, and the fact that the majority of subjects had been on treatment for much

longer than 36 weeks before beginning Randomization 3, infants under one year of age are not represented in this population. Only four children under 2 years of age were included, the youngest of whom was 1 year 9 months old at randomization. Efficacy in this population is based upon pharmacokinetic data from PENTA 15 which demonstrate matching drug exposures to adults.

Many of the adolescents enrolled in ARROW were ineligible to participate in Randomization 3 because they had already been receiving the ABC+3TC fixed-dose combination tablet (EPZICOM or KIVEXA) once daily during the primary randomizations. There were a total of 22 subjects who were at least 12 years of age at study entry, of which 8 were in the BID group and 14 were in the QD group. Thirteen of the 22 subjects were between 12 and 13 years of age, and the remaining 9 were 13-16 years old: 4 in the BID arm and 5 in the QD arm.

> **Medical Officer Comment:** The efficacy of a once-daily regimen for adolescents is adequately supported by the data in this supplement, and the historical knowledge that adolescents' response to ART is similar to that in adults. The lack of data in infants is more problematic, given the lower rates of efficacy observed in children receiving solution formulations of ARVs. This issue will be further discussed below.

Formulation Effect

Additional analyses were performed to identify groups with lower rates of efficacy within the study, irrespective of randomization to the BID or QD group. The most notable finding was a lower rate of virologic suppression among children who received solution formulations. The difference in response rate occurred during the primary randomizations and remained relatively unchanged during Randomization 3: 29/56 children (52%) who received solutions were suppressed at baseline and 31/56 (55%) were suppressed at Week 48; in contrast, 458/613 children (75%) who received tablets were suppressed at baseline and 447/613 children (73%) were suppressed at Week 48. Hence, this finding is not influenced by dosing interval (BID versus QD dosing). These results are summarized in Table 8.

Table 8: Analysis of the Impact of ARV Formulation on Virologic Suppression

HIV1 RNA < 80 c/mL	BID Dosing (n=333)		QD Dosing (n=336)	
	Solution N=26	Tablet N=307	Solution N=30	Tablet N=305
Mean Age (year)	2.9	6.3	2.9	6.8
Week 0 N (%)	14 (53.9%)	236 (76.9%)	15 (50%)	222 (72.8%)
Week 48 N (%)	14 (53.9%)	229 (74.6%)	17 (56.7%)	223 (73.1%)
Week 96 N (%)	13 (50%)	222 (72.3%)	17 (56.7%)	213 (69.8%)

Source: Analysis Performed by Dr. Fang Li, Pharmacometrics Reviewer

The reason for this finding is unclear but likely multifactorial. One factor that was discussed extensively by the review team was the impact of lower 3TC exposures on efficacy. There has been documented evidence that young children attain lower 3TC exposures than adults in a number of studies, including PENTA-13, NUCA2002, and NUCA2005 (Phase 1 and 2 pediatric studies). Physiologic factors such as increased drug clearance at young ages may also contribute.

There is also evidence that the solution formulation has lower bioavailability compared to tablets, as seen in IMPAACT Study P1069 and ARROW PK Substudy 2 (PK2). IMPAACT P1069 was conducted in Thailand by Chokephaibulkit *et al* and compared the fixed-dose combination tablet GPO-VIR Z30 (ZDV+3TC+NVP) with the respective oral solutions [3]. This study demonstrated that AUC_{0-12} was comparable between the two formulations for ZDV, lower for 3TC, and higher for NVP. In addition, AUC_{0-12} was lower than the adult historical control for both 3TC and NVP. The results of PK Substudy 2, which was a cross-over study of children who were started on solutions and transitioned to tablets, demonstrated lower 3TC exposures with the solution than with tablets, while exposures were equivalent for ZDV and ABC [4]. Some but not all subjects who participated in PK2 also participated in Randomization 3. Key findings from PK2 are summarized in Table 9.

Table 9: Comparison of Key Pharmacokinetic Parameters of Solution and Tablet Formulations in ARROW Pharmacokinetic Substudy 2

Dose-normalized Geometric Mean Ratio (90% CI) of Tablet: Solution	3TC (N=19)	ABC (N=19)	ZDV (N=19)
$AUC_{0\text{-}12}$, mg·h/l	1.58 (1.37, 1.81)	0.96 (0.83, 1.12)	1.01 (0.87, 1.18)
C_{max}, mg/l	1.55 (1.33, 1.81)	1.02 (0.89, 1.17)	1.07 (0.92, 1.25)
C_{min}, mg/l	1.29 (1.00, 1.66)	0.92 (0.62, 1.37)	1.10 (0.86, 1.41)
CL/F/kg, l/h/kg	0.63 (0.55, 0.72)	1.04 (0.89, 1.20)	0.94 (0.82, 1.08)

Source: Kasirye *et al* Table 2

Medical Officer Comment: There is a growing body of evidence that 3TC solution is not bioequivalent to 3TC tablets for young children, but the clinical consequences of this finding remain unclear. The ARROW study suggests that lower exposures may confer a lower probability of treatment success. However, other factors may also be contributing, such as lower adherence or imbalances in baseline viral load at study initiation.

An information request was sent to ViiV on November 12, 2014 to seek the company's impression on why subjects dosed with solution had poorer outcomes than those dosed with tablets.

In the ARROW study, subjects who received lamivudine oral solution had a significantly lower response rate (HIV-1 RNA ≤ 80 copies) than subjects who received lamivudine tablets. The difference in response rate was evident at the beginning of Randomization 3: 51.8% (29/56) of oral solution subjects were suppressed, compared to 74.8% (458/612) of subjects who received tablets. The treatment difference was maintained over the course of Randomization 3: at Week 48 of Randomization 3, 55.4% (31/56) of oral solution subjects were suppressed compared to 73.9% (452/612) of subjects who received tablets. The response rate does not appear to be affected by twice daily versus once daily dosing.

The Agency is interested in understanding whether specific factors, including the lower exposure of lamivudine, baseline HIV-1 RNA, and prior treatment experience, may have contributed to the observed lower efficacy. Historical information in the literature and ARROW PK substudy results indicate the oral solution of lamivudine is associated with lower exposure (AUC) than tablets in pediatric patients, likely due to lower bioavailability.

Please provide your interpretation of these virologic suppression observations and any data or literature supporting your interpretation.

The company responded on December 12, 2014, and identified several possible factors contributing to this observation:

- Higher viral load burden and slower viral decay in young children
- Adherence: difficulties for caregivers to accurately measure and deliver multiple drugs with oral solutions
- Treatment regimen and formulation: Subjects receiving ABC+3TC solution received ZVD or NVP as the third drug in the ART regimen, whereas children receiving tablets also had the option to receive EFV. The increased potency of EFV relative to NVP, and certainly ZDV, may be contributing
- Possible interaction with sorbitol in the NVP and ABC solutions, which may lower bioavailability of 3TC

The response concluded with the following summary:
ViiV and the ARROW Trial Team have attempted to explore and describe a range of factors which may influence antiviral response in these pediatric patients. However, it is clear that, apart from the differences in PK exposure noted here and elsewhere, there are several inextricably linked factors which may also have a role, including younger age linked to higher plasma RNA, reliance on caregivers, third drug options, and adherence difficulties. ViiV has noted a tendency in individual patient profiles that viral load may decline over time, and as the child moves from solution to tablet formulation, which will occur concurrently with increasing age and time on treatment. However, it is not possible to determine whether this is also linked to any other factor, such as the naturally lower HIV-1 levels with increased age, slower decay rate and longer time to suppression in younger patients (i.e., continued decline in viral load over time while on ART), improved adherence, or other factors. While acknowledging the lower PK exposure and lower suppression rate provided by the solution formulation compared with the tablet, it remains important to note that this does not appear to be affected by dosing frequency, whether once or twice daily.

Medical Officer Comment: Each of the factors that the company has identified could contribute to lower efficacy among subjects who receive solution. Each factor was considered independently to the extent possible given the data available, and I agree with the majority of the Applicant's conclusions. The section below will discuss the issues where my conclusion differs.

- Treatment regimen and formulation: Subjects receiving ABC+3TC solution received ZVD or NVP as the third drug in the ART regimen, whereas children receiving tablets also had the option to receive EFV. The increased potency of EFV relative to NVP, and certainly ZDV, may be contributing to the observed lower rates of efficacy. In order to explore this issue, the rates of virologic success based on regimen and formulation were explored, and summarized in Table 10.

Table 10: Proportion of Subjects with HIV-1 RNA PCR < 80 copies/ml by Regimen and Formulation

HIV-1 RNA PCR < 80 copies/ml	Baseline (Rand. 3) N(%)		Week 48 N(%)		Week 96 N(%)	
	Solution	Tablet	Solution	Tablet	Solution	Tablet
ZDV	11/24 (46%)	128/202 (63%)	12/24 (50%)	115/202 (57%)	11/24 (46%)	104/202 (51%)
NVP	18/32 (56%)	236/287 (82%)	19/32 (59%)	231/287 (80%)	19/32 (59%)	232/287 (81%)
EFV	N/A	94/122 (77%)	N/A	100/122 (82%)	N/A	97/122 (80%)

As previously noted, subjects on an NNRTI-based regimen had higher rates of virologic success than those on a triple-NRTI regimen. However, subjects treated with NVP tablets had similar rates of virologic suppression as subjects treated with EFV. Thus, the enhanced potency of EFV did not seem to confer a substantial advantage to subjects receiving tablets. This does not help clarify why subjects receiving NVP solution had lower rates of virologic suppression than those receiving tablets. The possibility of excipient effect (next bullet point) adds another confounding factor. The possibility of higher viral load among the younger children who received solutions remains a factor as well, which would require a higher potency ART regimen to bring down viral load to < 80 copies/ml in the same timeframe as those who begin with a lower viral load at baseline.

- Possible interaction with sorbitol in the NVP and ABC solutions: There has been some speculation that the sorbitol present in NVP and ABC solutions may lower the bioavailability of 3TC solution. This concept was described by Garcia-Arieta [5] who proposes that certain excipients, including sorbitol, can reduce the bioavailability of drugs that have high intestinal permeability. By way of example, he cites bioequivalence studies for risperidone which compared two generic formulations containing equal doses of the active pharmaceutical doses but different quantities of sorbitol. Both products failed to demonstrate bioequivalence with the reference listed product.

  It is difficult to determine the extent to which the presence of sorbitol may be affecting efficacy in ARROW subjects. Of the 19 subjects in PK2, only 3 were receiving concurrent NVP (the remaining were receiving ZDV), but all subjects

demonstrated lower bioavailability. However, all subjects received ABC solution, which confounds this comparison.

Medical Officer's Conclusion: ARROW subjects who were treated with solution formulations had lower rates of virologic response than those who were treated with tablets. Determination of the cause for this observation is highly confounded, but low 3TC exposure may be a contributing factor. It is unclear whether the lower exposure is due to lower bioavailability of the solution itself or in combination with other ARVs, suboptimal or incorrect dosing due to human factors, or a combination of factors. Correlation with resistance data may contribute to our understanding, but the data are unavailable during this review cycle. A postmarketing requirement to explore the effect of sorbitol on 3TC bioavailability is also being considered.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant seeks to harmonize the dosing recommendations in the US prescribing information with the WHO dose recommendations. This would not result in any changes to the solution dose, which is based on weight, but results in some adjustments in the weight band dosing for tablets. In all cases, WHO dosing results in a higher dose/weight band than the US dose. The safety implications for the higher exposure will be discussed in Section 7.

As discussed in Section 6.1.7, children who received 3TC as oral solution had lower 3TC exposures and a lower rate of virologic success than those who received a tablet formulation. This observation prompted a discussion regarding whether a higher dose of 3TC solution would be appropriate, such that the exposure obtained from 3TC solution was equivalent (or more similar to) the exposure from 3TC tablets. However, it is unclear to what extent the lower 3TC exposure is impacting the lower observed rates of virologic success.

Please see Dr. Su-Young Choi's clinical pharmacology review and Dr. Fang Li's pharmacometrics review for additional details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Week 48 and Week 96 data from the ARROW study demonstrate durability of virologic response with both QD and BID dosing of an ABC + 3TC containing regimen. Though Week 48 was the primary endpoint, Week 96 data will be included in labeling to document the durability of response.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

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 SAEs, Grade 3 or 4 AEs, or laboratory abnormalities compared to BID dosing.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review is based upon data from Randomization 3 of the ARROW study. All children who were randomized and received at least one dose of study medication were included in the safety population. The tables presented in Section 7 of this review were generated by the clinical reviewer using JReview and JMP software. There were no significant differences between the FDA analyses and the Applicant's analyses.

Safety data from PENTA 13 and PENTA 15 were also reviewed. The types of AEs reported in these small studies were consistent with the findings from ARROW and the general safety profile of ABC and 3TC. Given the small number of subjects and lack of significant findings in these studies, they will not be further discussed in this review.

7.1.2 Categorization of Adverse Events

In the ARROW study, adverse events were reported using investigator-reported terms. MedDRA terms were not used. A coding dictionary file was provided with the datasets to provide a complete listing of all reported terms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Only data from ARROW are presented in this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Dosing in the ARROW study was based upon WHO dosing guidelines, which are modestly higher in some weight bands than the US prescribing information, but similar overall. This study was conducted in Zimbabwe and Uganda, where use of WHO dosing guidelines is standard.

7.2.2 Explorations for Dose Response

Adverse event rates by weight band were assessed in order to determine whether the higher exposures resulting from WHO dosing were associated with a higher rate of adverse events. Such a relationship was not observed. Of note, this comparison is limited because the largest upward shift in dosing occurs among older/heavier subjects, which are represented in small numbers in Randomization 3.

7.2.3 Special Animal and/or In Vitro Testing

Not Applicable. New nonclinical studies were not performed.

7.2.4 Routine Clinical Testing

Subjects underwent full physical examinations 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 detect intercurrent illness or symptoms of HIV disease progression; assessment for adverse events and relationship to study medication; anthropometric measures; hematology and chemistry labs; CD4 count and percentage. Investigators received all laboratory results from 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.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known safety profiles of the ARVs used in this study were taken into consideration during the safety review.

7.3 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-limited settings. Hence, collection of adverse event (AE) data was focused on more severe events (Grade 3 and 4), and data on the occurrence of mild to moderate (Grade 1 and 2) events were not routinely collected or analyzed. 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.

7.3.1 Deaths

Five children died while on study: 4 in the BID arm and 1 in the QD arm. These cases are summarized below.

1. Subject D013022 was an (b) (6) year old boy who was randomized to the BID arm. He died from pulmonary tuberculosis on Study Day (b) (6) (Study Week (b) (6)). His HIV-1 viral load and CD4 count at Week 48 were 50,000 copies/mL and 34 cells/ml, respectively.
2. Subject F013064 was a (b) (6) y/o girl who was randomized to the BID arm. She was lost to follow up at Week 79 and died on Study Day (b) (6) (Study Week (b) (6)). Her death occurred (b) (6) following a febrile illness, but details are unavailable. She was virologically suppressed at baseline but had a viral load of 31,000 copies/mL at Week 48 and 484,280 copies/mL at Week 96. Her CD4 count and percentage at Week 84 were 469 cells/mL and 13%, respectively.
3. Subject L036175 was an (b) (6) year old boy who was randomized to the BID arm. He died from pneumonia and HIV-related cerebral disease on Study Day (b) (6) (Week (b) (6). His viral load at Week 48 was 14,000 copies/mL and his CD4 count at Week 60 was 209 cells/mL.
4. Subject L043092 was a (b) (6) year old boy who was randomized to the BID arm. He died from cor pulmonale, bronchiectasis and lymphoid interstitial pneumonia on Study Day (b) (6) (Week (b) (6) His HIV-1 viral load and CD4 percentage at Week 48 were 183,000 copies/mL and 10%, respectively.

5. Subject M036156 was a (b) (6) year old boy who was randomized to the QD arm. He died from acute pulmonary failure on Study Day (b) (6) (Week (b) (6). His viral load was < 80 copies/mL at Week 48. His CD4 count and percentage at Week 60 were 348 cells/mL and 25%, respectively.

   Medical Officer Comment: Each of the subjects in the BID arm had poor virologic control and low CD4 count/percentage, which put them at high risk of mortality from infection. In contrast, the subject in the QD arm was virologically suppressed at baseline for Randomization 3 and maintained a CD4 percentage > 25% throughout the study period. No clinical adverse events were reported and his laboratory values were within the reference range throughout the study prior to his death. Limited details are available of the events surrounding his death, but he appears to have succumbed to an acute process.

7.3.2 Nonfatal Serious Adverse Events

Collection of SAEs was limited to events that were NOT HIV-1 related, as determined by the investigator. As such, the total number of events reported does not reflect the full range of serious events that occurred during the study, and does not include the deaths reported in Section 7.3.1, which were all deemed HIV-related.

There were a similar number and type of SAEs in the BID and QD study group. A total of 3 events, all malaria, were deemed life-threatening by the study investigator: 1 case in a 4 year old subject in the BID arm and 2 cases in the QD arm in subjects ages 3 years and 6 years. None of the events were assessed as being related to study drug. The events are summarized in Table 11.

Table 11: Serious Adverse Events (Not Related to HIV)

Event name	BID Dosing N=333 N(%)	QD Dosing N=336 N(%)	Total Subjects N=669 N(%)
Total Subjects	37 (11%)	30 (9%)	669 (100%)
P falciparum malaria	25 (8%)	19 (6%)	44 (7%)
Measles	3 (1%)	1 (0%)	4 (1%)
Gastroenteritis	1 (0%)	0 (0%)	1 (0%)
Hypersensitivity reaction	1 (0%)	0 (0%)	1 (0%)
Hyperthyroidism	1 (0%)	0 (0%)	1 (0%)
Bronchiectasis	1 (0%)	0 (0%)	1 (0%)
Bone fracture	1 (0%)	0 (0%)	1 (0%)
Non-fatal trauma	1 (0%)	0 (0%)	1 (0%)
Other malaria	1 (0%)	0 (0%)	1 (0%)
Acute diarrhoea	1 (0%)	2 (1%)	3 (0%)
Pneumonia no organism	1 (0%)	2 (1%)	3 (0%)

identified			
Presumed septicaemia/bacteremia	1 (0%)	2 (1%)	3 (0%)
Psychosis, mania	1 (0%)	0 (0%)	1 (0%)
Vomiting	1 (0%)	0 (0%)	1 (0%)
Coma	0 (0%)	1 (0%)	1 (0%)
Dog bite	0 (0%)	1 (0%)	1 (0%)
Paraffin poisoning	0 (0%)	1 (0%)	1 (0%)
Anaemia with clinical symptoms	0 (0%)	3 (1%)	3 (0%)

Medical Officer Comment: The majority of events are related to infections or injuries, most notably malaria. This is not unexpected in this study setting. The occurrence of adverse events is balanced between study groups, with no suggestion that QD dosing confers a substantially higher risk of drug toxicity.

7.3.3 Dropouts and/or Discontinuations

There was a high rate of subject retention throughout the study. Children remained in Randomization 3 for a median of 114 weeks (range 48 to 134 weeks). All 669 randomized subjects completed the first 48 weeks of treatment, and 657/669 continued until the end of the study. The reasons for discontinuation of the 12 subjects who did not complete the study are summarized in Table 12.

Table 12: Discontinuations in the ARROW Study Through End of Study

Reason for Discontinuation (n)	BID Dosing (n=333)	QD Dosing (n=336)
Death	4	1
Moved from Study Site	1	1
Switched to Herbal Remedy	1	0
Withdrew, no Reason Stated	0	1
Lost to Follow-Up	1	2

No AEs were reported among the 3 children who were lost to follow-up. Hence, no subjects discontinued study due to AEs.

7.3.4 Significant Adverse Events

All Grade 3 and 4 AEs were collected, irrespective of association with study drug or underlying HIV infection. Clinical events were reported equally in both study groups, but laboratory AEs were unequally reported because investigators did not see Grade 3 laboratory abnormalities among CDM subjects (randomization 2) unless they

specifically asked for them. In order to address this reporting imbalance, the Applicant added a category to the AE analysis in the Clinical Study Report which accounted for Grade 3 and 4 laboratory abnormalities that were identified via chart review.

I was concerned that this approach could lead to duplications in reporting in some cases and lack of reporting in others. Therefore, clinical adverse events were assessed separately from laboratory AEs. Table 13 summarizes the occurrence of the clinical events, and laboratory AEs will be discussed in Section 7.4.2.

Table 13: Grade 3 and 4 Clinical Adverse Events

Adverse Event	BID Dosing N=333 N(%)	QD Dosing N=336 N(%)	Total Subjects N=669
P falciparum malaria	13 (4%)	12 (4%)	25 (4%)
Anaemia with clinical symptoms	5 (2%)	6 (2%)	11 (2%)
Measles	3 (1%)	1 (<%)	4 (1%)
Presumed septicaemia/bacteremia	3 (1%)	3 (1%)	6 (1%)
Acute diarrhoea not investigated	2 (1%)	2 (1%)	4 (1%)
Pneumonia no organism identified	2 (1%)	2 (1%)	4 (1%)
Gastroenteritis	1 (<1%)	0 (0%)	1 (<1%)
Bronchiectasis	1 (<1%)	0 (0%)	1 (<1%)
Bone fracture	1 (<1%)	0 (0%)	1 (<1%)
Psychosis, mania	1 (<1%)	0 (0%)	1 (<1%)
Febrile convulsions	1 (<1%)	0 (0%)	1 (<1%)
Bronchopneumonia	1 (<1%)	0 (0%)	1 (<1%)
Vomiting	1 (<1%)	0 (0%)	1 (<1%)
Acute febrile episode	0 (0%)	2 (1%)	2 (<1%)
Cataract	0 (0%)	1 (<1%)	1 (<1%)
Coma	0 (0%)	1 (<1%)	1 (<1%)
Dog bite	0 (0%)	1 (<1%)	1 (<1%)
Hepatitis cause unknown	0 (0%)	1 (<1%)	1 (<1%)
Paraffin poisoning	0 (0%)	1 (<1%)	1 (<1%)
Acute diarrhoea no pathogen, idiopathic AIDS enteropathy	0 (0%)	1 (<1%)	1 (<1%)

The following laboratory AEs were removed from the analysis due to the methodology of AE collection: Anemia with no clinical symptoms, hypoglycemia, hyperthyroidism, hypoglycemia, hyponatremia, leucopenia, neutropenia, raised ALT, raised AST, raised Bilirubin, raised creatinine, raised liver enzymes, thrombocytopenia

One event, "hepatitis cause unknown" was considered possibly drug-related. All other events were considered to be unrelated to study drugs.

Medical Officer Comment: No new concerns regarding drug-related toxicity have emerged and there is no significant difference in AEs between the BID and QD groups to suggest poor tolerance of QD dosing. As was the case with SAEs, the majority of AEs are due to infection or injury. Many malaria events were Grade 2 severity but required hospitalization; hence, there are more malaria SAEs than Grade 3 or 4 malaria AEs. A similar imbalance is observed in the category of "anemia with clinical symptoms": there are more Grade 3 and 4 AEs than there are SAEs, because some subjects who experienced severe symptomatic anemia did not meet criteria for an SAE.

7.3.5 Submission Specific Primary Safety Concerns

Drug-induced hypersensitivity reactions (HSR) are a concern with ABC treatment. Subjects who carry the HLA B5701 allele are at higher risk for HSR, but this phenotype is more common among Caucasians. Given that the ARROW study was conducted in an African population with low prevalence of the HLA B5701 allele, HSR reactions are expected to be infrequent. However, HSR have been reported in subjects who are HLA B5701 negative.

Only one subject experienced symptoms consistent with HSR in the ARROW study. This 12 year old girl in the BID group was receiving ABC+3TC+NVP when symptoms began, including fever, generalized skin rash, and abdominal pain. The event was considered a Grade 2 HSR related to NVP. NVP was discontinued and replaced by LPV/r. Her symptoms rapidly abated and no recurrences were reported.

Medical Officer Comment: The rapid improvement of symptoms upon cessation of NVP is consistent with a NVP-associated HSR. The fact that she improved with ongoing ABC exposure is reassuring that ABC did not contribute to the episode.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Data regarding the occurrence of Grade 1 and 2 adverse events were not collected in the ARROW study. Please refer to prior sections for a discussion of Grade 3 and 4 events.

7.4.2 Laboratory Findings

Basic chemistry and hematology labs were collected every 12 weeks. Laboratory results were reviewed for each subject to identify abnormal values which met the definitions for Grade 3 and 4 events based on the DAIDS Toxicity Grading Scale. The results are summarized in Tables 14 and 15. Neutropenia was the most commonly

observed laboratory abnormality, which is consistent with prior experience with NRTIs. There were no significant differences between the BID and QD groups.

Table 14: Grade 3 and 4 Chemistry Results

Chemistry Parameter and Toxicity Grade	BID Dosing N=333 N(%)	QD Dosing N=336 N(%)	Total Subjects N=669 N(%)
ALT Elevated			
3 (5.1 - <10 x ULN)	7 (2%)	4 (1%)	11 (2%)
4 (≥10 x ULN)	4 (1%)	4 (1%)	8 (1%)
AST Elevated			
3 (5.1 - <10 x ULN)	5 (2%)	4 (1%)	9 (1%)
4 (≥10 x ULN)	2 (1%)	6 (2%)	8 (1%)
Bilirubin Elevated			
3 (2.6 - <5 x ULN)	1 (<1%)	0 (0%)	1 (0%)
4 (≥5 x ULN)	2 (1%)	2 (1%)	4 (1%)
Creatinine Elevated			
3 (1.9 – <3.5 x ULN)	0 (0%)	0 (0%)	0 (0%)
4 (≥3.5 x ULN)	3 (1%)	1 (<1%)	4 (1%)

Table 15: Grade 3 and 4 Hematology Results

Hematology Parameter and Toxicity Grade	BID Dosing N=333 N(%)	QD Dosing N=336 N(%)	Total Subjects N=669 N(%)
Hemoglobin Decreased			
3 (6.6 – 7.7 g/dL)	8 (2%)	5 (1%)	13 (2%)
4 (≤6.5 g/dL)	3 (1%)	4 (1%)	7 (1%)
Neutrophils Decreased			
3 (0.26 – 0.5 x 10^3 cells/mL)	15 (5%)	20 (6%)	35 (5%)
4 (≤0.25 x 10^3 cells/mL)	0 (0%)	3 (1%)	3 (0%)
Leukocytes Decreased			
3 (1.1 – 1.5 x 10^3 cells/mL)	1 (<1%)	1 (<1%)	2 (<1%)
4 (≤1 x 10^3 cells/mL)	1 (<1%)	0 (0%)	1 (<1%)
Platelets Decreased			
3 (26 – 50 x 10^3 cells /mL)	4 (1%)	8 (2%)	12 (2%)
4 (≤25 x 10^3/mL)	4 (1%)	4 (1%)	8 (1%)

7.4.3 Vital Signs

Routine vital sign monitoring was not included in the clinical study protocol.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained during the study. Neither 3TC nor ABC has been found to be arrhythmogenic.

7.4.5 Special Safety Studies/Clinical Trials

Additional safety studies were not conducted, and such studies are not needed.

7.4.6 Immunogenicity

See section 7.3.5 regarding ABC-associated hypersensitivity reactions.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There is no indication of severe toxicity or intolerance when the total daily dose of ABC and 3TC is delivered once a day, rather than dividing the dose into two separate doses. The possibility of an imbalance of mild to moderate events should be considered, since information about Grade 1 and Grade 2 AEs was not collected.

7.5.2 Time Dependency for Adverse Events

Time dependency for AEs cannot be adequately assessed in the ARROW study because 1) AEs that occurred during the primary randomizations are not included in this submission and 2) only Grade 3 and 4 AEs were collected.

7.5.3 Drug-Demographic Interactions

No significant drug-demographic interactions were appreciated in this study. The occurrence of AEs was similar between age groups and gender. The racial composition of the study population is homogenous, which precludes the assessment of variation by racial group. However, prior clinical trials and post-marketing studies have not revealed any differences, with the exception of the risk of ABC hypersensitivity reactions among patients who are HLA-B5701 positive, a trait more common among Caucasians.

7.5.4 Drug-Disease Interactions

Treatment of HIV-1 infection with combination ART reduces viral load and maintains viral suppression.

7.5.5 Drug-Drug Interactions

Formal drug-drug interaction studies were not conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

New studies have not been performed and are not needed.

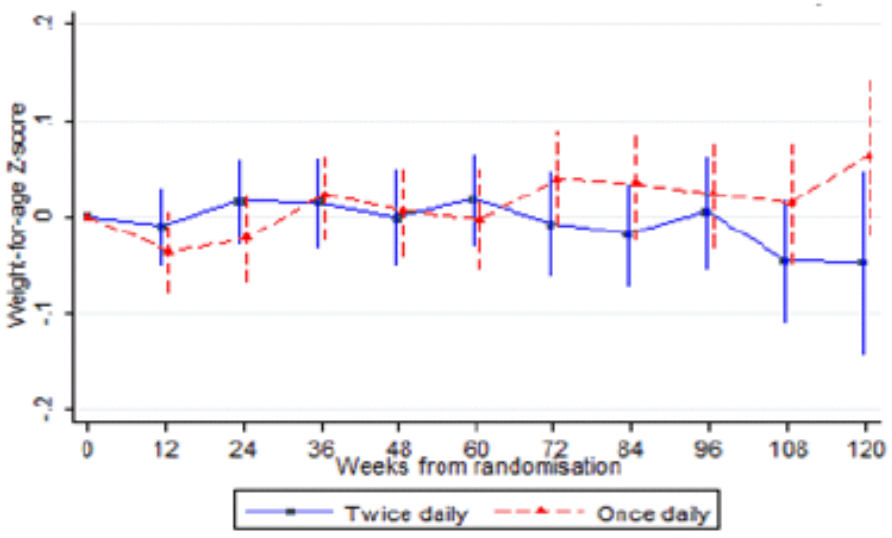
7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies among study subjects during the study period.

7.6.3 Pediatrics and Assessment of Effects on Growth

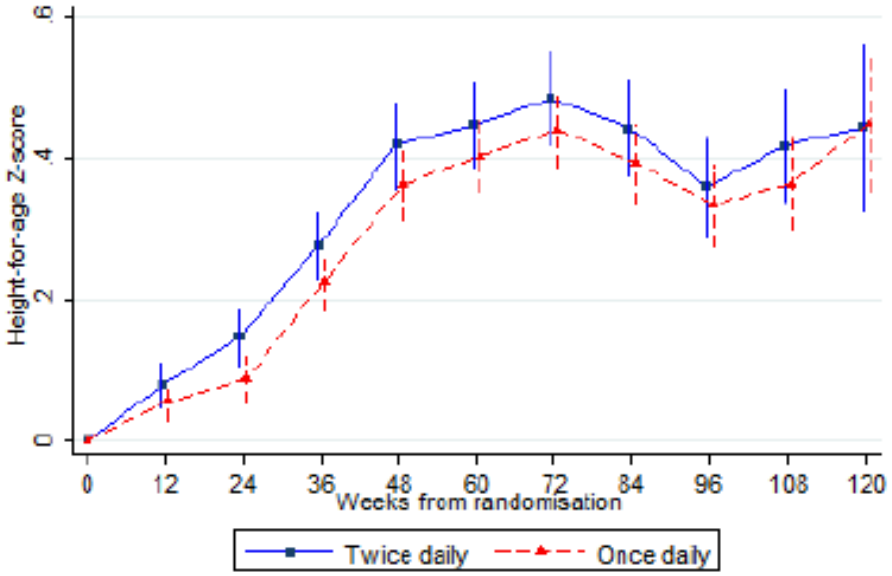
Children's height and weight were assessed every 12 weeks and Z scores were followed over time to determine whether switching from BID to QD dosing had any impact on growth. The subjects had similar growth parameters at baseline and continued to have similar growth velocities during the study period (Figures 4 and 5).

Figure 4: Mean Change (95% CI) in Weight-for-Age Z Score



Source: Figure 18, Integrated Summary of Safety

Figure 5: Mean Change (95% CI) in Height-for-Age Z Score



Source: Figure 19, Integrated Summary of Safety

Medical Officer Comment: It is likely that both groups experienced more substantial gains in height and weight from treatment initiation to the beginning of Randomization 3, which is commonly observed as a "return to health" phenomenon that accompanies reductions in HIV-1 viral load. As predicted during the maintenance stage of treatment, more modest gains in height-for-age, were observed during Randomization 3, and neither group experienced substantive gains in weight-for-age during this period. This is not surprising, as increases in weight gain velocity often precede gains in linear growth velocity.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

ABC and 3TC have a wide therapeutic window and little abuse potential. Abrupt cessation/withdrawal of 3TC could cause a hepatic flare in patients co-infected with Hepatitis B.

7.7 Additional Submissions / Safety Issues

No additional concerns.

8 Postmarket Experience

ABC and 3TC have been marketed for over 15 years and their safety profiles have been well-established. No recent changes have been made to the US prescribing information based on post-marketing reports.

9 Appendices

9.1 Literature Review/References

1. 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. Accessed January 13, 2015.

2. DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. Lancet 2010 Jan 9; 375(9709): 123 – 131.

3. Chokephaibulkit K, Cressey TR, Capparelli E, Sirisanthana V, Muresan P, Hongsiriwon S, Ngampiyaskul C, Limwongse C, Wittawatmongkol O, Aurpibul L, Kabat B, Toye M, Smith ME, Eksaengsri A, McIntosh K, Yogev R; IMPAACT P1069 Team. Pharmacokinetics and safety of a new paediatric fixed-dose combination of zidovudine/lamivudine/nevirapine in HIV-infected children. Antivir Ther. 2011;16(8):1287-95.

4. Kasirye P, Kendall L, Adkison KK, Tumusiime C, Ssenyonga M, Bakeera-Kitaka S, Nahirya-Ntege P, Mhute T, Kekitiinwa A, Snowden W, Burger DM, Gibb DM, Walker AS; ARROW Trial Team. Pharmacokinetics of antiretroviral drug varies with formulation in the target population of children with HIV-1. Clin Pharmacol Ther. 2012 Feb;91(2):272-80.

5. Garcia-Arieta A. Interactions between active pharmaceutical ingredients and excipients affecting bioavailability: impact on bioequivalence. Eur J Pharm Sci. 2014;65:89-97.

9.2 Labeling Recommendations

Since labeling discussions were ongoing at the time this review was finalized, general concepts will be discussed in this section. Changes to the ABC and 3TC labeling will be discussed together because they will be identical in nearly all instances.

Section 2. DOSAGE AND ADMINISTRATION

- Once-daily dosing guidelines will be added for tablet and solution. Due to the lower response rates among subjects receiving solutions, a phrase may be added to advise providers to consider viral load and CD4 count/percentage when determining a dosing interval at treatment initiation in subjects receiving solutions.
- Weight band dosing for the tablet formulation will be adjusted to align with the WHO dosing guidelines.
- A footnote will be added to state that the approval of once daily dosing is based on data from a switch study.

Section 6. ADVERSE REACTIONS

- A paragraph will be added stating that the occurrence of Grade 3 and 4 events was similar between the QD and BID groups.

Section 14. CLINICAL STUDIES

- The design of the ARROW study will be described in detail to inform providers about how Randomization 3 fits into the overall study design.
- Week 96 efficacy data will be presented using the FDA Snapshot table format.

9.3 Advisory Committee Meeting

An advisory committee meeting will not be convened.

9.4 Clinical Investigator Financial Disclosure Review Template

Application Numbers: 20977/S-027, 20978/S-031, 20564-S-033, 20596/S-032
Submission Date: March 23, 2014
Applicant: ViiV Healthcare
Products: ZIAGEN (abacavir) and EPIVIR (lamivudine)
Reviewer: Prabha Viswanathan, MD
Date of Review: January 14, 2015
Covered Clinical Study (Name and/or Number): ARROW (COL105677), PENTA-15 (COL104929), and PENTA-13 (EPV40002)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: ARROW: 9 PENTA-15: 9 PENTA-13: 2		
Number of investigators who are sponsor employees (including both full-time and		

part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not Applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

No financial interests or arrangements have been identified that would affect the approvability of this application.

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

/s/

PRABHA VISWANATHAN
02/13/2015

LINDA L LEWIS
02/14/2015
I concur with Dr. Viswanathan's findings and conclusions.