U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	20977 20978 20564 20596
Supplement #:	S-027 S-031 S-033 S-032
Drug Name:	Ziagen® (abacavir) and Epivir® (lamivudine)
Indication(s):	Once daily dosing for treatment of HIV-1 infection in children ≥ 3 months of age
Applicant:	ViiV Healthcare Company
Date(s):	Submission Date: May 23, 2014
	Primary Review Due Date: February 16, 2015
	PDUFA Date: March 23, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Fraser Smith, Ph.D.
Concurring Reviewers:	Greg Soon, Ph.D.
Medical Division:	Division of Antiviral Products.
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Keywords: HIV-1 infection, pediatrics, Ziagen (abacavir sulfate), Epivir (lamivudine), ARROW, switch trial

Link to keywords:

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

Table of Contents

1 EXECUTIVE SUMMARY

Brief summary of COL105677 AntiRetroviral Research fOr Watoto (ARROW)

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

ARROW = AntiRetroviral Research fOr Watoto

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

Outcome	Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Virologic Success (≤80 copies/mL)	242 (73)	233 (69)	232 (70)	226 (67)
Risk Difference and 95% CI	-3.3% (-10% to +4%)		-2.4% (-9% to +5%)	
Virologic Failure (>80 copies/mL)	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	90 (27)	95 (28)	90 (27)	100 (30)
Prior change in antiretroviral therapy	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	1 (<1)	5 (1)	4 (1)	3 (1)
Discontinued due to AE or Death[a]	0	0	3 (1)	1 (<1)
Discontinued due to other reasons	0	0	0	1 (<1)

[a] Deaths only; none of the subjects discontinued due to AEs
Source: Reviewer's analysis

At Week 48, 73% and 69% of the subjects were responders in BID and QD arms with a risk difference of -3.3% (95% CI: -10% to +4%). . At Week 96 response rates decreased to 70% and 67% in the BID and QD arms with a risk difference of -2.4% (95% CI: -9% to +5%).

There were very few subjects who discontinued since to be eligible for the twice versus once daily lamivudine (3TC) and abacavir (ABC) randomization children must have been on ART for at least 36 weeks and must have been taking twice daily 3TC and ABC. Only about 70% of the subjects had HIV-1 RNA viral loads that were suppressed below 80 copies/mL prior to randomization to continue twice-daily abacavir and lamivudine treatment or transition to once-daily abacavir and lamivudine treatment.

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

disappeared after adjusting for the baseline HIV RNA imbalance where subjects with baseline HIV RNA levels > 80 copies/mL had very low Week 48 and 96 response rates. Therefore the statistics reviewer agrees with the applicant's conclusion that the QD regimen was NI to the BID regimen.

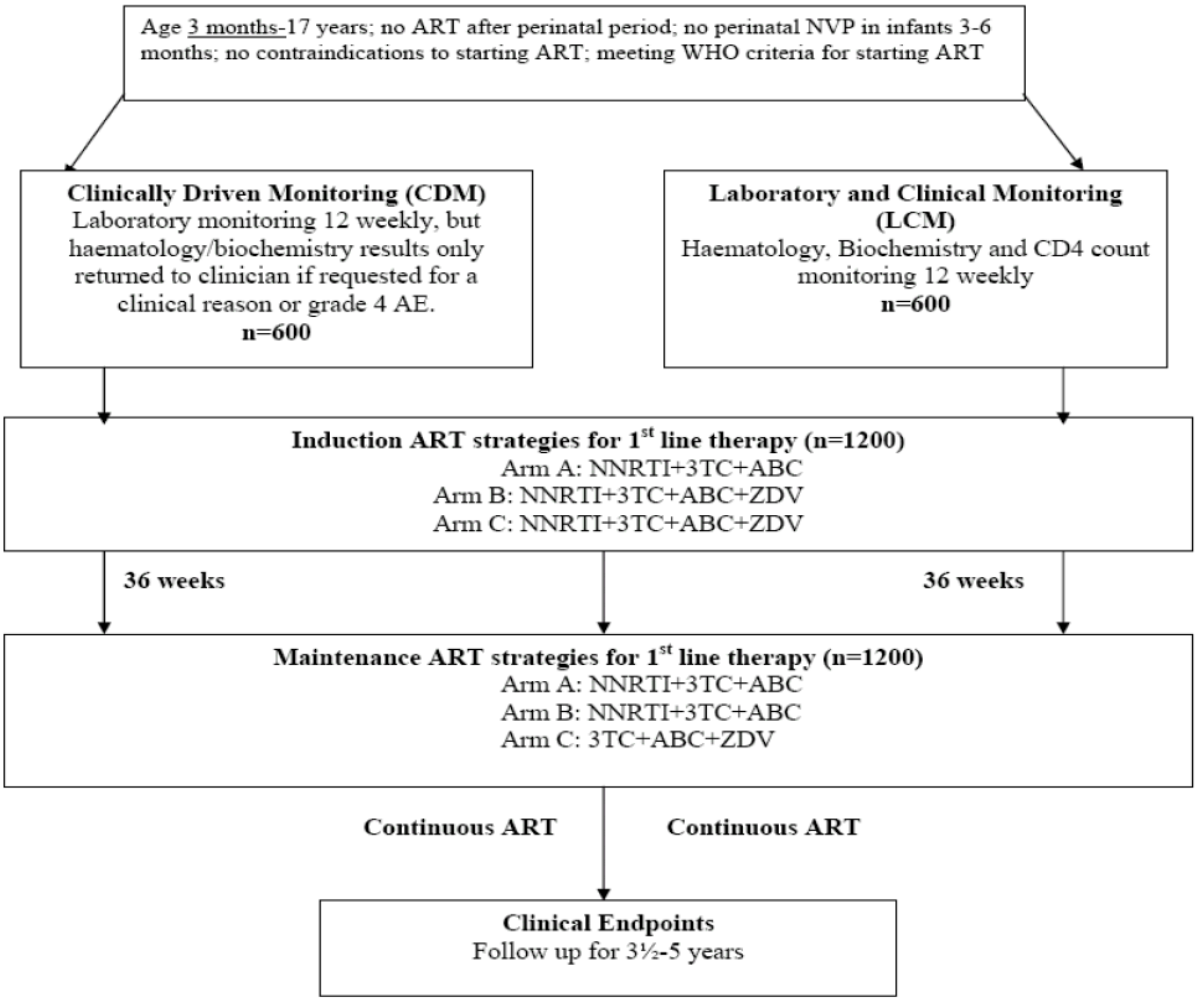
2 INTRODUCTION

2.1 Overview

List of all studies included in analysis

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

Figure 1 ARROW Trial Schema



Source: Clinical Study Report

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

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

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

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

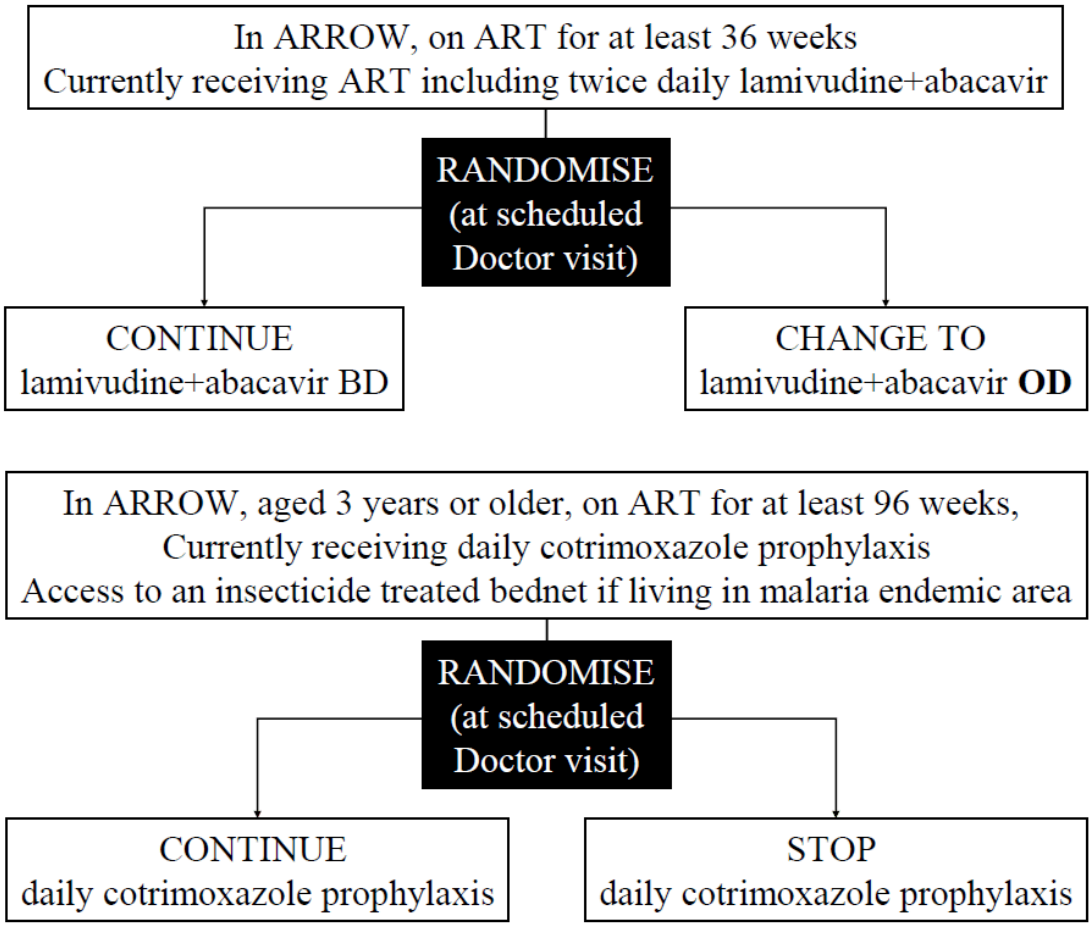
Table 1 First and second-line drug regimens for ARROW

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

a. Lopinavir/ritonavir

Source: Clinical Study Report

Figure 2 Secondary Randomisations: Simplification of Long-Term ART



Source: Clinical Study Report

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

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

Data from Randomization 3 form the basis for this pediatric efficacy supplement.

Table 2 Guidelines for Substituting for Toxicity

	Substitution[1]	
Event	if on three drugs:	if on four drugs
ZDV toxicity	Substitute ZDV with d4T or ddI or NVP or EFV (>3 years)	Stop ZDV
3TC toxicity	Substitute 3TC with ZDV or ddI or NVP or EFV (>3 years)	Stop 3TC
ABC toxicity	Substitute ABC with ZDV or NVP or EFV (>3 years) or TDF (adolescents)	Stop ABC
NVP toxicity	Substitute NVP with EFV (>3 years) or ZDV or TDF (adolescents) or Lopinavir/ritonavir	Stop NVP

1. Choice of substitution depends upon (i) other drugs being taken (ii) available formulations (e.g. solutions/size of tablet). If possible, preferred substitution would be within same class.

Source: Clinical Study Report

Table 2 summarizes guidelines for substituting for Toxicity. Subjects with grade 1 or 2 AEs were to continue study drugs while subjects with grade 3 or 4 AEs, following confirmation of toxicity and lack of other cause data were to substitute immediately if not too sick. Otherwise, according to the applicant subjects with grade 3 or 4 AEs stopped all drugs and restarted with substituted drugs when the condition improved.

If on four drugs, the principle was to stop the causal drug and continue on three drugs. If a child did not tolerate an individual drug/drug formulation, an alternative drug may have been substituted if this was considered appropriate by the investigator (Table 2) and other drugs restarted. According to the applicant wherever possible, substitutes were made within class. ZDV and 3TC were available as separate drugs for children who needed to stop one drug for toxicity or intolerance.

For further details, see Section 4.4.1 of the Clinical Study Report entitled "Investigational Products and Reference Therapy."

2.2 Data Sources

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

The application was submitted electronically and can be found on the following FDA network drive: \\CDSESUB1\evsprod\NDA020977\0105.

The clinical study report and datasets submitted with the sNDA can be found in the m5 folder. The direct path to the clinical study report is \\CDSESUB1\evsprod\NDA020977\0105\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5351-stud-rep-contr\arrow-col105677.

The direct path to the SAS transport files that were submitted with the sNDA is \\CDSESUB1\evsprod\NDA020977\0105\m5\datasets\arrow-col105677\analysis\legacy\datasets.

After the sNDA was submitted, there were further corrections that had to be made to the adeffout dataset. Statistics questions and the applicant's responses are found in the corresponding cover letters for each submission using the following links:

\\CDSESUB1\evsprod\NDA020977\0116\m1\us\102-cover-letters
\\CDSESUB1\evsprod\NDA020977\0117\m1\us\102-cover-letters

The direct path to the corresponding updated adeffout datasets is \\CDSESUB1\evsprod\NDA020977\0116\m5\datasets\arrow-col105677\analysis\legacy\datasets

The direct path to the final version of the updated adeffout dataset submitted in October 2014 is \\CDSESUB1\evsprod\NDA020977\0117\m5\datasets\arrow-col105677\analysis\legacy\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Review the quality and integrity of the submitted data. Examples of relevant issues include the following:

- Whether it is possible to reproduce the primary analysis dataset, and in particular the primary endpoint, from the original data source. *Yes.*
- Whether it is possible to verify the randomized treatment assignments. *No.*
- Findings from the Division of Scientific Investigation or other source(s) that question the usability of the data. *Not inspected*
- Whether the applicant submitted documentation of data quality control/assurance procedures (see ICH E3,[1] section 9.6; also ICH E6,[2] section 5.1). *See below*
- Whether the blinding/unblinding procedures were well documented (see ICH E3, section 9.4.6). *N/A since open-label.*
- Whether a final statistical analysis plan (SAP) was submitted and relevant analysis decisions (e.g., pooling of sites, analysis population membership, etc.) were made prior to unblinding. *Did not review SAP – only Pre-sNDA Meeting Package (NDA 20564 SDN 491, received June 17, 2013). According to the applicant, statistical analyses for the entire ARROW study were presented in the ARROW Statistical Analysis Plan, Version 1.3, dated 02 July 2012.*

At the Pre-sNDA Meeting on July 17, 2013 the sponsor proposed for the main ARROW study to provide safety and efficacy datasets to include the 48-week and 96-week viral load data from the fully powered once-daily versus twice-daily randomization (Randomization 3). Viral load and safety datasets would be provided in SAS transport file format, following dataset standards defined at the start of the study (i.e., not CDISC).

The DAVP agreed with this proposal to submit safety and efficacy datasets through Week 96 for ARROW. However, based on review of the sample datasets MRC (Medical Research Council, the ARROW Study Sponsor) provided with the meeting package, the Division had concerns about the ability to review the safety data from the ARROW trial. For example, in some of the safety datasets there are no subject identification numbers, no start or end dates for adverse events or duration of adverse events. Also, we are not able to determine adverse event grades or causality. From previous communications ViiV indicated that the datasets were being reformatted from Excel spreadsheets and we are concerned that, as currently submitted, there were insufficient data provided for full review of the safety data from ARROW.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf
[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

The Division requested that ViiV clarify the exact safety data available from ARROW including ViiV's ability to provide data in an acceptable format for regulatory review for the following:

1. Subject ID (unique identifier) for all datasets
2. Demographic and baseline characteristics data
3. Adverse event data: all grades of AEs, SAEs, fatal variable, date of onset, duration of event (or dates of start and end of event), resolution of event, causality assessment
4. Laboratory data with dates, study Week, grading of events
5. Concomitant medications, not limited to ART
6. CD4 cell count data
7. Treatment as randomized and as received

Additionally the division asked ViiV to clarify the specific data standards that were used for these trials, the differences between the trials and any significant data variables used for typical safety or efficacy analyses that were not captured or are missing.

DAVP requested that after addressing the above issues, ViiV provide updated sample datasets for the ARROW trial.

DAVP emphasized the need for the datasets to be complete to allow for full regulatory review of the efficacy and safety data to support the indication. We also noted that submitting data in non-CTD (CDISC) format was acceptable (within regulations and guidance) but not preferred. (See the memorandum of meeting minutes for sNDA 20564/20596 for further details. The meeting minutes were filed in DARRTS on August 8, 2013.)

Sample datasets were subsequently provided in their submission received February 27, 2014 (NDA 20977 SDN (b) (4) and met expectations. The sponsor addressed many of these concerns by creating new SAS analysis datasets. The sponsor submitted the following sample analysis datasets for the ARROW trial:

Datasets for study col105677	
Dataset	Description of dataset
adherenc	Adherence
ae34	Grade 3/4 Adverse events
ae4	Grade 4 Adverse events
aecode	Adverse events dictionary
artchng	ART Treatment Changes
cd4	CD4
conmeds	Concomitant Meidcations
cyrs_3tc	Child Years 3TC
cyrs_abc	Child Years ABC
cyrs_cbv	Child Years CBV
cyrs_kiv	Child Years KIV
death	Death
event_wt	Adverse events by weight band
lab_bio	Biochemistry
lab_haem	Haematology
partb1_r	Part 1 Viral Load
pyrs	Person years
sae	Serious Adverse events
snapshot	Snapshot
vl_partc	Viral Load
who34	WHO stage 3/4 events

Subsequently the statistics team requested that the sponsor submit our standardized HIV adeffout dataset. This dataset is designed to be "One Statistical Procedure Away" from the statistical results wherever possible. This approach eliminates or greatly reduces the amount of programming required by the statistical reviewers.

Efficacy outcomes and related covariates on the adeffout dataset have one record only per subject and include the following information:

1. Demographic variables
2. Baseline characteristics (including Baseline Genotypic and Phenotypic Data, stratification factors, etc.)
3. Exposure variables (first and last dosing date, etc.)
4. Population flags (ITT, PP, etc.)
5. Efficacy outcomes (primary, secondary, etc.)

6. Covariates and subgroup variables
7. Subject disposition variables

After the sNDA was submitted numerous issues were identified including variable discrepancies, inconsistencies between adeffout and other datasets, and variables with no data. For example, snapshot responses using a cutoff of 400 copies/mL were not included in the original datasets. See the Appendix for Biometrics questions and applicant's responses.

Further information provided by GSK pertaining to Data Quality Assurance, including General Responsibilities, Data Management and Monitoring, the Central Merged Database, Serious Adverse Event Reporting and the Data Monitoring Committee can be found in the Appendix.

3.2 Evaluation of Efficacy

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

3.2.1 Study Design and Endpoints

Brief summary of COL105677 AntiRetroviral Research fOr Watoto (ARROW)

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

Trial Specification:

Trial Phase: IV
Region: Africa

Multicenter: Yes (4 clinical centers)

Blinding: Unblinded

Control: Active

Randomization: Yes
Method: not stated

Stratification: No

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

Control: continue ABC+3TC twice daily

Allocation Ratio: 1:1

Sample Size Per Treatment Group: **N**=333 to BID, 336 to switch from BID to QD arm
Statistic = Risk Difference, Δ=0 (70% response rate in both groups),
α =2-sided 0.05, **1 - β = 90%** **NI Margin** =12% (originally 10% but increased to 12% due to slow recruitment),

See appendix for further details about the sample size calculations and justification of the 12% NI margin.

Analysis Populations

According to the applicant Intent-to-Treat analyses were performed on all randomized children, except those randomized in error and not ever receiving ARROW study drugs and not being followed after enrollment for this reason. The applicant stated that children randomized under the incorrect stratum were analyzed using their randomized stratum rather than the stratum they should have been randomized under.

Interim Analyses

Data from the once daily versus twice daily ABC+3TC part of the study were reviewed twice by the independent Data Monitoring Committee as part of their annual reviews of ARROW data (May 2010, June 2011).

3.2.2 Statistical Methodologies

Original Analysis of Viral Load

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

The statistics reviewer carried out sensitivity analyses adjusting for different potential confounding covariables in order to examine the robustness of the Applicant's findings. The statistics reviewer also performed Breslow-Day interaction tests for selected baseline covariates using the snapshot efficacy analysis.

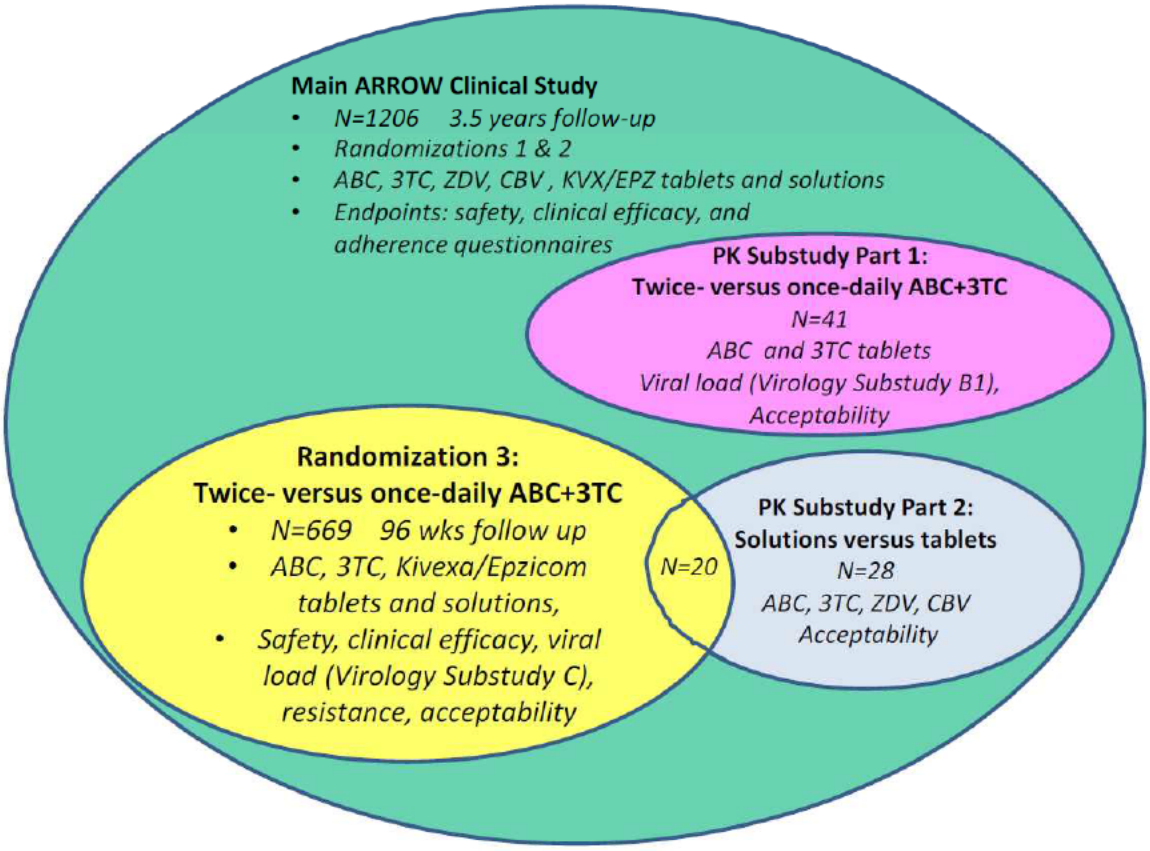
The applicant also performed numerous subgroup analyses of responders using cutoff values of 80 and 400 copies/mL.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The main ARROW clinical trial enrolled 1206 ART-naïve HIV-1–infected subjects aged three months to 17 years.

According to the applicant, all eligible subjects were given the option to be included in Randomization 3 once they had completed ≥36 weeks in the main study (i.e., had been receiving ABC+3TC dosed twice daily for ≥36 weeks). In Randomization 3, 669 subjects were assigned to either continue their twice-daily dosing or switch to once-daily dosing of ABC+3TC. The applicant noted that administration of ABC and 3TC followed 2006 WHO weight-band dosing either as solution or scored tablet, which differed slightly from the approved US label.

Figure 1 ARROW Study Populations



3TC = lamivudine; ABC = abacavir sulfate; ARROW = AntiRetroviral Research fOr Watoto; CBV = COMBIVIR; KVX/EPZ = KIVEXA or EPIZICOM; 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.

Source: ISE

The HIV-1 RNA viral load data from this population were collected in Virology Substudy C. Forty-one subjects (aged 3 years to ≤12 years) were enrolled in the ARROW PK Substudy Part 1 as they completed 36 weeks of twice-daily dosing using scored tablets in Arm A or B of the full ARROW study. The HIV-1 RNA viral load data from this population were collected in Virology Substudy B1.

Table 3 Subject Characteristics at Randomisation into the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

By Monitoring Group	LCM n (%)	CDM n (%)	Total N (%)
Total	322 (48.1)	347 (51.9)	669 (100)
Twice Daily	159 (23.8)	174 (26.0)	333 (49.8)
Once Daily	163 (24.4)	173 (25.9)	336 (50.2)

By Treatment Arm	Arm A n (%)	Arm B n (%)	Arm C n (%)	Total N (%)
Total	210 (31.4)	238 (35.6)	221 (33.0)	669 (100)
Twice Daily	105 (15.7)	118 (17.6)	110 (16.4)	333 (49.8)
Once Daily	105 (15.7)	120 (17.9)	111 (16.6)	336 (50.2)

By Study Centre	Entebbe n (%)	JCRC n (%)	Harare n (%)	PIDC n (%)	Total N (%)
Total	130 (19.4)	151 (22.6)	174 (26.0	214 (32.0)	669 (100)
Twice Daily	65 (9.7)	74 (11.1)	87 (13.0)	107 (16.0)	333 (49.8)
Once Daily	65 (9.7)	77 (11.5)	87 (13.0)	107 (16.0)	336 (50.2)

Source: Clinical Study Report

According to GSK, a total of 732 subjects were eligible to participate in the once daily versus twice daily ABC+3TC part of the study. Of those, the applicant stated that 669 subjects (91%) consented to participate and 63 (9%) refused. A total of 333 subjects (50%) were randomized to receive twice daily ABC+3TC and 336 subjects (50%) were randomized to receive once daily ABC+3TC.

Similar proportions of subjects were randomized into the once daily and twice daily groups by monitoring group, treatment arm, and study center (Table 3).

Table 4 Subject Characteristics at Follow-up in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

Weeks Follow-up	Twice Daily	Once Daily	Total
All children, n	**333**	**336**	**669**
Median (weeks follow-up)	114	114	114
IQR	106 to 125	106 to 124	106 to 125
Range	51 to 134	48 to 134	48 to 134
In Follow-up at Trial End, n	**326**	**331**	**657**
Median (weeks follow-up)	114	114	114
IQR	106 to 125	106 to 125	106 to 125
Range	90 to 134	85 to 134	85 to 134
Withdrawn/Lost to Follow-up, n	**3**	**4**	**7**
Median (weeks follow-up)	66	91	66
IQR	60 to 72	57 to 118	60 to 116
Range	60 to 72	48 to 121	48 to 121
Died, n	**4**	**1**	**5**
Years Follow-up			
All children, n	333	336	669
Total (years follow-up)	726.8	735.1	1462.0
Median (years follow-up)	2.2	2.2	2.2
IQR	2.0 to 2.4	2.0 to 2.4	2.0 to 2.4
Range	1.0 to 2.6	0.9 to 2.6	0.9 to 2.6

Source Data: Statistical Report
IQR = Interquartile range
Source: Clinical Study Report

Subject characteristics at follow-up were summarized in Table 4 of the Clinical Study Report. Subjects in both treatment arms stayed in the trial for a median of 114 days (2.2 years). A total of three subjects in the BID arm and four subjects in the QD arm withdrew or were lost to follow-up prior to the end of the study while four subjects in the BID arm and one subject in the QD arm died.

Table 6 Demographic and Anthropometric Characteristics at Randomisation into the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW (After ≥36 weeks on ART)

	Twice Daily	Once Daily	Total
Randomised, n (%)	333 (100)	336 (100)	669 (100)
Sex, n (%)			
Male	161 (48.3)	163 (48.5)	324 (48.4)
Female	172 (51.7)	173 (51.5)	345 (51.6)
Age (years) at last birthday, n (%)			
0-2	38 (11.4)	36 (10.7)	74 (11.1)
3-6	180 (54.1)	164 (48.8)	344 (51.4)
7-12	111 (33.3)	131 (39.0)	242 (36.2)
13+	4 (1.2)	5 (1.5)	9 (1.3)
Median	5.1	5.9	5.5
IQR	3.6 to 8.3	3.8 to 8.6	3.7 to 8.5
Range	1.8 to 14.7	1.9 to 16.9	1.8 to 16.9
Years since ART initiation			
Median	1.8	1.8	1.8
IQR	1.4 to 2.3	1.4 to 2.1	1.4 to 2.1
Range	0.9 to 3.0	0.9 to 3.0	0.9 to 3.0
ART line at randomisation, n (%)			
First	333 (100.0)	336 (100.0)	669 (100.0)
Second	0	0	0
Vertical exposure, n (%)	330 (99.1)	336 (100.0)	666 (99.6)

Source: Clinical Study Report

Demographic Characteristics were summarized in Table 6 of the Clinical Study Report. Slightly more than 50% of the randomized subjects were female. Over 50% of the randomized subjects were age 3-6, 36% were age 7-12, 11% were age 0-2 while only 1% of the subjects were age 13 and above. At the time of randomization the median years since ART initiation was 1.8 in both arms. All of the subjects had first line ART therapy at the time of randomization and nearly all of the subjects became infected with HIV-1 through vertical (mother-to-child) transmission.

Table 10 Treatment Regimen at Randomisation into the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily n (%)	Once Daily n (%)	Total N (%)
Total	333 (100)	336 (100)	669 (100)
3TC+ABC+NVP	171 (51.4)	148 (44.0)	319 (47.7)
3TC+ABC+ZDV	112 (33.6)	115 (34.2)	227 (33.9)
3TC+ABC+EFV	49 (14.7)	73 (21.7)	122 (18.2)
3TC+ ABC+D4T	1 (0.3)	0 (0.0)	1 (0.1)

Source: Clinical Study Report

Almost 50% of the subjects were receiving NVP in addition to ABC+3TC at randomization compared to 34% receiving ZDV, 18% receiving EFV and only one subject receiving D4T (See Table 10 in the Clinical Study Report).

Table 11 Treatment Formulation Received at Randomisation into the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily n (%)	Once Daily n (%)	Total N (%)
Total	333 (100)	336 (100)	669 (100)
Any solution	26 (7.8)	30 (8.9)	56 (8.4)
All tablets	307 (92.2)	306 (91.1)	613 (91.6)

Note: Some children were taking both solution and tablet formulations for different ART drugs in their regimen.
Source: Clinical Study Report

The majority of subjects (92%) were receiving tablets while the remaining 8% were receiving the solution at randomization (Table 11).

Table 12 Subjects Receiving Second Line Therapy in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily n (%)	Once Daily n (%)	Total N (%)
On first-line ART at randomisation	333 (100)	336 (100)	669 (100)
Switched to second-line ART after randomisation	6 (1.8)	7 (2.1)	13 (1.9)

Source: Clinical Study Report

All of the subjects were receiving first-line ART at randomization (Table 12). After randomization 2% of the subjects in each treatment arm switched to second-line ART.

Table 13 Adherence to Strategy in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily n (%)	Once Daily n (%)	Total N (%)
Randomised	333 (100)	336 (100)	669 (100)
Continued/changed 3TC and ABC dosing as planned			
Yes	333 (100)	334 (99.4)	667 (99.7)
No	0 (0.0)	2 (0.6)	2 (0.3)
Randomised as planned	333 (100)	334 (100)	667 (100)
Remained on twice daily/once daily as planned			
Yes	322 (96.7)	316 (94.6)	638 (95.7)
No	11 (3.3)	18 (5.4)	29 (4.3)
Weeks until subjects changed ART to not as planned			
n	11	18	29
Median	50.1	29.7	38.4
IRQ	18.0 to 61.6	6.0 to 72.0	6.1 to 61.6
Range	0 to 105	0 to 120	0 to 120

Source: Clinical Study Report

All but two of the subjects randomized to the QD regimen switched to QD dosing as planned (Table 13). Of the 669 randomized subjects, 638 (96%) remained on their regimen as planned. For the 29 who did not, the median number of weeks until subjects changed their ART was 50 for the BID arm and 30 for the QD arm.

3.2.4 Results and Conclusions

Table 15 Data Completeness for Plasma HIV-1 RNA Results in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Week 0 of Once versus Twice Daily Randomisation (after ≥36 Weeks on Treatment in Main ARROW Study) n (%)	Week 48 of Once versus Twice Daily Randomisation n (%)	Week 96 of Once versus Twice Daily Randomisation n (%)
Total randomised	669 (100)	669 (100)	669 (100)
Has Plasma HIV-1 RNA result	666 (99.6)	661 (98.8)	657 (98.2)
No result available	3 (0.4)	8 (1)	3 (0.4)
Died before this time point	0	0	4 (0.6)
Lost to Follow-up before this time point	0	0	5 (0.7)

Source: Clinical Study Report

Almost 100% of the subjects at baseline, 99% of the subjects at Week 48 and 98% of the subjects at Week 96 had HIV-1 RNA results (Table 15).

Table 17 Proportions of Subjects with Plasma HIV-1 RNA <80 copies/mL in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily n (%)	Once Daily n (%)	Total N (%)
Week 0 (after 36 weeks on Treatment)	331 (100)	335 (100)	666 (100)
Plasma HIV-1 RNA <80 c/mL	250 (76)	237 (71)	487 (73)
Plasma HIV-1 RNA ≥80 c/mL	81 (24)	98 (29)	179 (27)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16		
Week 48	331 (100)	330 (100)	661 (100)
Plasma HIV-1 RNA <80 c/mL	242 (73)	236 (72)	478 (72)
Plasma HIV-1 RNA ≥80 c/mL	89 (27)	94 (28)	183 (28)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65		
Week 96	326 (100)	331 (100)	657 (100)
Plasma HIV-1 RNA <80 c/mL	234 (72)	230 (69)	464 (71)
Plasma HIV-1 RNA ≥80 c/mL	92 (28)	101 (31)	193 (29)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52		

Source: Clinical Study Report

The applicant used a Completers Analysis for the primary efficacy endpoint, which consisted of randomized subjects with HIV-1 RNA values at a given visit (Table 17 of the Clinical Study Report). At baseline they found that 76% of the subjects randomized to BID treatment and 71% of the subjects randomized to QD treatment had HIV-1 RNA <80 copies/mL. This was unlike many of the other switch trials we have reviewed because of the relatively high number of subjects (27%) who were not suppressed at baseline.

Only about 70% of the subjects had HIV-1 RNA viral loads that were suppressed below 80 copies/mL prior to randomization to continue twice-daily abacavir and lamivudine treatment or transition to once-daily abacavir and lamivudine treatment. The applicant claimed that as the lower bound of the CIs fell within the non-inferiority margin of -12% that these results further demonstrated the non-inferiority of once- to twice-daily dosing.

Note that the 12% non-inferiority margin has not been justified by the applicant and may have been too large for a switch trial where subjects were initially virologically suppressed, did not have problems with compliance, and did not experience many AEs leading to discontinuation. In adult switch trials, NI margins using the appropriate amount of discounting are typically 6-8%. However since response rates were lower (around 70% instead of 90% observed in switch trials in other NDAs) the larger margin was of less concern.

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

Outcome	Week 48[a]		Week 96[b]	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Virologic Success (≤80 copies/mL)	242 (73)	233 (69)	232 (70)	226 (67)
Risk Difference and 95% CI	-3.3% (-10% to +4%)		-2.4% (-9% to +5%)	
Virologic Failure (>80 copies/mL)	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	90 (27)	95 (28)	90 (27)	100 (30)
Prior change in antiretroviral therapy	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	1 (<1)	5 (1)	4 (1)	3 (1)
Discontinued due to AE or Death[c]	0	0	3 (1)	1 (<1)
Discontinued due to other reasons	0	0	0	1 (<1)

[a] Week 48 study days ranged from 255-424 with median of 336
[b] Week 96 study days ranged from 553-757 with median of 672
[c] Deaths only; none of the subjects discontinued due to AEs
Source: Reviewer's analysis

The statistics reviewer used all randomized subjects to perform the FDA snapshot analysis at Weeks 48 and 96. Given the small number of subjects who did not have HIV-1 RNA values at Weeks 48 and 96, efficacy results did not change that much; response rates were at most 3% lower than the applicant's estimates and lower bounds of the 95% CI for risk differences between QD and BID still exceeded the -12% NI margin,

Table 7 Summary of Study Outcomes (<80 copies/mL) at Weeks 48 and 96 Using Snapshot Analysis

Outcome	Week 0		Week 48		Week 96	
	Twice-Daily Dosing N=333 n (%)	Once-Daily Dosing N=336 n (%)	Twice-Daily Dosing N=333 n (%)	Once-Daily Dosing N=336 n (%)	Twice-Daily Dosing N=333 n (%)	Once-Daily Dosing N=336 n (%)
Virological success (<80 copies/mL)	250 (75)	237 (71)	242 (73)	233 (69)	232 (70)	226 (67)
Virological failure (≥80 copies/mL)	81 (24)	98 (29)	89 (27)	97 (29)	94 (28)	105 (31)
Data in window not below threshold	81 (24)	98 (29)	89 (27)	94 (28)	90 (27)	100 (30)
Prior change in antiretroviral therapy	Not applicable	Not applicable	0	3 (<1)	4 (1)	5 (1)
No virological data	2 (<1)	1 (<1)	2 (<1)	6 (2)	7 (2)	5 (1)
Missing data during window but on study	2 (<1)	1 (<1)	2 (<1)	6 (2)	7 (2)	4 (1)
Discontinued for other reasons	Not applicable	Not applicable	Not applicable	Not applicable	0	1 (<1)

Source: ISE

However the applicant did provide a snapshot table in the ISE after corresponding with FDA. The number and percentage of responders were the same as those obtained by the statistics reviewer.

The statistics reviewer also counted two subjects (13081 and 13093) that the applicant counted as having no virologic data as virologic failures at Week 48. [As described in the FDA Question 1 in August 2014 and the applicant's response (see Appendix), these subjects had very discrepant results on two viral samples in the Week 48 window, with HIV-1 RNA values at Week 48 in the viral load dataset of 1196 and 4988; they were also counted as virologic failures at Week 96.]

The sub-category for 'Discontinuations due to AE or Death' was missing in this table because the sponsor did not account for deaths that occurred in the trial. Instead subjects who should have been listed as discontinuing due to AE or Death were included in the 'Missing data during window but on study' sub-category (none at week 48, three in BID arm and one in QD arm at week 96).

Table 3 Summary of Study Outcomes (<80 copies/mL) at Weeks 48 and 96 Using Snapshot Analysis

Outcome	Week 0		Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Virological success (<80 copies/mL)	250 (75)	237 (71)	242 (73)	233 (69)	232 (70)	226 (67)
Virological failure (≥80 copies/mL)	81 (24)	98 (29)	89 (27)	97 (29)	94 (28)	105 (31)
Data in window not below threshold	81 (24)	98 (29)	89 (27)	94 (28)	90 (27)	100 (30)
Prior change in antiretroviral therapy	0	0	0	3 (<1)	4 (1)	5 (1)
No virological data	2 (<1)	1 (<1)	2 (<1)	6 (2)	7 (2)	5 (1)
Missing data during window but on study	2 (<1)	1 (<1)	2 (<1)	6 (2)	4 (1)	3 (<1)
Discontinued due to AE or Death	0	0	0	0	3 (<1)	1 (<1)
Discontinued for other reasons	0	0	0	0	0	1 (<1)

Source: Applicant's October 2014 Response to Information Request

In response to Q2 in the October 2014 submission the applicant agreed that they had misclassified five deaths (with four occurring by Week 96). The applicant submitted the revised snapshot table shown in Table 3 above.

Table 8 ARROW Virology Substudy Part C: Primary Snapshot (MSDF) Analysis of the Number and Percentage of Subjects With Viral Load of <80 Copies/mL at Randomization to Twice- and Once-Daily Dosing (Week 0) and After 48 and 96 Weeks of Twice- and Once-Daily Dosing of Abacavir and Lamivudine

Time Point	Twice-Daily Dosing N=333 n (%)	Once-Daily Dosing N=336 n (%)	Total N=669 n (%)
Week 0			
Responder	250 (75)	237 (71)	487 (73)
Nonresponder	83 (25)	99 (29)	182 (27)
Risk difference (95% CI)	-4.5% (-11.3 – 2.2)		
Week 48			
Responder	242 (73)	233 (69)	475 (71)
Nonresponder	91 (27)	103 (31)	194 (29)
Risk difference (95% CI)	-3.3% (-10.2 – 3.5)		
Week 96			
Responder	232 (70)	226 (67)	458 (68)
Nonresponder	101 (30)	110 (33)	211 (32)
Risk difference (95% CI)	-2.4% (-9.4 – 4.6)		

MSDF = Missing, Switch, or Discontinuation = Failure.
Note: The primary analysis allowed up to 91 days of continual treatment interruption, reduction, or stop drug before a visit to still be considered a responder.
Source: ISE

Using the snapshot algorithm, the proportion (95% CI) of subjects with plasma RNA levels of <80 copies/mL was summarized by the applicant at Baseline, Week 48, and Week 96 for the primary (Table 8 of the ISE). The primary analysis allowed up to 91 days of continual treatment interruption (due to limited planned clinic visits), reduction, or stop drug before a visit to still be considered a responder.

For the primary snapshot analysis, the proportion of subjects with viral loads of <80 copies/mL remained decreased by approximately 2% at Week 48 and another 2% at Week 96 compared to baseline and the risk difference (95% CI) for once daily to twice daily narrowed from -4.5% (-11% to +2%) at Baseline (Week 0) to -3.3% (-10% to +4%) at Week 48 and -2.4% (-9% to +5%) at Week 96.

Table 9 **ARROW Virology Substudy Part C: Sensitivity Snapshot (MSDF) Analysis of the Number and Percentage of Subjects With Viral Load of <80 Copies/mL at Randomization to Twice- and Once-Daily Dosing (Week 0) and After 48 and 96 Weeks of Twice- and Once-Daily Dosing of Abacavir and Lamivudine**

Time Point	Twice-Daily Dosing N=333 n (%)	Once-Daily Dosing N=336 n (%)	Total N=669 n (%)
Week 0			
Responder	250 (75)	237 (71)	487 (73)
Nonresponder	83 (25)	99 (29)	182 (27)
Risk difference (95% CI)	-4.5% (-11.3 – 2.2)		
Week 48			
Responder	241 (72)	233 (69)	474 (71)
Nonresponder	92 (28)	103 (31)	195 (29)
Risk difference (95% CI)	-3% (-9.9 – 3.9)		
Week 96			
Responder	230 (69)	226 (67)	456 (68)
Nonresponder	103 (31)	110 (33)	213 (32)
Risk difference (95% CI)	-1.8% (-8.9 – 5.3)		

Note: The sensitivity analysis allowed up to 42 days of continual treatment interruption, reduction, or stop drug before a visit to still be considered a responder.
Source: ISE

For the sensitivity snapshot analysis, the window for allowing continual treatment interruption, reduction, or stoppage before the visit was shortened from 91 days to 42 days. The number and percentage of responders in the QD arm remained the same as before while the percentage of responders in the BID arm decreased by 1% at Weeks 48 and 96 with no change at Week 0.

The risk differences and CIs at Weeks 48 and 96 still excluded the -12% non-inferiority margin [Week 48, risk difference (95% CIs) of -3% (-10% to +4%); Week 96, risk difference (95% CIs) of -1.8% (-9% to +5%)] (Table 9 of the ISE).

Table 4 Summary of Study Outcomes (<400 copies/mL) at Weeks 48 and 96 Using Snapshot Analysis

Outcome	Week 0		Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Virological success (<400 copies/mL)	272 (82)	266 (79)	260 (78)	253 (75)	252 (76)	250 (74)
Virological failure (≥400 copies/mL)	59 (18)	69 (21)	71 (21)	77 (23)	74 (22)	81 (24)
Data in window not below threshold	59 (18)	69 (21)	71 (21)	74 (22)	70 (21)	76 (23)
Prior change in antiretroviral therapy	0	0	0	3 (<1)	4 (1)	5 (1)
No virological data	2 (<1)	1 (<1)	2 (<1)	6 (2)	7 (2)	5 (1)
Missing data during window but on study	2 (<1)	1 (<1)	2 (<1)	6 (2)	4 (1)	3 (<1)
Discontinued due to AE or Death	0	0	0	0	3 (<1)	1 (<1)
Discontinued for other reasons	0	0	0	0	0	1 (<1)

Source: Applicant's October 2014 Response to Information Request

Similar trends were observed for the cutoff value of 400 copies/mL with virologic success rates about 6% higher than they were using a cutoff value of 80 copies/mL.

Table 18 Proportions of Subjects with Plasma HIV-1 RNA <200 copies/mL in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily n (%)	Once Daily n (%)	Total N (%)
Week 0 (after 36 weeks on Treatment)	331 (100)	335 (100)	666 (100)
Plasma HIV-1 RNA <200 c/mL	268 (81)	255 (76)	523 (79)
Plasma HIV-1 RNA ≥200 c/mL	63 (19)	80 (24)	143 (21)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.1% to +1.4%), p=0.13		
Week 48	331 (100)	330 (100)	661 (100)
Plasma HIV-1 RNA <200 c/mL	253 (76)	249 (75)	502 (76)
Plasma HIV-1 RNA ≥200 c/mL	78 (24)	81 (25)	159 (24)
Risk difference (once daily-twice daily)	-1.0% (95% CI -7.5% to +5.5%), p=0.77		
Week 96	326 (100)	331 (100)	657 (100)
Plasma HIV-1 RNA <200 c/mL	246 (75)	242 (73)	488 (74)
Plasma HIV-1 RNA ≥200 c/mL	80 (25)	89 (27)	169 (26)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.0% to +4.3%), p=0.49		

Source: Clinical Study Report

The applicant also performed Completers Analyses in the Clinical Study Report using cutoffs of 200 and 400 copies/mL (Tables 18 and 19) which overestimated response rates by 1-3%.

Table 19 Proportions of Subjects with Plasma HIV-1 RNA <400 copies/mL in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily n (%)	Once Daily n (%)	Total N (%)
Week 0 (after 36 weeks on Treatment)	331 (100)	335 (100)	666 (100)
Plasma HIV-1 RNA <400 c/mL	272 (82)	266 (79)	538 (81)
Plasma HIV-1 RNA ≥400 c/mL	59 (18)	69 (21)	128 (19)
Risk difference (once daily-twice daily)	-2.8% (95% CI -8.8% to +3.2%), p=0.36		
Week 48	331 (100)	330 (100)	661 (100)
Plasma HIV-1 RNA <400 c/mL	260 (79)	256 (78)	516 (78)
Plasma HIV-1 RNA ≥400 c/mL	71 (21)	74 (22)	145 (22)
Risk difference (once daily-twice daily)	-1.0% (95% CI -7.3% to +5.3%), p=0.76		
Week 96	326 (100)	331 (100)	657 (100)
Plasma HIV-1 RNA <400 c/mL	254 (78)	255 (77)	509 (77)
Plasma HIV-1 RNA ≥400 c/mL	72 (22)	76 (23)	148 (23)
Risk difference (once daily-twice daily)	-0.9% (95% CI -7.3% to +5.5%), p=0.79		

Source: Clinical Study Report

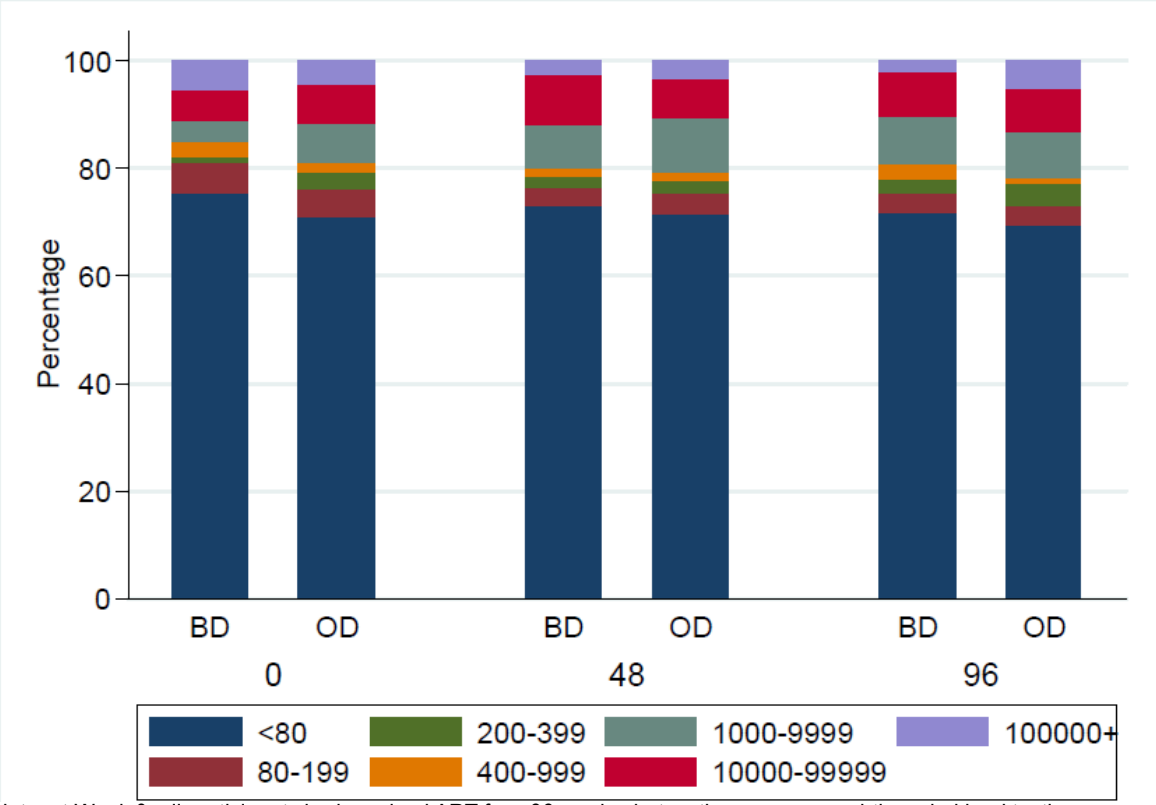
Table 22 Proportions of Subjects in Plasma HIV-1 RNA Categories over Time in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily n (%)	Once Daily n (%)	Total N (%)
Week 0 (after 36 weeks on Treatment)	331 (100)	335 (100)	666 (100)
Plasma HIV-1 RNA <80 c/mL	250 (76)	237 (71)	487 (73)
Plasma HIV-1 RNA 80-199 c/mL	18 (5)	18 (5)	36 (5)
Plasma HIV-1 RNA 200-399 c/mL	4 (1)	11 (3)	15 (2)
Plasma HIV-1 RNA 400-999 c/mL	9 (3)	5 (1)	14 (2)
Plasma HIV-1 RNA 1000-9999 c/mL	13 (4)	25 (7)	38 (6)
Plasma HIV-1 RNA 10000-99999 c/mL	19 (6)	24 (7)	43 (6)
Plasma HIV-1 RNA 100000+ c/mL	18 (5)	15 (4)	33 (5)
Week 48	331 (100)	330 (100)	661 (100)
Plasma HIV-1 RNA <80 c/mL	242 (73)	236 (72)	478 (72)
Plasma HIV-1 RNA 80-199 c/mL	11 (3)	13 (4)	24 (4)
Plasma HIV-1 RNA 200-399 c/mL	7 (2)	7 (2)	14 (2)
Plasma HIV-1 RNA 400-999 c/mL	5 (2)	6 (2)	11 (2)
Plasma HIV-1 RNA 1000-9999 c/mL	26 (9)	33 (10)	59 (9)
Plasma HIV-1 RNA 10000-99999 c/mL	31 (9)	24 (7)	55 (8)
Plasma HIV-1 RNA 100000+ c/mL	9 (3)	11 (3)	20 (3)
Week 96	326 (100)	331 (100)	657 (100)
Plasma HIV-1 RNA <80 c/mL	234 (72)	230 (69)	464 (71)
Plasma HIV-1 RNA 80-199 c/mL	12 (4)	12 (4)	24 (4)
Plasma HIV-1 RNA 200-399 c/mL	8 (2)	13 (4)	21 (3)
Plasma HIV-1 RNA 400-999 c/mL	9 (3)	4 (1)	13 (2)
Plasma HIV-1 RNA 1000-9999 c/mL	29 (9)	28 (8)	57 (9)
Plasma HIV-1 RNA 10000-99999 c/mL	27 (8)	27 (8)	54 (8)
Plasma HIV-1 RNA 100000+ c/mL	7 (2)	17 (5)	24 (4)

Source: Clinical Study Report

The applicant summarized the proportions of completers in plasma HIV-1 RNA categories by treatment group in Table 22 and Figure 7 of the Clinical Study Report. There were comparable percentages of BID and QD completer subjects in most of the categories over 80 copies/mL.

Figure 7 **Proportions of Subjects in Plasma HIV-1 RNA Categories over Time in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW**



Note: at Week 0, all participants had received ART for ≥36 weeks, but as there was no real-time viral load testing, some children were not virologically suppressed at this time.
Source: Clinical Study Report

See the Appendix for additional secondary efficacy analyses that were performed by the applicant.

3.3 Evaluation of Safety

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

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

Randomization Arm	Week 48 p-value	Week 96 p-value
Subgroup		
Baseline Age (≤3, 4-6, 7+)	0.94	0.84
Gender	0.62	0.71
Center (Entebbe, Harare, JCRC, PIDC)	0.22	0.13

Source: Reviewer's Analysis

The statistics reviewer did not find any statistically significant interactions between treatment effects and baseline age, gender or center at Weeks 48 or 96.

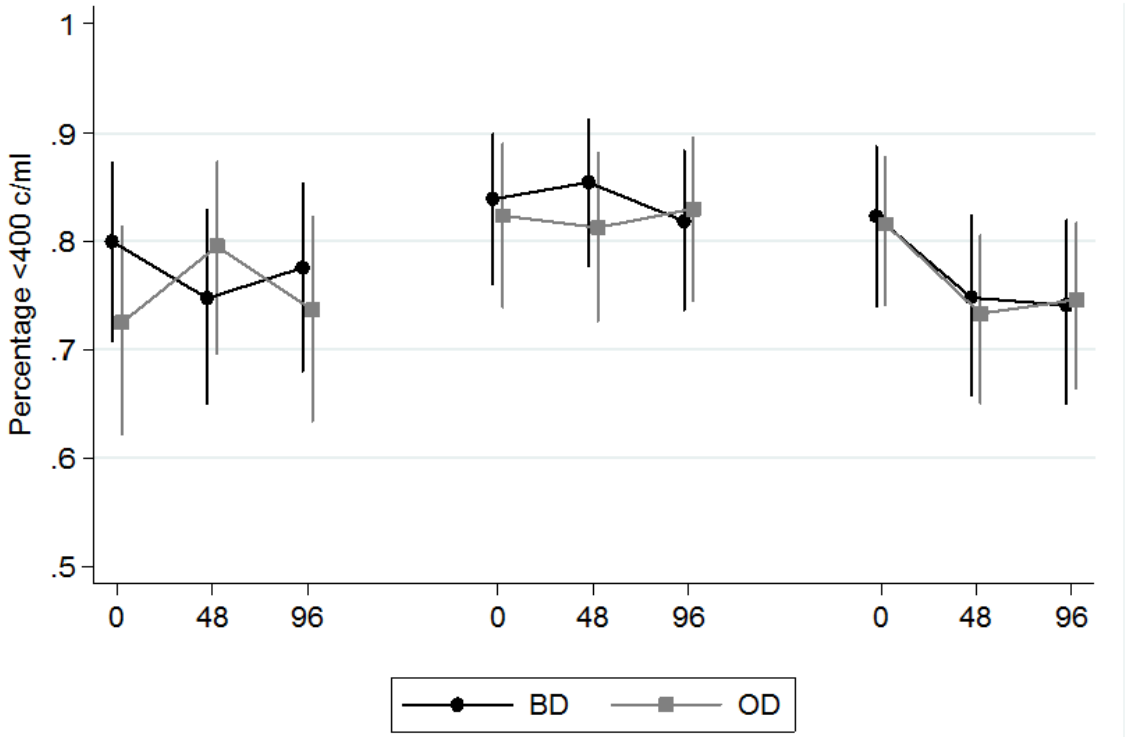
However the applicant did provide the following subgroup analyses by baseline age and gender.

Table 25 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by Age Group

	Twice Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
1-3 years	80/100 (80)	66/91 (73)
4-6 years	99/118 (84)	89/108 (82)
7+ years	93/113 (82)	111/136 (82)
P-value[a]	0.71	
Week 48		
1-3 years	74/99 (75)	70/88 (80)
4-6 years	100/117 (85)	87/107 (81)
7+ years	86/115 (75)	99/135 (73)
P-value[a]	0.51	
Week 96		
1-3 years	76/98 (78)	67/91 (74)
4-6 years	95/116 (82)	88/106 (83)
7+ years	83/112 (74)	100/134 (75)
P-value[a]	0.81	

a. Test for heterogeneity of once daily versus twice daily comparison across levels.
Source: Clinical Study Report

Figure 10 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by Age Group**



Note: Left points are 1-3 years, middle 4-6 years, right 7+ years
Source: Clinical Study Report

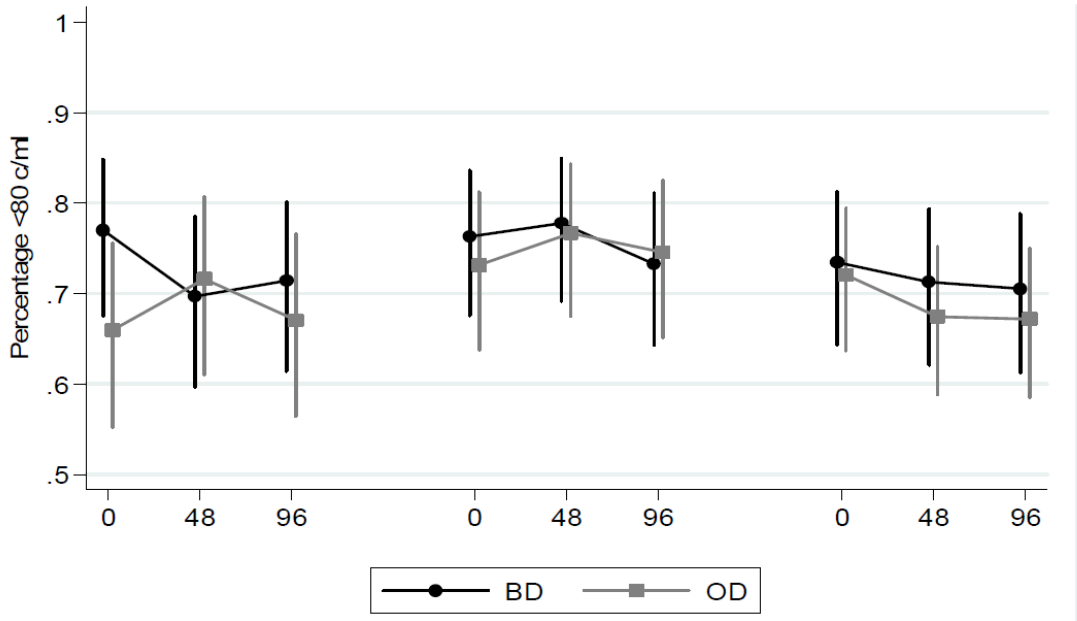
Table 34 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Age Group

	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
1-3 years	77/100 (77)	60/91 (66)
4-6 years	90/118 (76)	79/108 (73)
7+ years	83/113 (73)	98/136 (72)
P-value[a]	0.52	
Week 48		
1-3 years	69/99 (70)	63/88 (72)
4-6 years	91/117 (78)	82/107 (77)
7+ years	82/115 (71)	91/135 (67)
P-value[a]	0.81	
Week 96		
1-3 years	70/98 (71)	61/91 (67)
4-6 years	85/116 (73)	79/106 (75)
7+ years	79/112 (71)	90/134 (67)
P-value[a]	0.80	

a. Test for heterogeneity of once daily versus twice daily comparison across levels.

Source: Clinical Study Report

Figure 17 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Age Group

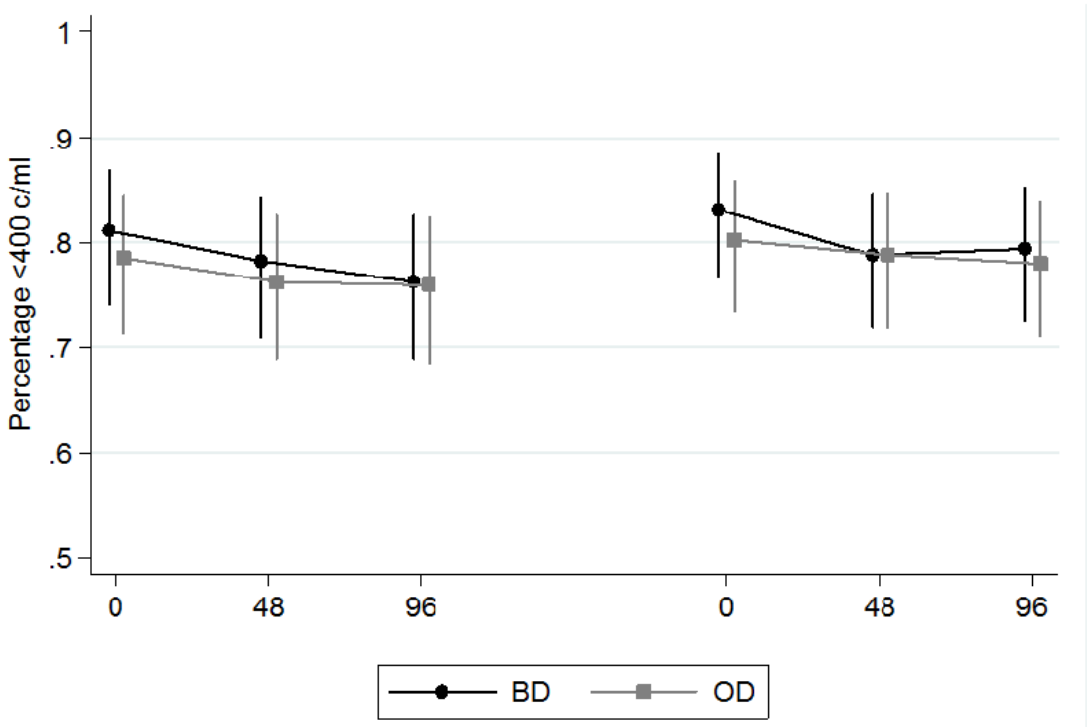


Note: Left points are 1-3 years, middle 4-6 years, right 7+ years

a. Test for heterogeneity of once daily versus twice daily comparison across levels.

Source: Clinical Study Report

Figure 9 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by Sex**



Note: Left points are M, right F
Source: Clinical Study Report

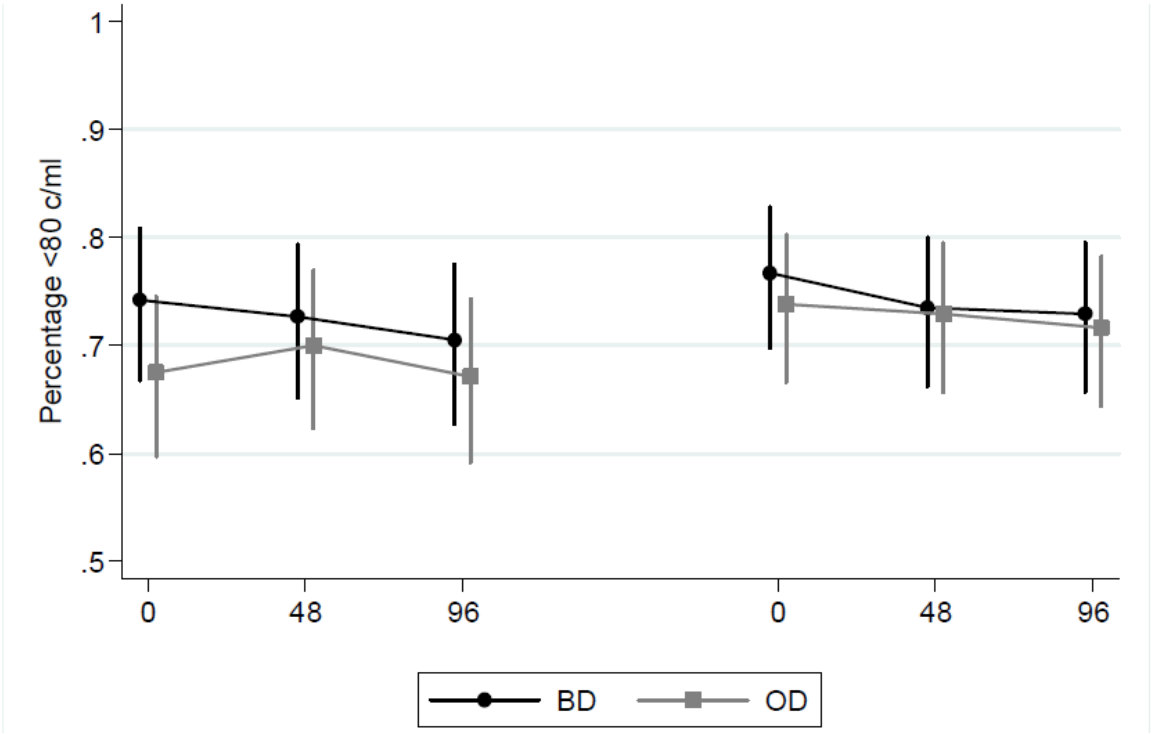
Table 33 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Sex

	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Male	118/159 (74)	110/163 (67)
Female	132/172 (77)	127/172 (74)
P-value[a]	0.63	
Week 48		
Male	117/161 (73)	112/160 (70)
Female	125/170 (74)	124/170 (73)
P-value[a]	0.77	
Week 96		
Male	110/156 (71)	106/158 (67)
Female	124/170 (73)	124/173 (72)
P-value[a]	0.78	

a. Test for heterogeneity of once daily versus twice daily comparison across levels.

Source: Clinical Study Report

Figure 16 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Sex**



Note: Left points are M, right F
Source: Clinical Study Report

4.2 Other Special/Subgroup Populations

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

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

Source: Reviewer's analysis

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

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

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

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

The statistics reviewer obtained results that were similar to the unadjusted primary efficacy analysis after adjusting for center, baseline age, gender and US and WHO weight bands.

However treatment effects appeared to be confounded by baseline HIV viral load and after adjustment there were much smaller risk differences (-1 at Week 48 and -0.3 at Week 96 and the lower bounds of the 95% CI were only -6% and -5% at Weeks 48 and 96).

Summary of Primary Efficacy Analysis by Baseline Viral Load

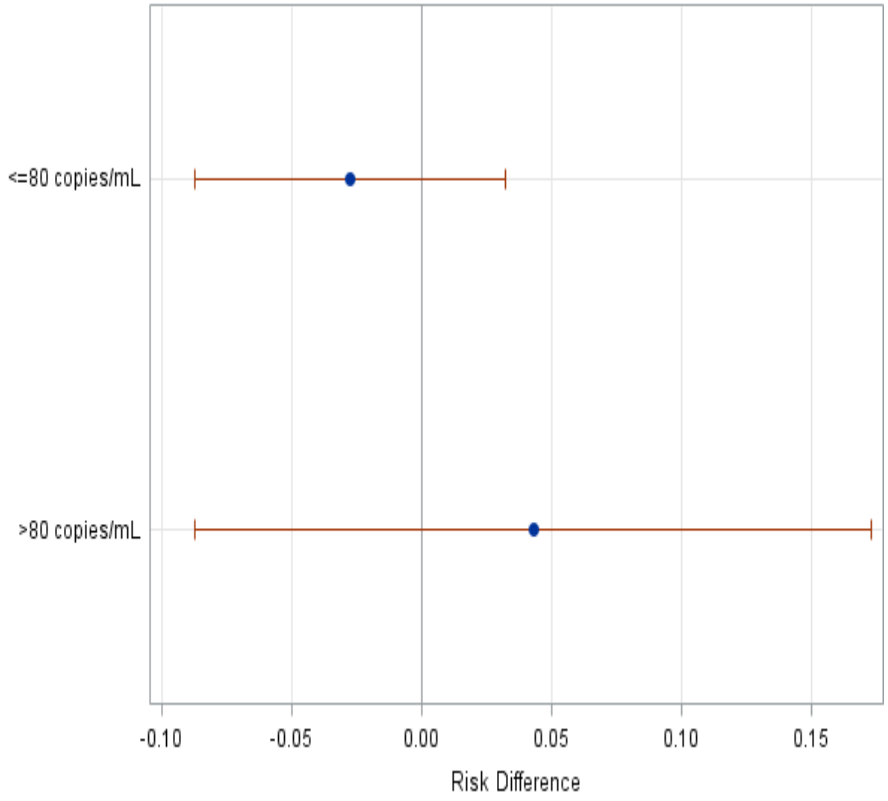
Outcome	Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Baseline Viral Load ≤80 copies/mL				
Snapshot Responders (≤80 copies/mL)	88% (221/250)	86% (203/237)	87% (218/250)	85% (201/237)
Risk Difference and 95% CI[a]	-2.7% (-9% to +3%)		-2.4% (-9% to +4%)	
p-value[b]	0.42		0.51	
Baseline Viral Load >80 copies/mL				
Snapshot Responders (≤80 copies/mL)	25% (21/83)	30% (29/98)	17% (14/83)	24% (24/98)
Risk Difference and 95% CI[a]	+4.3% (-9% to +17%)		+8% (-4% to +19%)	
p-value[a]	0.62		0.27	

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

Upon further investigation, there appeared to be a higher percentage of snapshot responders in the QD regimen than in the BID regimen for subjects with baseline HIV-1 RNA>80 copies/mL. The trend appeared to be slightly reversed for subjects with lower baseline viral loads with about 2% more responders in the BID arm compared to the QD arm. However neither of these interactions was statistically significant as shown previously using the Breslow-Day test and none of the differences in the four strata between QD and BID were statistically significant using Fisher's exact test.

There were much lower response rates for subjects with baseline viral loads >80 copies/mL compared with subjects with low baseline viral loads. Since there were more subjects in the BID arm than the QD arm with low baseline viral loads and more subjects in the QD arm than in the BID arm with high baseline viral loads, this may have led to confounding of the results, making the QD arm look worse than it was compared to the BID arm because subjects with higher baseline viral loads were much more likely to be virologic failures than subjects with low baseline viral loads.

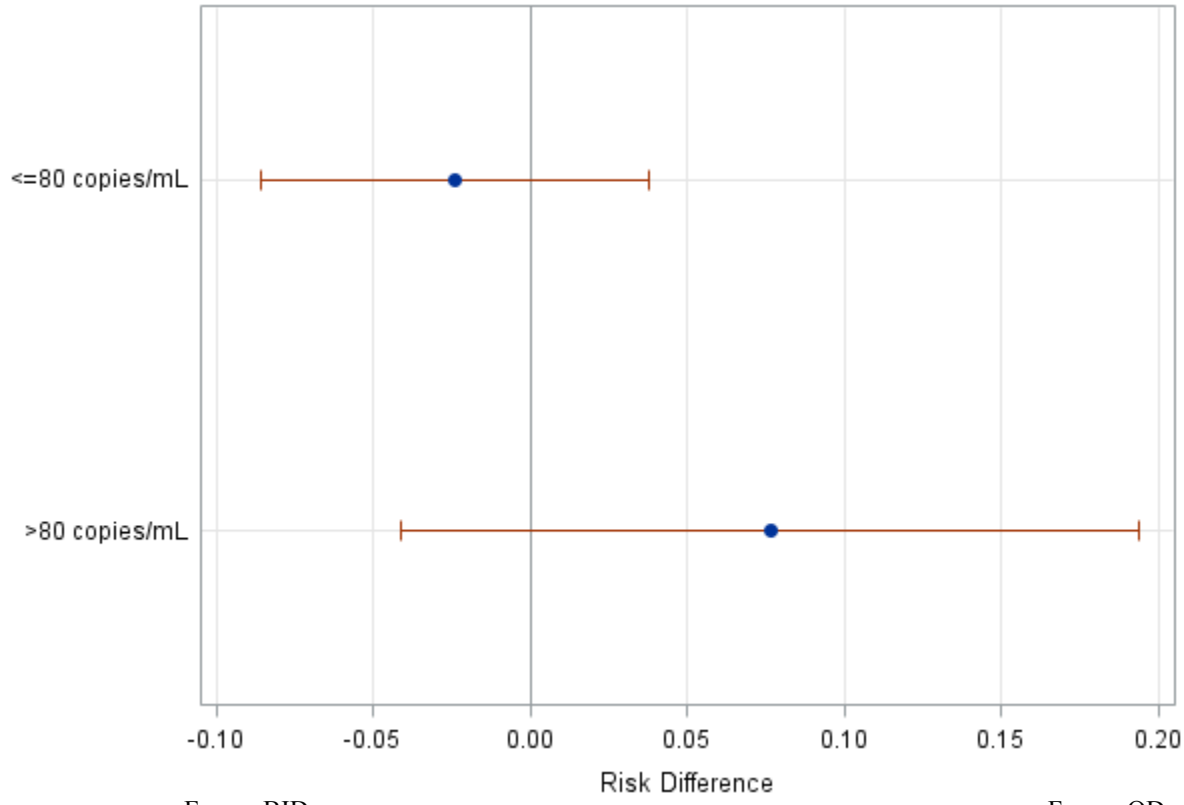
Week 48 Risk Differences with 95% Wald Confidence Intervals by Baseline Viral Load



Favors BID Favors QD

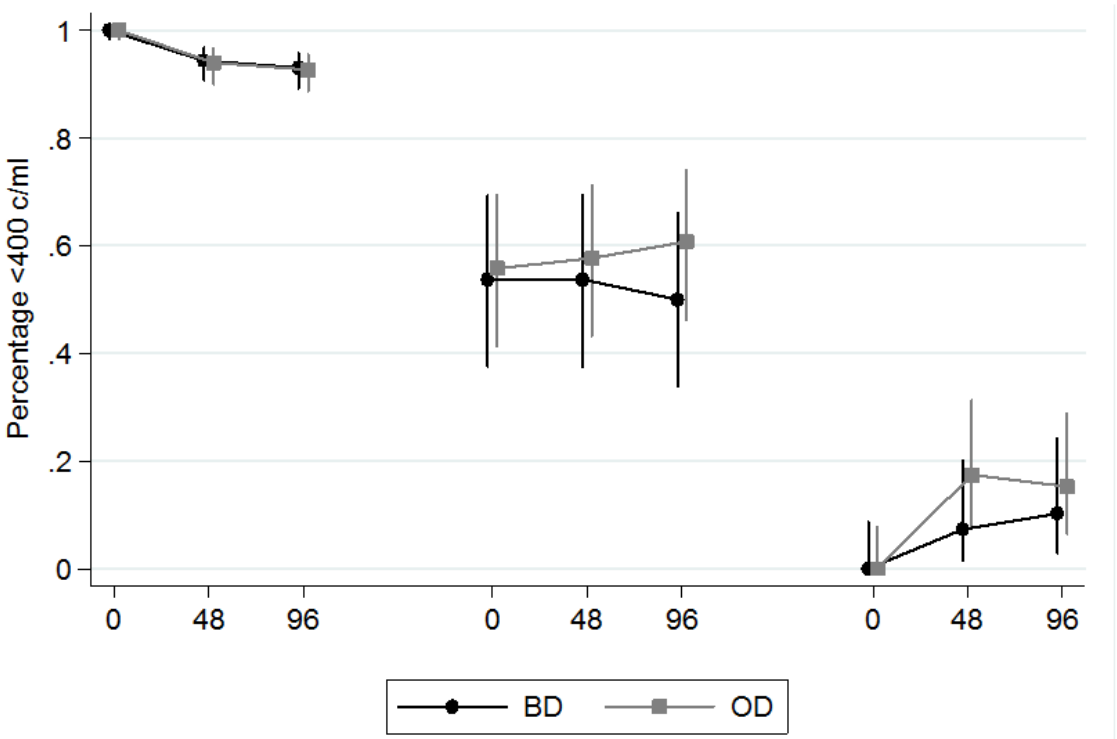
Source: Reviewer's analysis

Week 96 Risk Differences with 95% Wald Confidence Intervals by Baseline Viral Load



Source: Reviewer's analysis

Figure 11 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by Plasma HIV-1 RNA at Randomisation**



Note: Left points are <80 c/mL, middle 80-4999 c/mL, right 5000+ c/mL at randomization to once daily versus twice daily ABC+3TC
Source: Clinical Study Report

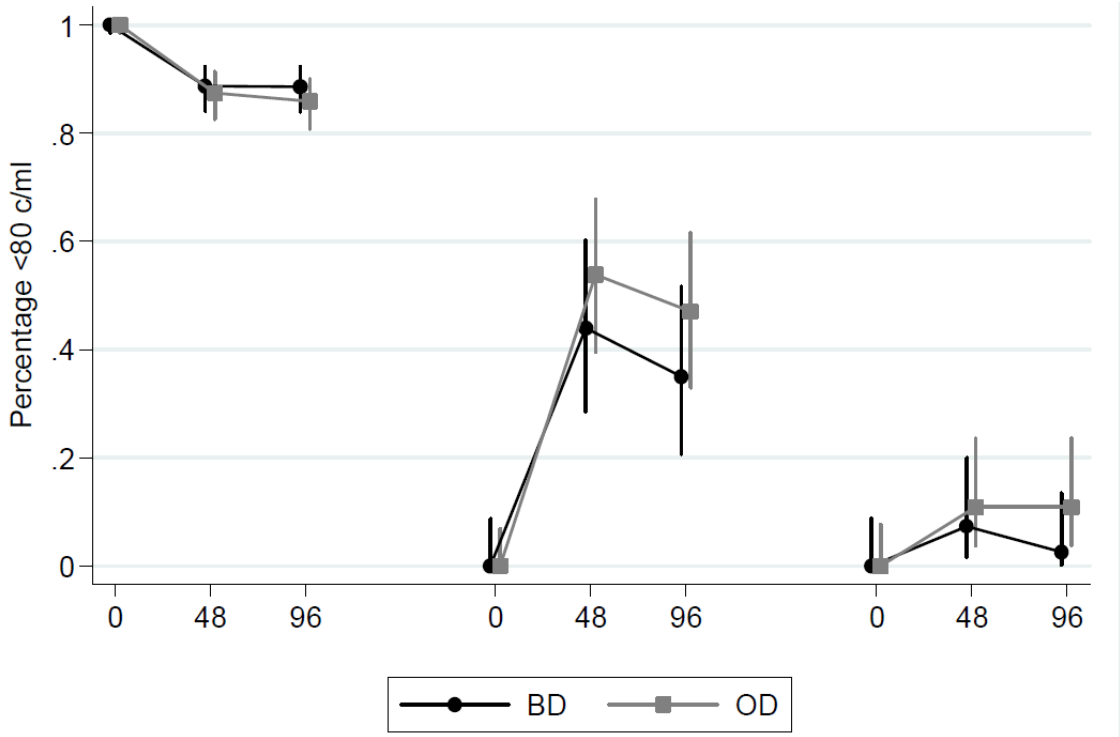
When subjects were stratified by viral load at randomization, the applicant found no statistically significant differences between the QD and BID ABC+3TC effects between subgroups (See Figures 11 and 18 and Tables 26 and 35).

Table 26 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by Plasma HIV-1 RNA at Randomisation

	Twice Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
< 80 c/mL at randomisation	250/250 (100)	237/237 (100)
80-4999 c/mL at randomisation	22/41 (54)	29/52 (56)
5000+ c/mL at randomisation	0/40 (0)	0/46 (0)
Week 48		
< 80 c/mL at randomisation	235/249 (94)	218/232 (94)
80-4999 c/mL at randomisation	22/41 (54)	30/52 (58)
5000+ c/mL at randomisation	3/41 (7)	8/46 (17)
P-value[a]	0.43	
Week 96		
< 80 c/mL at randomisation	230/247 (93)	217/234 (93)
80-4999 c/mL at randomisation	20/40 (50)	31/51 (61)
5000+ c/mL at randomisation	4/39 (10)	7/46 (15)
P-value[a]	0.62	

Source: Clinical Study Report

Figure 18 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Plasma HIV-1 RNA at Randomisation**



Note: Left points are <80 c/mL, middle 80-4999 c/mL, right 5000+ c/mL at randomisation to once daily versus twice daily ABC+3TC

Source: Clinical Study Report

Table 35 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-RNA <80 copies/mL: Subgroup Analysis by Plasma HIV-1 RNA at Randomisation

	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
< 80 c/mL at randomisation	250/250 (100)	237/237 (100)
80-4999 c/mL at randomisation	0/41 (0)	0/52 (0)
5000+ c/mL at randomisation	0/40 (0)	0/46 (0)
Week 48		
< 80 c/mL at randomisation	221/249 (89)	203/232 (88)
80-4999 c/mL at randomisation	18/41 (44)	28/52 (54)
5000+ c/mL at randomisation	3/41 (7)	5/46 (11)
P-value[a]	0.53	
Week 96		
< 80 c/mL at randomisation	219/247 (89)	201/234 (86)
80-4999 c/mL at randomisation	14/40 (35)	24/51 (47)
5000+ c/mL at randomisation	1/39 (3)	5/46 (11)
P-value[a]	0.12	

a. Test for heterogeneity of once daily versus twice daily comparison across levels. Week 0 was not estimable since it defines subgroups

Source: Clinical Study Report

Summary of Snapshot Responses by Randomized Monitoring Arm (Randomization 1)

Outcome	Week 48		Week 96	
	Clinical only N=347 n (%)	Laboratory and Clinical N=322 n (%)	Clinical only N=347 n (%)	Laboratory and Clinical N=322 n (%)
Virologic Success (≤80 copies/mL)	242 (70%)	233 (72%)	234 (67%)	224 (70%)
Risk Difference and 95% CI	+2.6% (-4% to +9%)		+2.1% (-5% to +9%)	
p-value[a]	0.50		0.56	

[a]Fisher's exact p-value
Source: Reviewer's analysis

Randomized Monitoring Arm (Randomization 1) had no statistically significant impact on response rates using a cutoff of 80 copies/mL at Weeks 48 or 96.

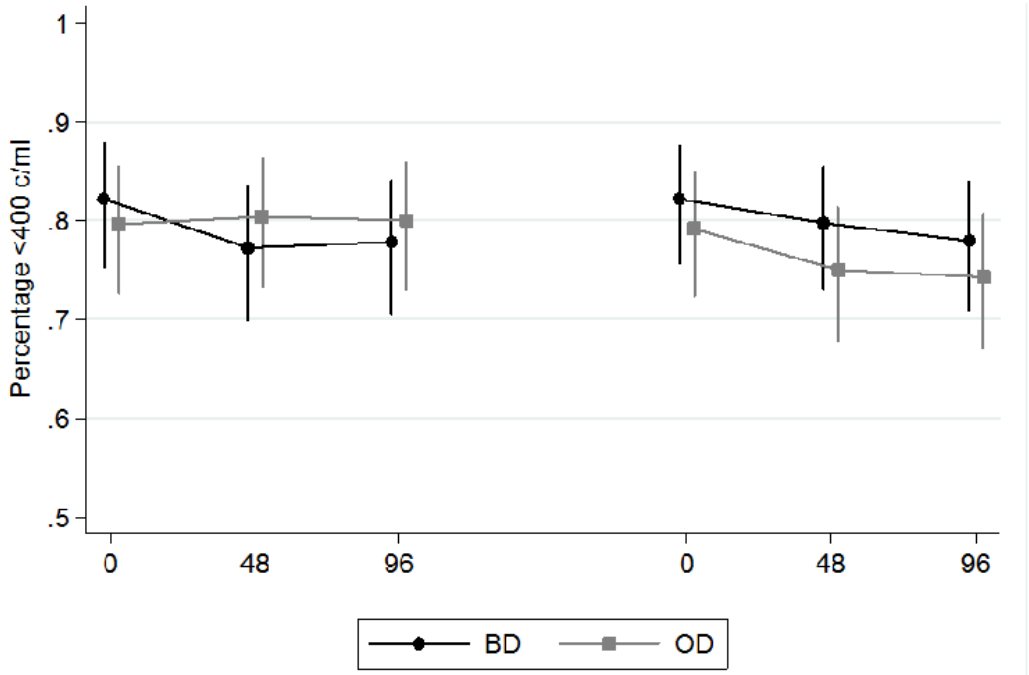
Table 23 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by ARROW Monitoring Randomisation (1) LCM vs CDM

	Twice Daily Plasma HIV-1 RNA <400 c/mL n/N (%)	Once Daily Plasma HIV-1 RNA <400 c/mL n/N (%)
Week 0 (after 36 weeks on Treatment)		
Laboratory and Clinical Monitoring	129/157 (82)	129/162 (80)
Clinically Driven Monitoring	143/174 (82)	137/173 (79)
P-value[a]	0.94	
Week 48		
Laboratory and Clinical Monitoring	122/158 (77)	127/158 (80)
Clinically Driven Monitoring	138/173 (80)	129/172 (75)
P-value[a]	0.22	
Week 96		
Laboratory and Clinical Monitoring	123/158 (78)	128/160 (80)
Clinically Driven Monitoring	131/168 (78)	127/171 (74)
P-value[a]	0.37	

a. Test for heterogeneity of once daily versus twice daily comparison across levels using Mantel-Haenzel
Source: Clinical Study Report

When subjects were stratified by whether their original randomization in the main ARROW protocol was LCM or CDM (Randomization 1), the applicant observed no statistically significant differences between the once daily and twice daily ABC+3TC effect between subgroups for cutoffs of 400 and 80 copies/mL (Table 23 and 32 and Figures 8 and 15).

Figure 8 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by Monitoring Randomisation LCM vs CDM**



Note: Left points are LCM, right CDM
Source: Clinical Study Report

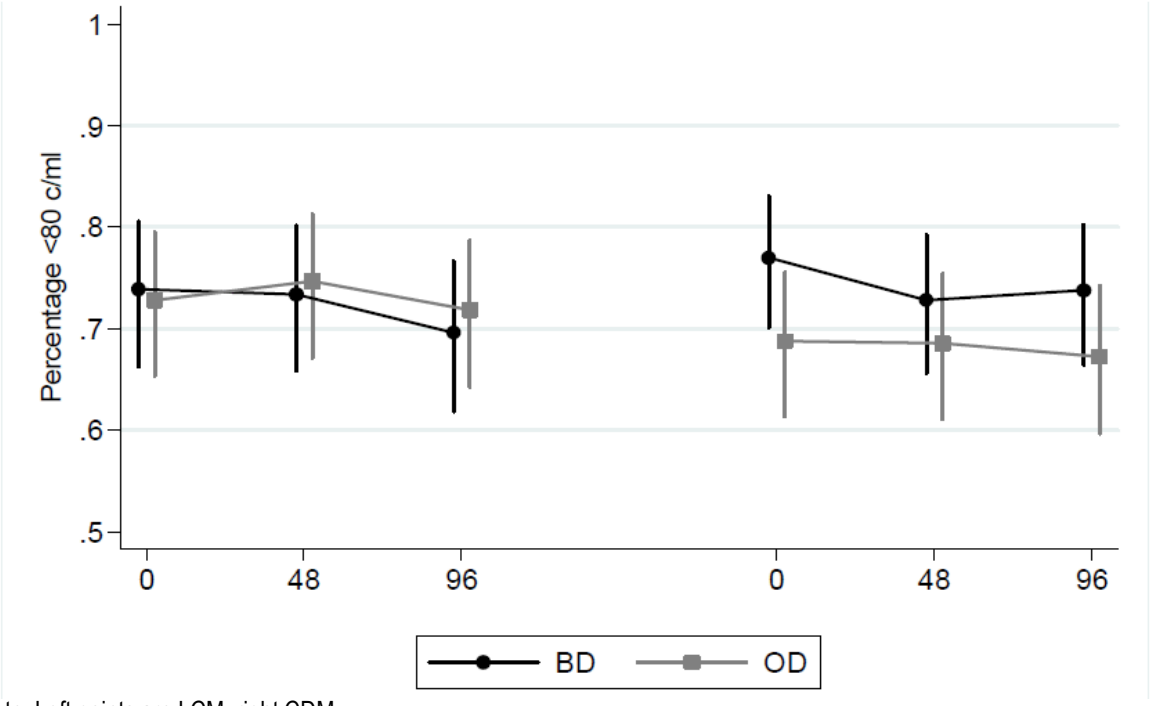
Table 32 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by ARROW Monitoring Randomisation (1) LCM vs CDM

	Twice Daily Plasma HIV-1 RNA <80 c/mL n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL n/N (%)
Week 0 (after 36 weeks on Treatment)		
Laboratory and Clinical Monitoring	116/157 (74)	118/162 (73)
Clinically Driven Monitoring	134/174 (77)	119/173 (69)
P-value[a]	0.30	
Week 48		
Laboratory and Clinical Monitoring	116/158 (73)	118/158 (75)
Clinically Driven Monitoring	126/173 (73)	118/172 (69)
P-value[a]	0.44	
Week 96		
Laboratory and Clinical Monitoring	110/158 (70)	115/160 (72)
Clinically Driven Monitoring	124/168 (74)	115/171 (67)
P-value[a]	0.22	

a. Test for heterogeneity of once daily versus twice daily comparison across levels using Mantel-Haenzel

Source: Clinical Study Report

Figure 15 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Monitoring Randomisation LCM vs CDM**



Note: Left points are LCM, right CDM
Source: Clinical Study Report

Summary of Snapshot Responses by Randomized ART strategies for first-line therapy (Randomization 2)

Outcome	Week 48			Week 96		
	Arm A N=210 n (%)	Arm B N=238 n (%)	Arm C N=221 n (%)	Arm A N=210 n (%)	Arm B N=238 n (%)	Arm C N=221 n (%)
Virologic Success (≤80 copies/mL)	161 (77%)	186 (78%)	128 (58%)	157 (75%)	186 (78%)	115 (52%)
p-value[a]	<0.001			<0.001		

[a]Fisher's exact p-value
Arm A (standard): NNRTI+ABC+3TC continuously
Arm B (induction maintenance): NNRTI+ZDV+ABC+3TC for 36 weeks, then NNRTI+ABC+3TC (drop ZDV – same as ARM A)
Arm C (induction maintenance): NNRTI+ZDV+ABC+3TC for 36 weeks, then ZDV+ABC+3TC (drop NNRTI)
Source: Reviewer's analysis

There were statistically significantly lower response rates for Arm C first-line therapy compared to Arms A and B (Randomization 2), most likely because Arm C only contained one class of drugs (all NRTIs) after 36 weeks when they dropped the NNRTI .

Summary of Analysis of Snapshot Responders (≤80 copies/mL) by Randomization 2 arms

Outcome	Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Randomization 2				
Arm A (standard)	79% (83/105)	74% (78/105)	76% (80/105)	73% (77/105)
Arm B (induction maintenance: drop ZDV – same as ARM A)	75% (88/118)	82% (98/120)	76% (90/118)	80% (96/120)
Arm C: (induction maintenance: drop NNRTI)	65% (71/110)	51% (57/111)	56% (62/110)	48% (53/111)

Source: Reviewer's analysis

The statistics reviewer and applicant also summarized the percentage of responders for BID and QD treatment arms separately for each randomization 2 strata.

As seen in the previous table, consistently lower response rates were observed for Arm C first-line therapy compared to Arms A and B (Randomization 2).

The applicant found a statistically significant interaction difference (p=0.02) between the percentage of responders ≤400 copies/mL in the BID and QD treatment arms and randomization 2 strata at Week 48 (See Table 27 of the Clinical Study Report).

At Week 48, QD appeared somewhat better than BID in Arm B (ABC+3TC+ZDV, dropped ZDV) and somewhat worse in Arm A (standard) and worse in Arm C (ABC+3TC+ZDV, dropped NNRTI). However the applicant pointed out that there were no statistically significant interactions at the time of randomization to QD and BID ABC+3TC (Week 0), where the p-value was 0.22.

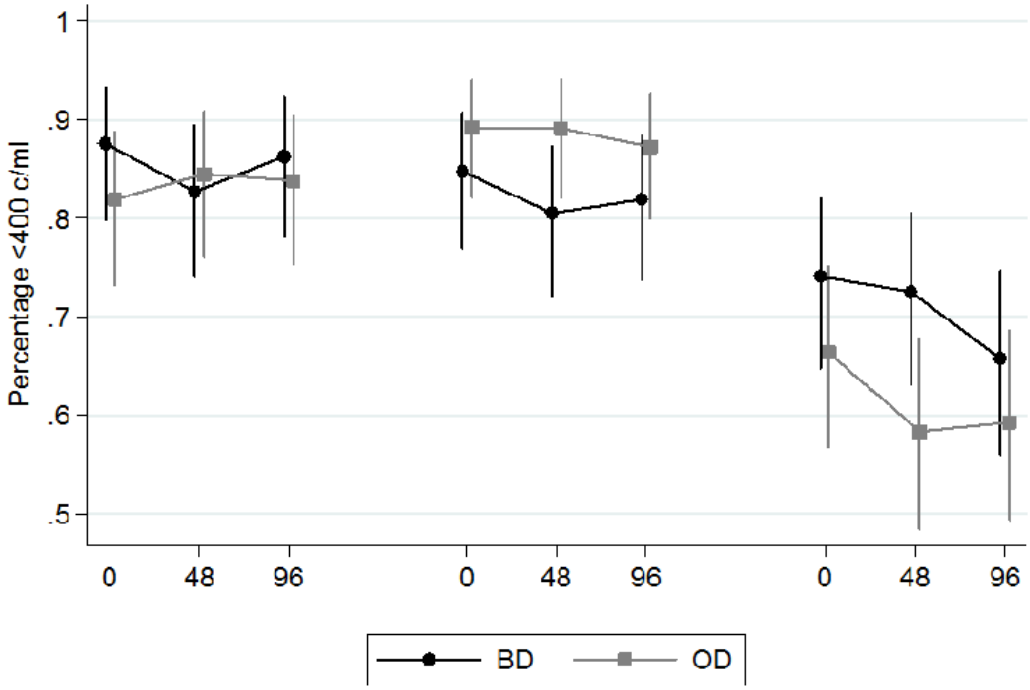
Table 27 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by ART Strategy Randomisation 2 (Four versus three drug induction-maintenance).

	Twice Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Arm A	92/105 (88)	86/105 (82)
Arm B	100/118 (85)	107/120 (89)
Arm C	80/108 (74)	73/110 (66)
P-value[a]	0.22	
Week 48		
Arm A	86/104 (83)	87/103 (84)
Arm B	95/118 (81)	106/119 (89)
Arm C	79/109 (72)	63/108 (58)
P-value[a]	0.02	
Week 96		
Arm A	88/102 (86)	88/105 (84)
Arm B	95/116 (82)	103/118 (87)
Arm C	71/108 (66)	64/108 (69)
P-value[a]	0.30	

a. Test for heterogeneity of once daily versus twice daily comparison across levels.

Source: Clinical Study Report

Figure 12 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by ART Strategy Randomisation**



Note: Left points are Arm A, middle Arm B, right Arm C
Source: Clinical Study Report

Table 36 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by ART Strategy Randomisation 2 (Four versus three drug induction-maintenance).

	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Arm A	83/105 (79)	76/105 (72)
Arm B	93/118 (79)	95/120 (79)
Arm C	74/108 (69)	66/110 (60)
P-value[a]	0.60	
Week 48		
Arm A	83/104 (80)	80/103 (78)
Arm B	88/118 (75)	99/119 (83)
Arm C	71/109 (65)	57/108 (53)
P-value[a]	0.05	
Week 96		
Arm A	81/102 (79)	79/105 (75)
Arm B	90/116 (78)	97/118 (82)
Arm C	63/108 (58)	54/108 (50)
P-value[a]	0.32	

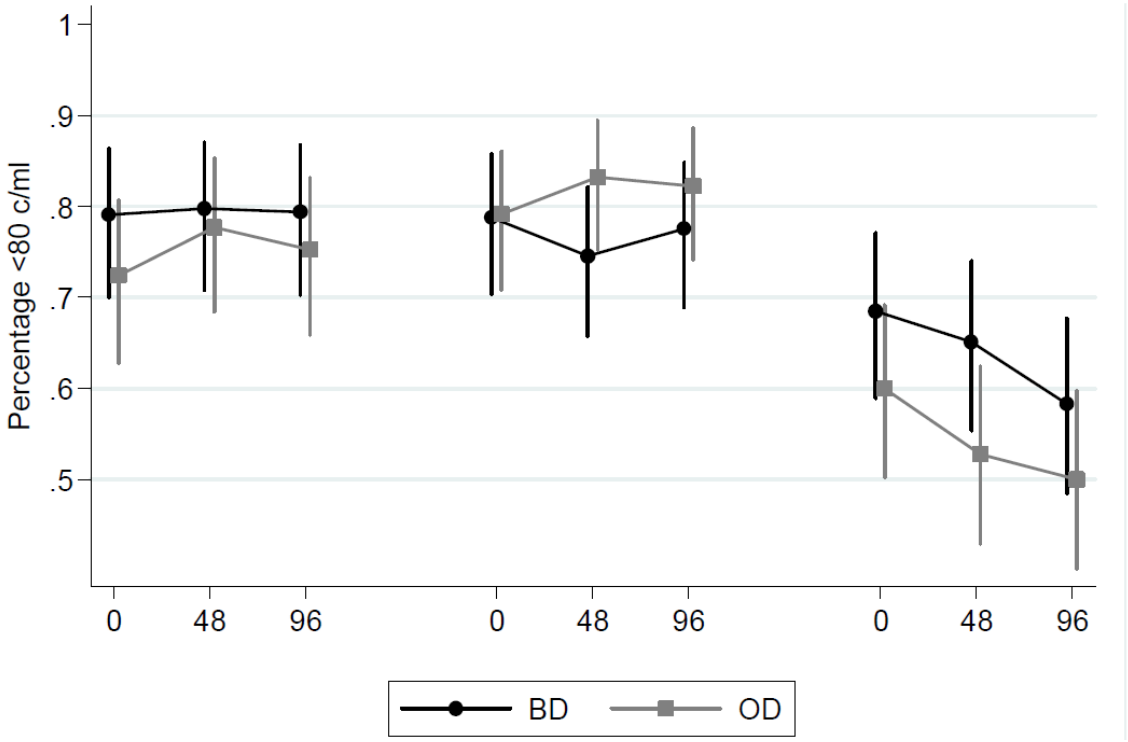
a. Test for heterogeneity of once daily versus twice daily comparison across levels.

Source: Clinical Study Report

The applicant also found a marginally statistically significant interaction difference (p=0.05) between the percentage of responders ≤80 copies/mL in the BID and QD treatment arms and randomization 2 strata at Week 48 (See Table 36 of the Clinical Study Report).

At Week 48, QD appeared somewhat better than BID in Arm B (ABC+3TC+ZDV, dropped ZDV) and somewhat worse in Arm C (ABC+3TC+ZDV, dropped NNRTI). However the applicant pointed out that there were no statistically significant interactions at the time of randomization to QD and BID ABC+3TC (Week 0) (p=0.60).

Figure 19 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by ART Strategy Randomisation**



Note: Left points are Arm A, middle Arm B, right Arm C

Source: Clinical Study Report

Table 28 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by ART Combination at Randomisation

	Twice Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
3TC ABC EFV[a]	39/49 (80)	67/73 (92)
3TC ABC NVP	152/171 (89)	126/148 (85)
3 NRTI[a]	81/111 (73)	73/114 (64)
P-value[c]	0.04	
Week 48		
3TC ABC EFV	39/49 (80)	66/71 (93)
3TC ABC NVP	143/170 (84)	126/147 (86)
3 NRTI[a]	78/112 (70)	64/112 (57)
	0.01	
Week 96		
3TC ABC EFV	39/48 (81)	69/72 (96)
3TC ABC NVP	144/167 (86)	122/147 (83)
3 NRTI[b]	71/111(64)	64/112 (57)
	0.01	

a. One child receiving 3TC+d4T+ABC; all others on 3TC+ZDV+ABC

d. Received a completely once daily regimen if randomized to once daily: all other children remained on twice daily ART

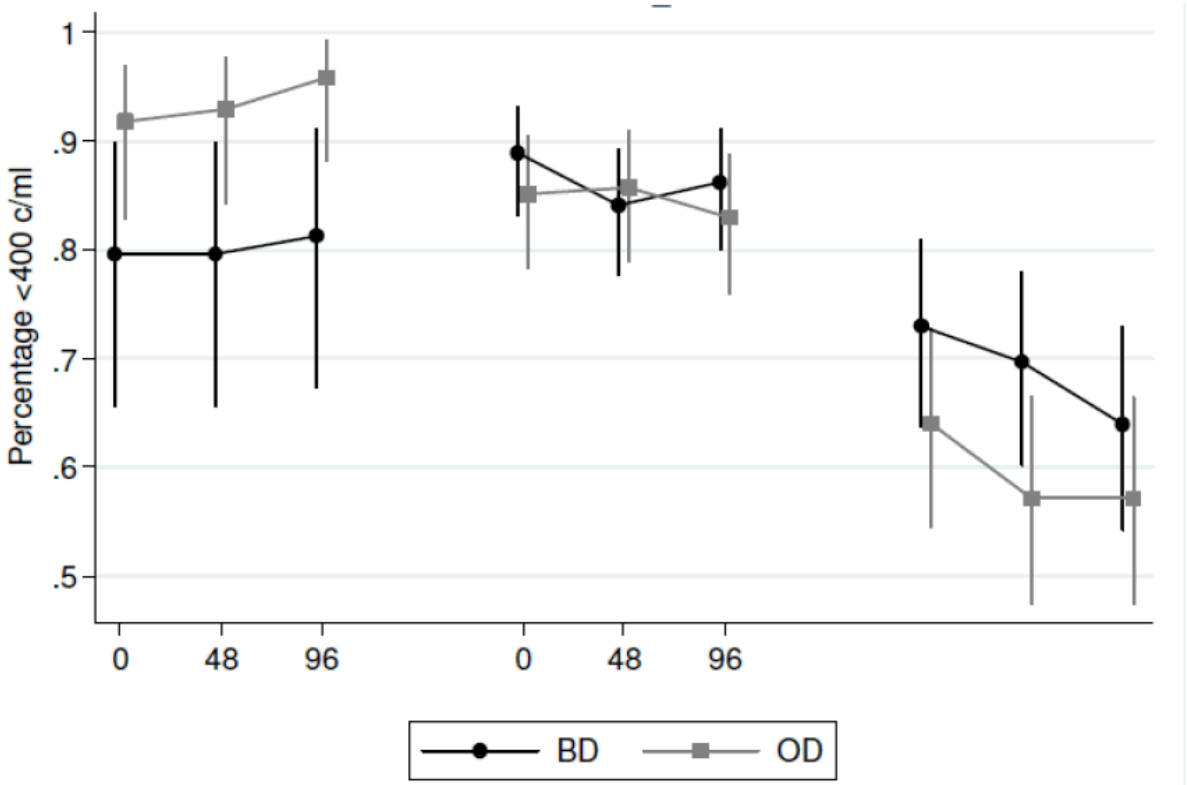
e. Test for heterogeneity of once daily versus twice daily comparison across levels.

Source: Clinical Study Report

When subjects were stratified by their ART combination at randomization, statistically significant differences in the once daily versus twice daily treatment effect were observed between subgroups at Weeks 0, 48 and 96 (Table 28 and Figure 13). However the applicant pointed out that at baseline, children whose third drug was EFV once daily, who were randomized to once daily ABC+3TC, had higher suppression rates than those randomized to twice daily ABC+3TC and vice versa for 3NRTIs (third drug ZDV twice daily). The applicant stated that this was a baseline imbalance which can only be due to chance because of the randomization.

At Weeks 48 and 96 after randomization, once daily remained somewhat better than twice daily with EFV, and somewhat worse with 3NRTIs; that is, the baseline imbalance persisted.

Figure 13 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by ART Combination at Randomisation**



Note: Left points are 3TC ABC EFV, middle 3TC ABC NVP, right 3 NRTI
Source: Clinical Study Report

Table 37 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by ART Combination at Randomisation

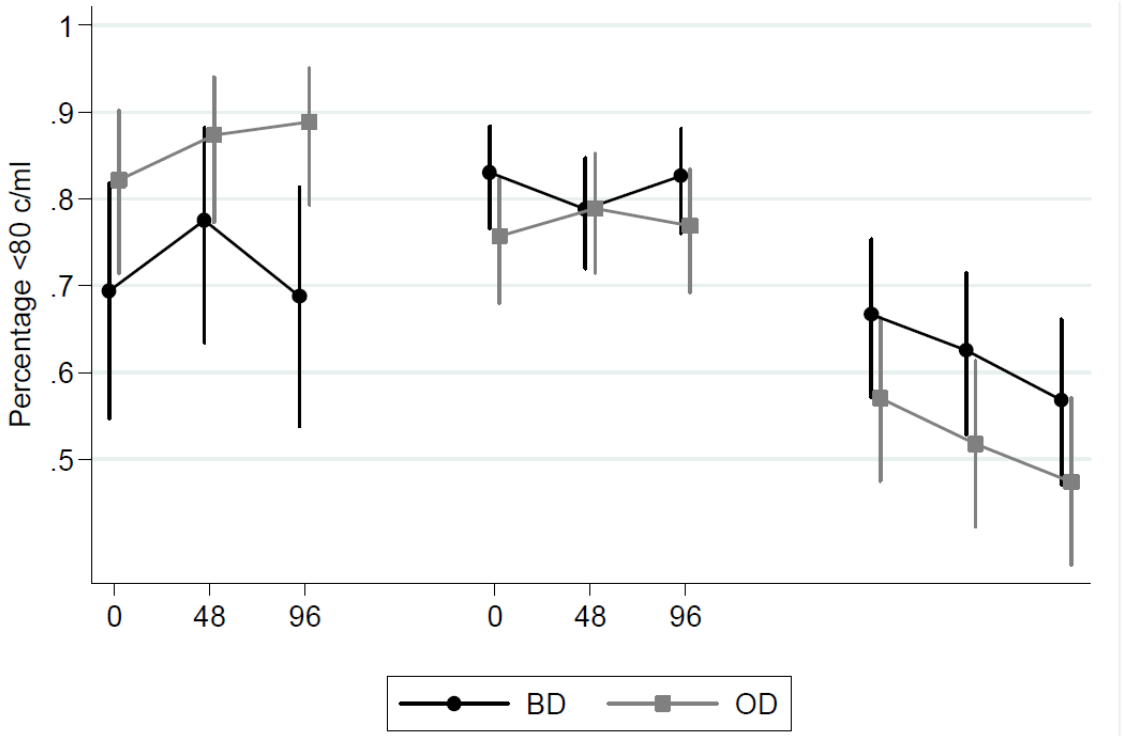
	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
3TC ABC EFV[a]	34/49 (69)	60/73 (82)
3TC ABC NVP	142/171 (83)	112/148 (76)
3 NRTI[a]	74/111 (67)	65/114 (57)
P-value[c]	0.05	
Week 48		
3TC ABC EFV	38/49 (78)	62/71 (87)
3TC ABC NVP	134/170 (79)	116/147 (79)
3 NRTI[a]	70/112 (62)	58/112 (52)
	0.12	
Week 96		
3TC ABC EFV	33/48 (69)	64/72 (89)
3TC ABC NVP	138/167 (83)	113/147 (77)
3 NRTI[b]	63/111 (57)	53/112 (47)
	0.004	

a. One child receiving 3TC+d4T+ABC; all others on 3TC+ZDV+ABC
b. Received a completely once daily regimen if randomised to once daily: all other children remained on twice daily ART
c. Test for heterogeneity of once daily versus twice daily comparison across levels.

Source: Clinical Study Report

The applicant did not find a statistically significant interaction between BID and QD response rates ≤80 copies/mL and ART combination at randomization at Week 48 but the interaction was statistically significant at Week 96 (p=0.004) and was marginally significant at Week 0 (p=0.05). The post-baseline interaction appeared to be due to the baseline imbalance.

Figure 20 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by ART Combination at Randomisation**



Note: Left points are 3TC ABC EFV, middle 3TC ABC NVP, right 3 NRTI

Source: Clinical Study Report

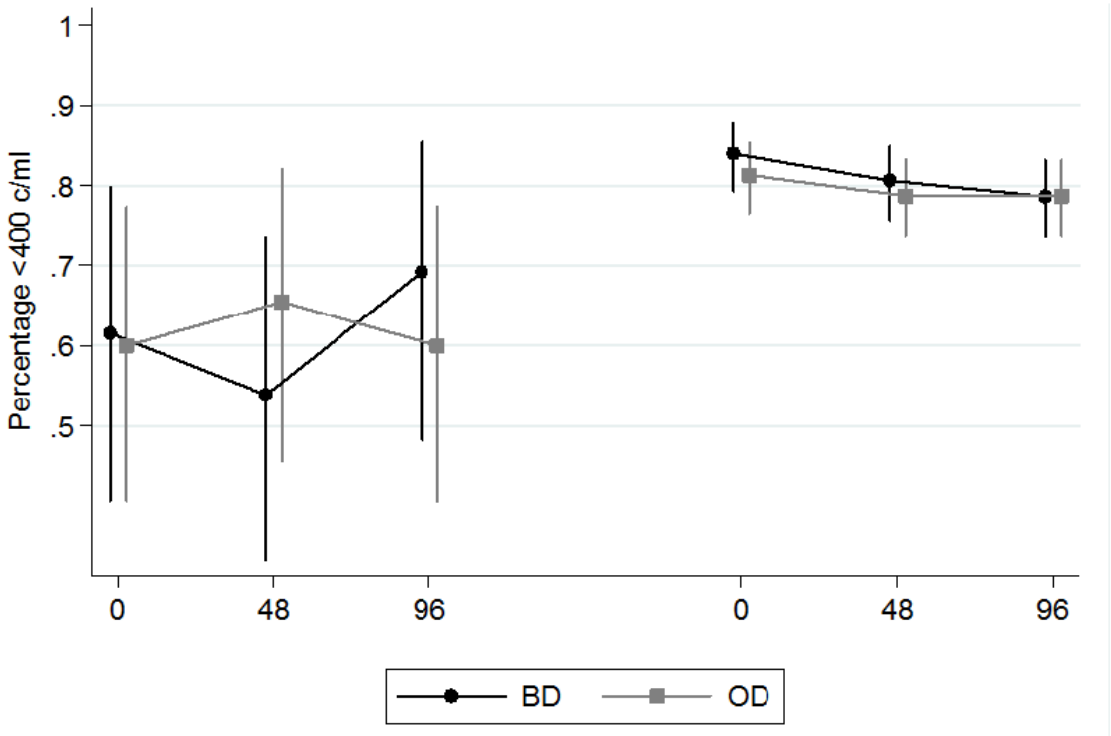
Table 29 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by Formulation

	Twice Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <400 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Any solution	16/26 (62)	18/30 (60)
All tablets	256/305 (84)	248/305 (81)
P-value[a]	0.84	
Week 48		
Any solution	14/26 (54)	19/29 (66)
All tablets	246/305 (81)	237/301 (79)
P-value[a]	0.31	
Week 96		
Any solution	18/26 (69)	18/30 (60)
All tablets	236/300 (79)	237/301 (79)
P-value[a]	0.50	

a. Test for heterogeneity of once daily versus twice daily comparison across levels.
Source: Clinical Study Report

The applicant did not find any statistically significant interactions between QD and BID responses and formulation subgroups at Week 0, 48 or 96 using either cutoff (80 or 400 copies/mL).

Figure 14 **Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <400 copies/mL: Subgroup Analysis by Formulation**



Note: Left points are any solution, right all tablets
Source: Clinical Study Report

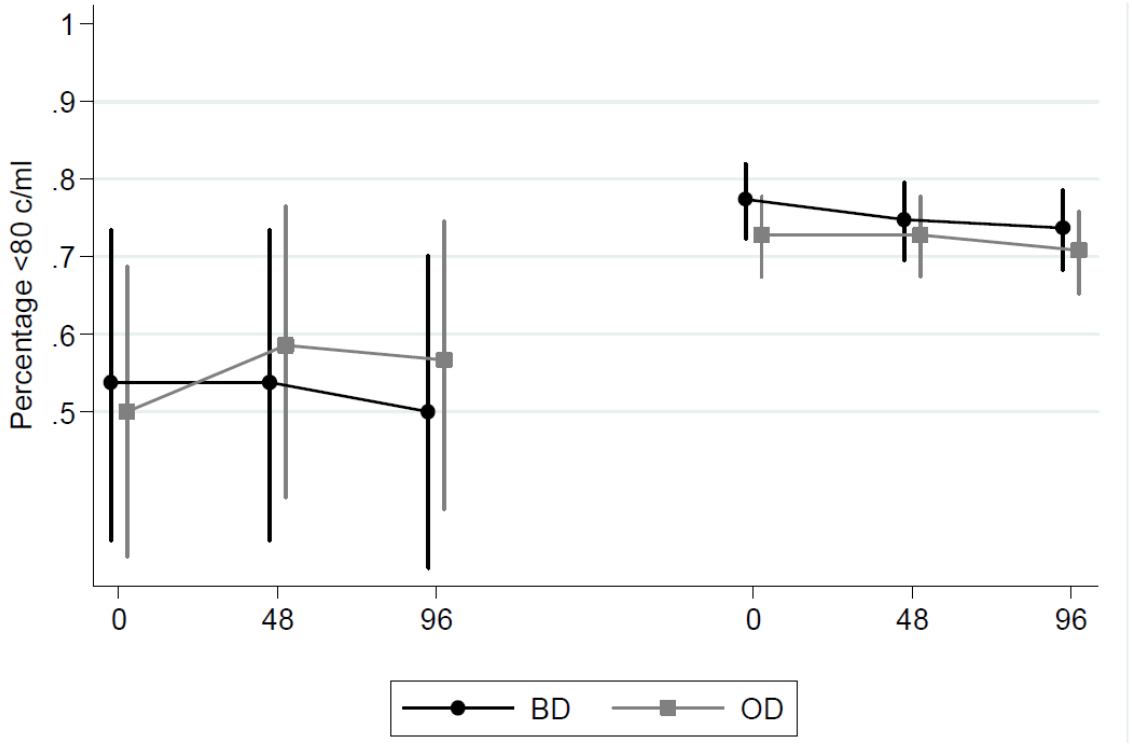
Table 38 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Formulation

	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Any solution	14/26 (54)	15/30 (50)
All tablets	236/305 (77)	222/305 (73)
P-value[a]	0.87	
Week 48		
Any solution	14/26 (54)	17/29 (59)
All tablets	228/305 (75)	219/301 (73)
P-value[a]	0.61	
Week 96		
Any solution	13/26 (50)	17/30 (57)
All tablets	221/300 (74)	213/301 (71)
P-value[a]	0.47	

a. Test for heterogeneity of once daily versus twice daily comparison across levels.

Source: Clinical Study Report

Figure 21 Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Formulation



Note: Left points are any solution, right all tablets
Source: Clinical Study Report

The applicant also conducted multivariate exploratory models involving subgroups. These are shown in the Appendix.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Brief summary of COL105677 AntiRetroviral Research fOr Watoto (ARROW)

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

ARROW = AntiRetroviral Research fOr Watoto

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

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

5.2 Collective Evidence

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

Outcome	Week 48		Week 96	
	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)	Twice-Daily ABC+3TC N=333 n (%)	Once-Daily ABC+3TC N=336 n (%)
Virologic Success (≤80 copies/mL)	242 (73)	233 (69)	232 (70)	226 (67)
Risk Difference and 95% CI	-3.3% (-10% to +4%)		-2.4% (-9% to +5%)	
Virologic Failure (>80 copies/mL)	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	90 (27)	95 (28)	90 (27)	100 (30)
Prior change in antiretroviral therapy	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	1 (<1)	5 (1)	4 (1)	3 (1)
Discontinued due to AE or Death[a]	0	0	3 (1)	1 (<1)
Discontinued due to other reasons	0	0	0	1 (<1)

[a] Deaths only; none of the subjects discontinued due to AEs
Source: Reviewer's analysis

At Week 48, 73% and 69% of the subjects were responders in BID and QD arms with a risk difference of -3.3% (95% CI: -10% to +4%). . At Week 96 response rates decreased to 70% and 67% in the BID and QD arms with a risk difference of -2.4% (95% CI: -9% to +5%).

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

5.3 Conclusions and Recommendations

Only about 70% of the subjects had HIV-1 RNA viral loads that were suppressed below 80 copies/mL prior to randomization to continue twice-daily abacavir and lamivudine treatment or transition to once-daily abacavir and lamivudine treatment. The applicant declared that since the NI margin was 12% that NI was demonstrated. As noted in Section 5.1, typically 12% NI

margins for switch trials may be too large. However since response rates were lower (around 70% instead of 90% in switch trials for other NDAs) the larger margin was of less concern. In addition, the lower bound of the 95% confidence intervals for treatment differences at Weeks 48 and 96 was also ≥-10%. The statistics reviewer also found that most of difference between response rates in the QD and BID arms disappeared after adjusting for the baseline HIV RNA imbalance where subjects with baseline HIV RNA levels > 80 copies/mL had very low Week 48 and 96 response rates. Therefore the statistics reviewer agrees with the applicant's conclusion that the QD regimen is NI to the BID regimen.

5.4 Labeling Recommendations (as applicable)

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

14.2 Pediatric Trials

(b) (4)

(b) (4)

(b) (4)

The sentence above (b) (4)

An additional

sentence should be added stating that [redacted] (b) (4)

The snapshot outcomes table below is more consistent with other NDAs (e.g., Complera) and other tables displayed in Section 14:

[redacted] (b) (4)

APPENDICES

Sponsor's Sample Size Considerations

The aim was to recruit all eligible ARROW children from the ARROW centers in Uganda (3) and Zimbabwe (1). Children were allocated in a 1:1 ratio to once or twice daily ABC+3TC.

The estimation of the sample size was based on the following assumptions:

(1) 70% children had HIV RNA <50 copies/mL at Week 48 on twice-daily dosing*

(2) 15% of randomized children had missing samples for HIV-1 RNA testing at Week 48, due to missing samples, missed visits, death, or loss to follow-up.

With these assumptions, at least 90% power and two-sided alpha=0.05, at least 934 children would be required to exclude a 10% lower suppression rate in the once daily group (lower 95% confidence limit of difference between once and twice daily -10%). During accrual to this randomization during 2009-2010, more children than initially projected were found to be ineligible due to already receiving full adult dose KIVEXA (ABC+3TC) once daily in the highest weight-bands. Therefore recruitment to the original target of 1000 could not be achieved. The revised target of 630 children is based on a 12% non-inferiority margin (also recommended by Food and Drug Administration [FDA]): at least 631 children would be required to exclude a 12% lower suppression rate in the once daily group with at least 90% power and two-sided alpha=0.05 (lower 95% confidence limit of difference between once and twice daily -12%). Of note, the revised sample size of 630 children retained at least 80% (rather than 90%) power to exclude a 10% (rather than 12%) lower suppression rate in the once daily group with one-sided alpha=0.05 (lower 90% confidence limit of difference between once and twice daily -10%).

*The sample size was based on a proportion <50 c/mL. However, when retrospective testing started the applicant said that it became quickly apparent that the blood volumes stored from these children (many of whom were relatively young) were too small to run undiluted on the Abbott m2000rt machine, and therefore 1 in 2 dilution was used, giving a lower threshold of <80 copies/mL. The 12% non-inferiority margin was carried over to this slightly higher threshold, and also applied to other clinically relevant VL thresholds (<200, <400, and <1000 copies/mL).

Justification of the 12% Non-Inferiority Margin

The 12% N.I. margin can be justified using Section 2.0 in the draft HIV Guidance Document. It states the following: Based on early studies with NNRTIs such as nevirapine and delavirdine, one NRTI in combination with an NNRTI was not sufficient to achieve and maintain undetectable HIV-RNA levels. Conservatively one could attribute half of the treatment effect to each NRTI. In two recent trials in treatment-naïve patients, the lower bound for the treatment effect for an EFV/tenofovir/emtricitabine regimen was 77% (pooled data from two trials). Therefore half of the treatment effect (38%) could be attributed to each NRTI. If one wanted to preserve an additional 50% of the effect, the margin is 19%. However clinically we do not want to lose more than 10-12% of the treatment effect (M2 margin). Similarly, for the reasons stated, an M2 of 10-12% is an acceptable margin for an endpoint of HIV-1 RNA below 50 copies/mL at 48 weeks.

This logic should also apply to similar endpoints like HIV-1 RNA < 80 copies/mL.

Similar arguments could be proposed for 3 NRTIs (ABC + 3TC + ZDV).

However as stated previously the 12% margin may not be applicable to switch trials.

DATASET QUESTIONS

In August 2014 the following issues were identified:

BIOMETRICS

FDA Question 1:

Subjects 13081 and 13093 appear to be virologic failures at Week 48 in the VL_PARTC dataset with Week 48 RNA=1196 and 4988. However the SNAPSHOT and ADEFFOUT datasets classify these patients as having 'No Virologic Data' with snapshot dataset variables outco2='Missing data during window but on study' and vlquery='discrepant duplicate results for this sample.'

RESPONSE:

To clarify, as recorded in the original ARROW VL report (page 8), information from the site was reported with respect to discrepant viral load samples. Specifically, for Subjects 13081 and 13093, duplicate Week 48 samples yielded very discrepant results on these samples. These discrepancies suggested that a sample identifier had been incorrectly entered into the assay machine. Without knowing which the "true" result was and without having enough residual sample to repeat the assay, MRC determined that these two subjects had insufficient information to contribute data to the Week 48 analysis. Therefore, these subjects were classified as non-responders due to "Missing data during window but on study" since the viral load measurements were unreliable.

Of note, three other discrepancies were also reported. Subjects 16041 and 16055 did not contribute reliable measurements to Week 0 for the same reason described above. And Subject 23156 did not contribute a reliable measurement due to a failed run where the negative control was reactive. Despite the provision of viral load measurements, these five values were not used in the analysis due to unreliability, as determined by the variable VLQUERY.

FDA Question 2:

In the ADEFFOUT dataset, the variable exendy (study day of end of treatment) is less than exdur (duration of treatment) for several subjects but should be greater than or equal to exdur. As an example subject 13054 has exendy= 43 while exdur= 920. As shown in your example in the Reviewer's Guide, since this child switched to 2nd line treatment (on study day 43) exendy= 43 days. However exdur= 920 which appears to reflect the number of days on any treatment including CBV which was part of their 2nd line regimen that did not include ABC. The variable exdur should only count the number of days of randomized treatment.

RESPONSE:

ADEFFOUT dataset has been revised according to the clarification of the definition for the variable EXDUR. Previously, we constructed this variable to capture time on study with all treatments to differentiate it from the variable EXENDY which captured time on randomized

study treatments. The new definition takes into account treatment changes and only counts days for which the subject is known to be receiving ABC+3TC treatment. Therefore, EXENDY is now greater than or equal to EXDUR.

EXENDY=Study Day corresponding to the end of randomized treatment

EXDUR=Duration of randomized treatment taking into account intermediate treatment changes to ABC+3TC

FDA Question 3:

There appears to be an error in the ADEFFOUT dataset for the variables v48_s80, v48_s80c, v96_s80 and v96_s80c. When subjects change to a 2nd line regimen that does not include ABC the variables in the primary efficacy outcome appear to be correct in the SNAPSHOT dataset but the corresponding snapshot outcome variables in the ADEFFOUT dataset appear to be incorrect. For example, in the SNAPSHOT dataset subject 13054 at weeks 48 and 96 has outco='Virologic Failure', outco2cd=7 and outco2='Prior change in ART' while in the adeffout dataset v48_s80 and v96_s80='Y' and v48_s80c and v96_s80c='Virologic success (HIV RNA <80 copies/mL)'. In addition, the reason for virologic non-response according to the snapshot algorithm should appear in the field for the variables v48_s80s and v96_s80s but they are blank.

RESPONSE:

With the clarification of the definition of EXDUR, the revision to the ADEFFOUT dataset ensures agreement between the variables pertaining to the snapshot algorithm in this dataset and the SNAPHOT dataset. Thank you for the advice. The updated dataset and corresponding documentation is provided with this submission.

Please note that while revising the ADEFFOUT variable definitions described above, another modification was made to the ADEFFOUT variable definitions for RFSTDT and RFSTDTC and the subsequent variables which depend on these variables (for example, ANYCHGDY, DGCHGDY, etc). The new derivations for these variables provide more complete records for certain subjects. The define.pdf remains unchanged. Importantly, the source tables in the application are unaffected as a result of this update because ADEFFOUT was not used in producing the statistical displays.

The following additional issues were addressed in September 2014:

BIOMETRICS

The variables for reason for virologic non-response according to the snapshot algorithm should appear in the field for the variables v48_s80s and v96_s80s but they are still

blank. Please review the revised datasets and resubmit the field for the variables as listed above as soon as possible.

RESPONSE:

ADEFFOUT was updated in September to include the subcategory reasons for variables V48_S80S and V96_S80S.

After the updated adeffout dataset was submitted in September 2014 the following issues pertaining to the adeffout dataset were identified during the review process:

BIOMETRICS

FDA Question 1:

The response to Question 2 indicates that you corrected the adeffout dataset so that study day of end of randomized treatment (exendy) always is greater than or equal to duration of randomized treatment (exdur). However, there still appear to be several subjects for whom exdur was greater than exendy. For example, Subject 13040 had continuous ABC or KIV treatment but exendy was only 227 days while exdur was 730 days.

RESPONSE:

As noted, the values for variables EXENDY and EXDUR did not match the criteria of EXENDY>=EXDUR for all subjects. This was the case for sixteen subjects in the previous ADEFFOUT data set. We believe the issue was due to STOPDATE in the ADHERENC data set, which was originally used in the calculation of EXENDY.

However, these stop dates for these 16 subjects were not supported by data from other data sets (CYRS_*, ARTCHNG, and PYRS) that show that these subjects were still ondrug after the STOPDATE in the ADHERENC data set. The treatment end date used to calculate EXENDY is now calculated using the earliest date between LINE2DAT and ENDDATE (both from PYRS).

EXDUR uses these variables in addition to CHNGDAT, COMB, and REASON_ in ARTCHNG dataset to identify the short periods when either ABC and/or 3TC were interrupted. STOPDATE was not used to calculate EXDUR and thus is not affected by this programming modification. EXENDY has been updated in ADEFFOUT dataset. Treatment details for the 16 subjects whose EXENDY value was modified are located in Table 1.

Table 1 ARROW: Listing of Subjects with Modified Study Day of End of Treatment (EXENDY)

Subj.	Date of BD/OD randomisation	Date when Stopped Early per ADHERENC	Date of follow-up end	Duration	Study day of end of Treatment	Date of ART change	Decode of Reason for change (REASON)
13040	18MAR2010	30OCT2010	16MAR2012	730	730	28JUL2011	Body size change
16015	18SEP2009	23JUL2011	16MAR2012	903	911	25FEB2010	Voluntary patient/carer decision
						05MAR2010	Restart ART/restart previous drug
						06JAN2012	Body size change
16048	11NOV2009	12NOV2009	16MAR2012	857	857		
16067	26AUG2009	17NOV2009	16MAR2012	934	934	18MAY2011	Body size change
						17APR2012	Child unable to attend clinic
						26APR2012	Restart ART/restart previous drug
23049	19NOV2009	25MAR2010	16MAR2012	847	849	28JUL2010	Other
						29JUL2010	Other
						09SEP2010	Other
						10SEP2010	Other
23078	01DEC2009	13AUG2010	16MAR2012	834	837	10AUG2010	Other
						11AUG2010	Other
						12AUG2010	Other
						13AUG2010	Other
						24AUG2010	Other
						25AUG2010	Other
23102	23NOV2009	19AUG2010	16MAR2012	828	845	02AUG2010	Child unable to attend clinic
						19AUG2010	Restart ART/restart previous drug

Subj.	Date of BD/OD randomisation	Date when Stopped Early per ADHERENC	Date of follow-up end	Duration	Study day of end of Treatment	Date of ART change	Decode of Reason for change (REASON)
23106	24FEB2010	06APR2010	16MAR2012	749	752	25FEB2010	Other
						10AUG2010	Other
						11AUG2010	Other
						24AUG2010	Other
						25AUG2010	Other
23144	18NOV2009	01OCT2010	16MAR2012	850	850		
23162	13OCT2009	14OCT2009	16MAR2012	886	886		
26099	04MAY2010	16JUN2010	16MAR2012	660	683	05MAY2010	Other
						15JUN2010	Other
						16JUN2010	Other
						27JUL2010	Restart ART/restart previous drug
						17JAN2012	Child unable to attend clinic
						07FEB2012	Restart ART/restart previous drug
33094	12MAY2010	23JUN2010	16MAR2012	675	675	23JUN2010	Voluntary patient/carer decision
33109	02JUN2010	05MAY2011	16MAR2012	654	654		
43062	12APR2010	14MAY2010	11MAR2011	334	334	14MAY2010	Other
						21JUN2010	Restart ART/restart previous drug
43085	25FEB2010	26FEB2010	16MAR2012	751	751		
43170	20JAN2010	08NOV2010	16MAR2012	787	787	17DEC2010	Voluntary patient/carer decision
						03JAN2011	Restart ART/restart previous drug

FDA Question 2:

For subjects who died, the reason for discontinuation and snapshot sub-category variables do not appear to capture this information. For example, the reason for discontinuation appears to be missing for Subject 13022 and the snapshot subcategory is missing data during window but on study at Week 96 when the subject died on study day (b) (6) The snapshot sub-category (outco2) should be discontinued study due to AE or Death. In another example, Subject 43092 started 2nd line regimen on study day 352

and died on study day (b) (6) According to the snapshot sub-category (outco2) this subject was classified as having "Data in window not below threshold." Shouldn't the snapshot sub-category be "discontinued study due to AE or Death?" In addition, dsterm and dsdecod indicated the subject completed the study.

RESPONSE:

Information related to the five deaths was not captured in the AE34, AE4, or SAE data sets, but only in the DEATH dataset. These subjects were not being considered as withdrawn or lost to follow-up in PYRS dataset. In the initial snapshot outcome variable (outco2), this subgroup category 'Discontinued due to AE or Death' was missed while creating the outcome variable. One of the five deaths (subject **13064**) has a viral load measurement at week 96 and passed away after that, so this subject falls in the category of **'Data in window not below threshold,'** rather than **'Discontinued study due to AE or Death.'** Four other deaths are in the category of '**Discontinued study due to AE or Death.**' ADEFFOUT details for these five fatalities are located in Table 2.

Table 2 ARROW: Listing of Subject Deaths

Subj.	Snapshot outcome cat. <80 cp/mL Wk48	Snapshot outcome subcat. <80 cp/mL Wk48	Snapshot outcome cat. <80 cp/mL Wk96	Snapshot outcome subcat. <80 cp/mL Wk96	Reported Term for the Disposition Event	Study day for death
13022	Virologic failure	Data in window not below threshold	No Virologic data	Discontinued due to AE or Death	DEATH	(b) (6)
13064	Virologic failure	Data in window not below threshold	Virologic failure	Data in window not below threshold	DEATH	(b) (6)
36156	Virologic success (HIV RNA <80 copies/mL)		No Virologic data	Discontinued due to AE or Death	DEATH	(b) (6)
36175	Virologic failure	Data in window not below threshold	No Virologic data	Discontinued due to AE or Death	DEATH	(b) (6)
43092	Virologic failure	Data in window not below threshold	No Virologic data	Discontinued due to AE or Death	DEATH	(b) (6)

FDA Question 3:

You provided snapshot outcomes using the threshold of 80 copies/mL. Please provide the same information for snapshot outcomes that use the threshold of 400 copies/mL.

RESPONSE:

Snapshot outcomes variables using the threshold of 400 copies/mL have been added to the ADEFFOUT dataset. The summary table of study outcomes for threshold of 400 copies/mL was generated and is displayed in the efficacy results section below.

The applicant's Snapshot results for 400 copies/mL were shown in the Efficacy Section.

Data Quality Assurance

General Responsibilities (Section 4.6.1 of the Clinical Study Report)

According to GSK, the Principal Investigators and co-Principal Investigators at each center had ultimate responsibility for ensuring that the trial met all its obligations to guidelines, regulations, and adherence to the protocol and quality management.

GSK stated that if these responsibilities were delegated, it had to be clear where the responsibility lay in a job description. Staff at the local clinical centers were responsible for the proper implementation of the protocol, for ensuring patient safety, for data accuracy, for timely completion and transmission of case report forms (CRFs) and for maintaining an accurate and up-to-date CRF folder for each patient.

Staff at the local trials center were responsible for data entry, raising data queries within the database, resolution of data queries with the clinical center, maintaining an accurate and up-to-date CRF for each patient, and training on aspects relating to data quality, and updating their local Trials Center Manual of Operations (MOP). All responsibilities were documented in a delegation log.

Staff at the Clinical Trials Unit (CTU) were responsible for raising data queries based on the central merged database, producing summary reports on data quality, developing training materials and clarification notes relating to data quality, and analysis.

Data Management and Monitoring (from Section 4.6.2 of the Clinical Study Report)

A Data Management Group (DMG) was set up with data management, computing and statistician members from each site and the MRC CTU, chaired by the Trial Statistician. This Committee was responsible for setting up the databases at each site and for coordination of timely merging of data from each site at MRC CTU, where the central database was held. The committee was responsible for ensuring that the system for data collection was working consistently across the sites, for developing the trial analysis plan and 'shell' tables to be

provided to the independent Data Monitoring Committee, and for making decisions about analyses.

Each site was responsible for maintaining its own database and for timely (twice monthly) transfer of checked data to the MRC CTU for merging of data with those from the other sites. Staff from MRC CTU visited clinical sites to validate and monitor data and this could also be done across sites (e.g., a data manager from Zimbabwe could visit Uganda), under the oversight of the Data Management Committee. Regular monitoring was conducted by an independent Trial Monitor in each of Zimbabwe and Uganda. The clinical investigators and participants, by giving consent, agreed that within the host country's Data Protection Law, the MRC CTU could consult and /or copy source records (clinical notes, laboratory values) in order to do this monitoring. Such information was treated as strictly confidential and was in no circumstances made publicly available. The monitoring adhered to MRC Good Clinical Practice guidelines (based on ICH guidelines). The following data were verified from source documents: all signed consent forms; dates of visits including laboratory results; eligibility and baseline values for all children; all clinical endpoints; all serious/severe adverse events; an ongoing random 5% sample of routine patient clinical and laboratory data; drug compliance; dates drug dispensed and (if necessary) drugs returned; pharmacy/clinic drug logs; concomitant medication.

Central Merged Database (from Section 4.6,3 of the Clinical Study Report)
Data from the ARROW clinical centers was merged twice monthly at the CTU. Consistency checks were run on merged data at least once a month and sent to centers for resolution in a timely manner together with the number of outstanding (>1 month) unverified forms (i.e., only first and not second data entry had occurred).

In addition to these checks, there were four targets for monthly QA that were run via the central database and which were reported back thrice monthly to centers. These targets were set as thresholds to ensure that overall trial targets regarding loss to follow-up were med, and that data were as up-to-date as possible for periodic analyses for DMC and other analyses (e.g., for presentations).

- potential loss to follow-up: <2% missed visits at each scheduled assessment (of those patients under follow-up)
- loss to follow-up: <5% participants not known to have died without any data in the last 3 months
- data entry: <20% participants without a doctor/nurse follow-up form on the database in the last 2 months
- data entry: a mean of <2 unverified forms per patient

Serious Adverse Event Reporting (Section 4.6.4 of the Clinical Study Report)
The CTU reported copies of all SAE reports to GlaxoSmithKline (GSK) according to the procedures of the ARROW contract. All SAEs which were reported by the center investigator completing the CRF as definitely or probably, or uncertain whether, related to ART drugs

provided by GSK were reported to GSK's Global Clinical Safety and Pharmacovigilance (GCSP) department. Such reporting was carried out in a timely manner. The CTU helped to facilitate any queries from GSK on reported SAEs either by answering from the database or by referring to centers.

Data Monitoring Committee (Section 4.6.5 of the Clinical Study Report)

An independent DMC was established and monitored all aspects of the trial, including all4 randomizations (LCM/CDM, induction-maintenance, stop/continue cotrimoxazole 4 randomizations (LCM/CDM, induction-maintenance, stop/continue cotrimoxazole prophylaxis, once/twice daily ABC+3TC). The DMC considered findings from any other relevant studies and reviewed trial data on recruitment, safety, adherence to randomized strategies and efficacy, in strict confidence approximately every 6-12 months. The DMC reported to the ARROW Trial Steering Committee and to the Ethics Committee in each country, if in their view the data provided proof beyond reasonable doubt that one of the allocated strategies was better than its comparator in terms of a difference of clinically significant magnitude in a primary outcome. The guiding statistical criteria for "proof beyond reasonable doubt" was a Haybittle-Peto type rule based on the 99.9% confidence interval (CI) of the relative hazard of disease progression in each interim analysis, but the DMC also considered clinical criteria. The ARROW Trial Steering Committee then decided whether to amend or stop the trial before the end of the planned follow-up.

MULTIVARIABLE EXPLORTORY MODELS FOR BASELINE SUBGROUPS

Table 30 Multivariable Model for Plasma HIV-1 RNA <400 copies/mL at 48 Weeks in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

Baseline Factor	Odds Ratio	95% CI	P-value
Once daily vs twice daily	1.30	0.72, 2.35	0.38
Age (per 1 year older)	0.79	0.70, 0.88	<0.0001
3TC+ABC+NVP vs 3TC+ABC+EFV	0.29	0.10, 0.81	0.02
3 NRTI vs 3TC+ABC+EFV	0.20	0.07, 0.52	0.001
Baseline HIV-1 RNA 81-199 vs <80 c/mL	0.47	0.16, 1.38	0.17
Baseline HIV-1 RNA 200-399 vs <80 c/mL	0.18	0.05, 0.68	0.01
Baseline HIV-1 RNA 400-999 vs <80 c/mL	0.01	0.003, 0.06	<0.0001
Baseline HIV-1 RNA 1000+ vs <80 c/mL	0.008	0.004, 0.02	<0.0001
Tablets vs solution	2.55	0.89, 6.39	0.08

Source Data: Virology Report

Note: Backwards elimination exit p=0.10 based on each factor considered for subgroup analyses (i.e. including all categories for ART regimen), forcing once daily versus twice daily into the model and adjusting for centre. Test for heterogeneity in effect of once daily versus twice daily by (3TC+ABC+EFV, 3TC+ABC+NVP, 3TC+ABC+ZDV) p=0.14.

Source: Clinical Study Report

The applicant conducted an exploratory multivariable model for plasma HIV-1 RNA < 400 copies/mL to compare subgroups at Week 48 (Table 30) and Week 96 (Table 31). All variables considered in the subgroup analyses above were considered for inclusion (monitoring randomization, sex, age group, RNA at randomization (grouped), ART strategy randomization, ART at randomization, formulation). As the study was not formally powered to identify effects of factors on viral load suppression, backwards elimination with exit p=0.1 was used for the primary endpoint time of 48 weeks, forcing once- versus twice- daily into the model and adjusting for center (i.e., center also forced into the model). Significance was considered on a per-factor basis (e.g., including all levels of categorical variables with >2 levels based on a joint test of significance). Interactions were checked between variables included in the final model (see footnotes to Table 30 and Table 31). The same final 48-week model was then fitted to the equivalent outcome at Week 96, checking that no other variables now provided additional information.

Statistically significant differences were observed for age, 3TC+ABC+NVP versus 3TC+ABC+EFV, three NRTIs versus ABC+3TC+EFV, and baseline HIV-1 RNA at Weeks 48 and 96, with a trend towards an effect for tablets versus solution at Week 48 only (most children had moved off solution to tablets by Week 96).

Table 31 Multivariable Model for Plasma HIV-1 RNA <400 copies/mL at 96 Weeks in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

Baseline Factor	Odds Ratio	95% CI	P-value
Once daily vs twice daily	1.24	0.72, 2.14	0.43
Age (per 1 year older)	0.86	0.77, 0.95	0.004
3TC+ABC+NVP vs 3TC+ABC+EFV	0.21	0.07, 0.58	0.003
3 NRTI vs 3TC+ABC+EFV	0.10	0.04, 0.27	<0.0001
Baseline RNA 81-199 vs <80 c/mL	0.31	0.12, 0.82	0.02
Baseline RNA 200-399 vs <80 c/mL	0.20	0.06, 0.72	0.01
Baseline RNA 400-999 vs <80 c/mL	0.05	0.01, 0.16	<0.0001
Baseline RNA 1000+ vs <80 c/mL	0.01	0.006, 0.02	<0.0001
Tablets vs solution	0.92	0.35, 2.46	0.87

Source Data: Virology Report

Note: Based on the same model as 48 weeks (no other factors selected with backwards elimination exit p=0.1). Test for heterogeneity in effect of once daily versus twice daily by (3TC+ABC+EFV, 3TC+ABC+NVP, 3TC+ABC+ZDV) p=0.25. The majority of children taking solution at randomisation to once daily versus twice daily had moved to tablets by 96 weeks.

Source: Clinical Study Report

Table 39 Multivariable Model for Plasma HIV-1 RNA <80 copies/mL at 48 Weeks in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

Baseline Factor	Odds Ratio	95% CI	P-value
Once daily vs twice daily	1.07	0.66, 1,73	0.78
Age (per 1 year older)	0.88	0.80, 0.96	0.006
3TC+ABC+NVP vs 3TC+ABC+EFV	0.39	0.17, 0.88	0.02
3 NRTI vs 3TC+ABC+EFV	0.27	0.12, 0.58	0.001
Baseline HIV-1 RNA 81-199 vs <80 c/mL	0.51	0.22, 1.23	0.13
Baseline HIV-1 RNA 200-399 vs <80 c/mL	0.32	0.10, 1.02	0.05
Baseline HIV-1 RNA 400-999 vs <80 c/mL	0.02	0.005, 0.11	<0.0001
Baseline HIV-1 RNA 1000+ vs <80 c/mL	0.02	0.008, 0.03	<0.0001

Note: Test for heterogeneity in effect of once daily versus twice daily by (3TC+ABC+EFV, 3TC+ABC+NVP, 3TC+ABC+ZDV) p=0.64.

Note: Backwards elimination exit p=0.10 based on each factor considered for subgroup analyses (i.e., including all categories for ART regimen), forcing twice daily versus once daily into the model and adjusting for centre.

Source: Clinical Study Report

Table 40 Multivariable Model for Plasma HIV-1 RNA <80 copies/mL at 96 Weeks in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

Baseline Factor	Odds Ratio	95% CI	P-value
Once daily vs twice daily	1.03	0.65, 1.64	0.91
Age (per 1 year older)	0.93	0.85, 1.01	0.10
3TC+ABC+NVP vs 3TC+ABC+EFV	0.64	0.30, 1.36	0.25
3 NRTI vs 3TC+ABC+EFV	0.25	0.12, 0.51	0.0001
Baseline RNA 81-199 vs <80 c/mL	0.31	0.14, 0.69	0.004
Baseline RNA 200-399 vs <80 c/mL	0.13	0.04, 0.39	0.0003
Baseline RNA 400-999 vs <80 c/mL	0.03	0.006, 0.14	<0.0001
Baseline RNA 1000+ vs <80 c/mL	0.02	0.008, 0.03	<0.0001

Note: Test for heterogeneity in effect of once daily versus twice daily by (3TC+ABC+EFV, 3TC+ABC+NVP, 3TC+ABC+ZDV) p=0.08. Heterogeneity trends suggested that there could be a greater beneficial impact of once daily versus twice daily on suppression <80 copies/mL at 96 weeks in those receiving 3TC+ABC+EFV (OR(once daily:twice daily)=3.87 (95% CI: 1.10,13.6, p=0.03) than those receiving 3TC+ABC+NVP (OR(once daily:twice daily)=0.83 (95% CI: 0.41, 1.70, p=0.62) or 3TC+ABC+ZDV (OR(once daily:twice daily)=0.83 (95% CI: 0.41, 1.67, p=0.60). However, there was also a baseline imbalance between combination regimen and baseline RNA, but data were too few to adjust for a full interaction between these two factors. Collapsing those >400 copies/mL in an additional interaction term between combination regimen and baseline RNA led to similar results for the heterogeneity in effect of once daily versus twice daily by baseline combination regimen.
Note: Based on the same model as 48 weeks (no other factors selected with backwards elimination exit p=0.1).

Source: Clinical Study Report

An exploratory multivariable model for plasma HIV-1 RNA < 80 copies/mL was used by the applicant to compare subgroups at Week 48 (Table 39) and Week 96 (Table 40). The same modelling strategy was used as for <400 copies/mL (Table 30 and Table 31). Statistically significant differences were observed for age at Week 48, 3TC+ABC+NVP versus 3TC+ABC+EFV, 3 NRTIs versus ABC+3TC+EFV at Weeks 48 and 96, and baseline HIV-1 RNA at Weeks 48 and 96.

At Week 48, the test for heterogeneity in effect of once daily versus twice daily by (3TC+ABC+EFV, 3TC+ABC+NVP, 3TC+ABC+ZDV) was p=0.64.

There was no significant effect of formulation (tablets versus solution) in a model for <80 copies/mL at Week 48, but the non-significant trend was in the same direction as for the <400 copies/mL model (in addition to factors above, adjusted odds ratio (OR) (tablets versus solution) = 1.45 (95% CI 0.57, 3.65, p=0.43).

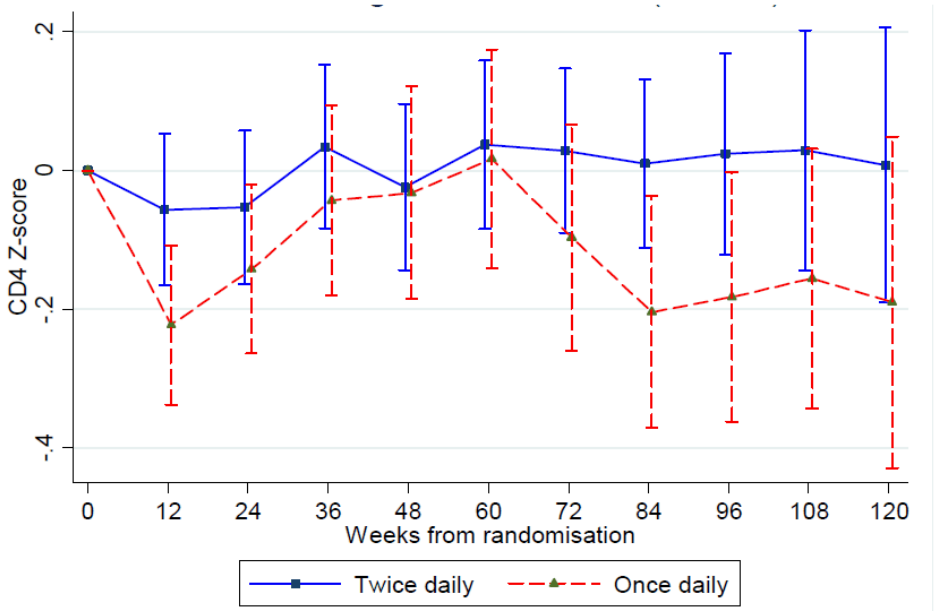
At Week 96, the test for heterogeneity in effect of once daily versus twice daily by (3TC+ABC+EFV, 3TC+ABC+NVP, 3TC+ABC+ZDV) was p=0.08. Heterogeneity trends suggested that there could be a greater beneficial impact of once daily versus twice daily on suppression <80 copies/mL at 96 weeks in those receiving 3TC+ABC+EFV (OR) (once daily:twice daily)=3.87 (95% CI 1.10, 13.6, p=0.03) than those receiving 3TC+ABC+NVP [OR

(once daily:twice daily)]=0.83 (95% CI 0.41, 1.70, p=0.62) or 3TC+ABC+ZDV [OR (once daily:twice daily)]=0.83 (95% CI 0.41, 1.67, p=0.60). However, the applicant noted that there was also a baseline imbalance between combination regimen and baseline RNA, but data were too few to adjust for a full interaction between these two factors. Collapsing those >400 copies/mL in an additional interaction term between combination regimen and baseline RNA led to similar results for the heterogeneity in effect of once daily versus twice daily by baseline combination regimen.

There was no significant effect of formulation (tablets versus solution) in a model for <80 copies/mL at Week 96; there was a very small effect in the same direction as for the 48 week model (in addition to factors above, adjusted OR (tablets versus solution)=1.24 (95% CI 0.51, 3.01, p=0.64). The majority of children taking solution at randomization to once daily/twice daily had moved to tablets by 96 weeks.

ADDITIONAL SECONDARY EFFICACY ANALYSES

Figure 22 Mean Change in CD4 Z-Score (95% CI) in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW



Global significance test of difference in change from randomization, p=0.14
Source: Clinical Study Report

The applicant claimed that the mean change in CD4 Z-scores was not significantly different between the once daily and twice daily ABC+3TC groups when analyzed using a global significant test of difference in change from randomization (p=0.14) (Figure 22 of the Clinical Study Report). The mean change in CD4 Z-scores was most similar at Weeks 0, 36, 48, and 60. Some differences were observed at Weeks 72 through 120, with higher CD4 Z-scores observed in the twice daily randomization group; however, the confidence intervals of the comparison treatments were overlapping.

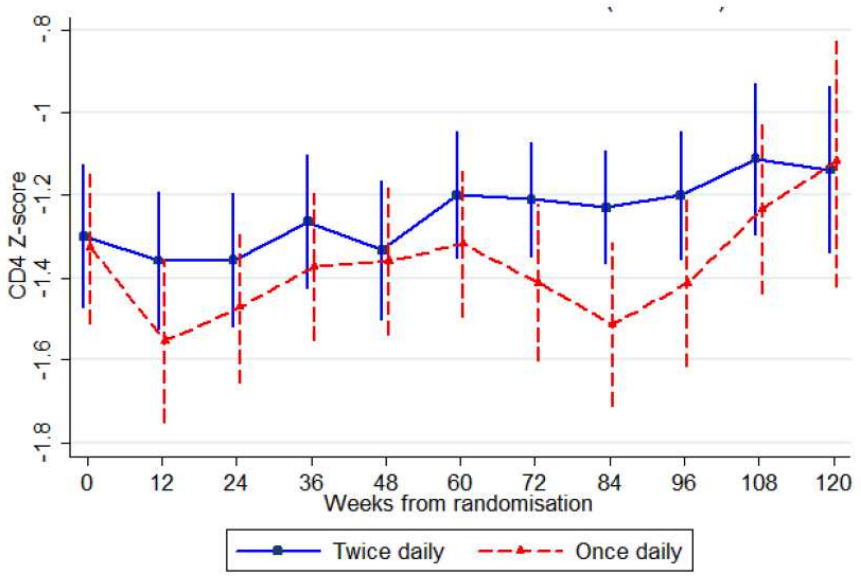
Table 41 Difference in CD4 Z-Scores between Once Daily and Twice Daily Treatment Arms at 48 and 96 Weeks in ARROW

	Mean Increase from Randomisation		P-value
	Twice daily	Once daily	
Week 48	-0.02	-0.03	0.94
Week 96	0.02	-0.18	0.08

Source: Clinical Study Report

There was no statistically significant difference between CD4 z-scores in the BID and QD arms at Week 48 (Table 41). However the difference was close to being statistically significant at the 0.05 level (p=0.08) at Week 96, in favor of the BID arm.

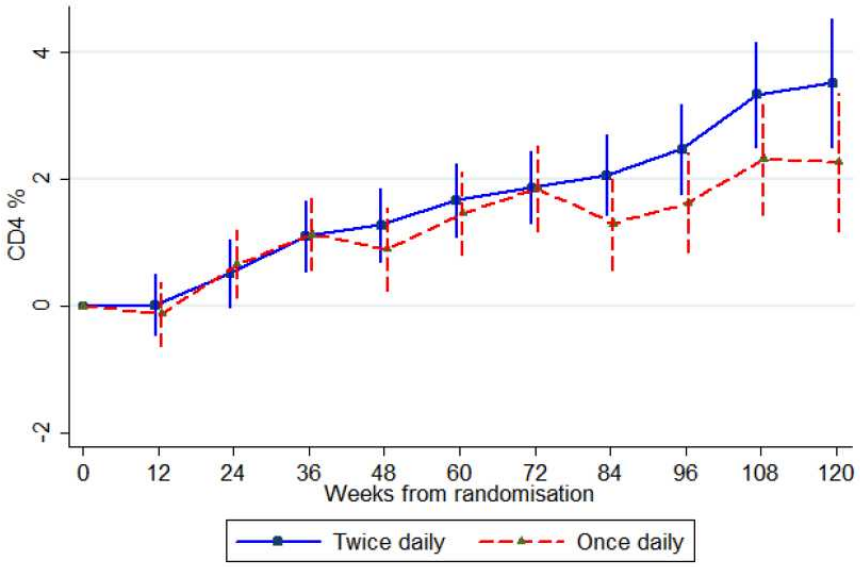
Figure 23 Mean Absolute CD4 Z-Score (95% CI) in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW



Source: Clinical Study Report

Mean absolute CD4 Z-scores were also similar between the once daily and twice daily ABC+3TC treatment groups (Figure 23).

Figure 24 Mean Change in CD4% (95% CI) in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW



Global significance test of difference in change from randomization, p=0.30
Source: Clinical Study Report

The applicant also found that the mean change in CD4% was not significantly different between the once daily and twice daily ABC+3TC groups when analyzed using a global significant test of difference in change from randomization (p=0.30).

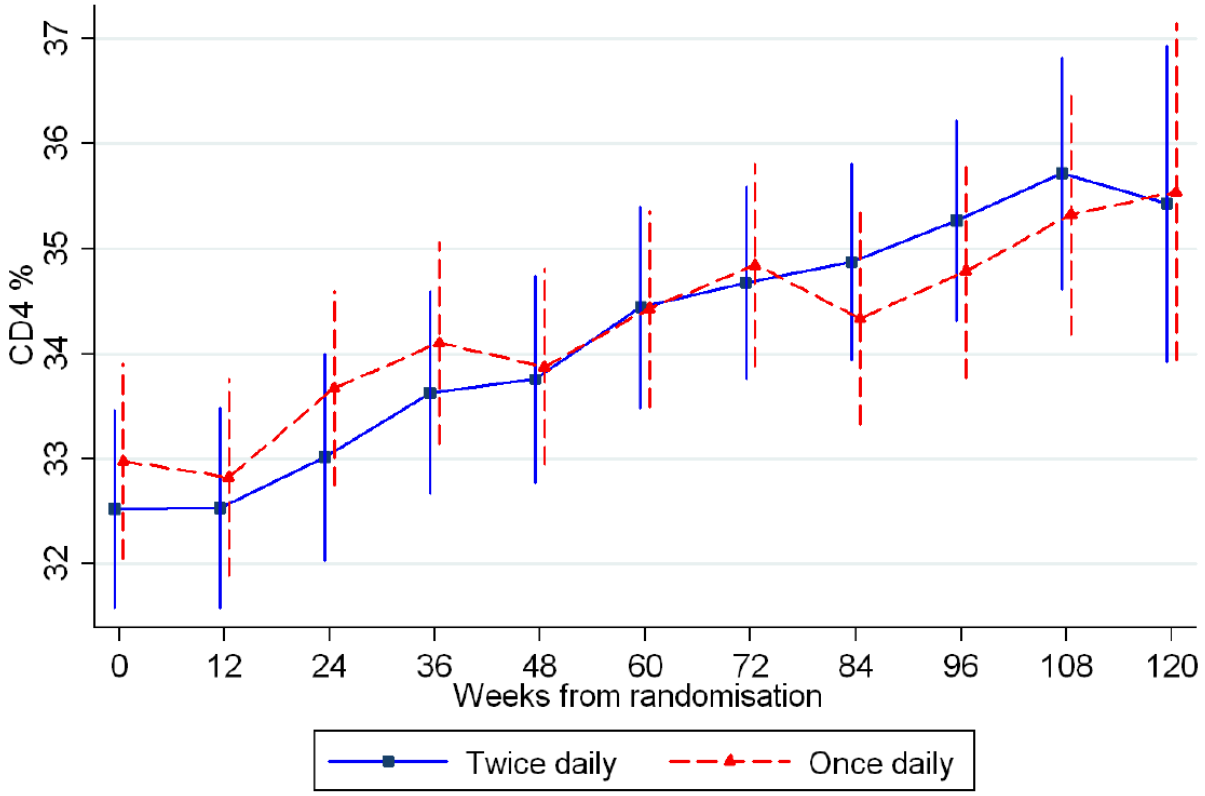
Table 42 Difference in increase in CD4% since randomisation between Once Daily and Twice Daily Treatment Arms at 48 and 96 Weeks

	Mean Increase from Randomisation		P-value
	Twice daily	Once daily	
Week 48	1.3%	0.9%	0.39
Week 96	2.5%	1.6%	0.12

Source: Clinical Study Report

There were no statistically significant differences between increase in CD4% since randomization in the BID and QD arms at Weeks 48 and 96 (Table 42).

Figure 25 **Mean Absolute CD4% (95% CI) in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW**



Source: Clinical Study Report

Mean absolute CD4% was also similar in QD and BID arms (Figure 25).

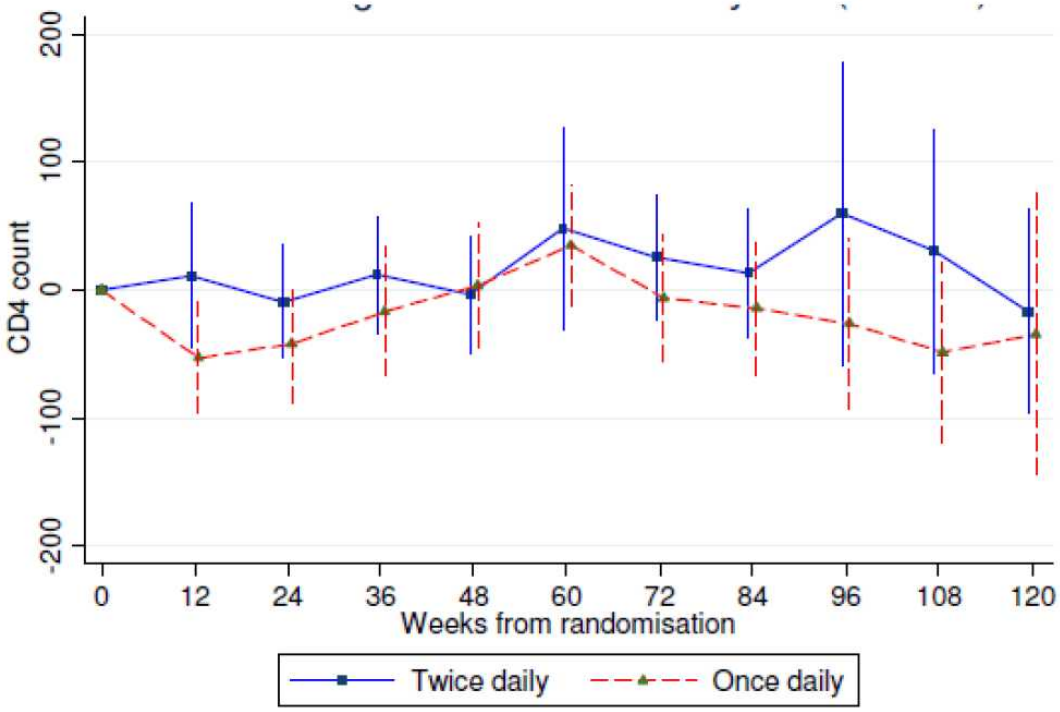
Table 43 **Change in CD4 Cell Count Since Randomisation Between Once Daily and Twice Daily Treatment Arms at 48 and 96 Weeks for Subjects Aged 5 or More Years at Enrolment**

	Mean increase from Randomisation		P-value
	Twice daily	Once daily	
Week 48	-3.3	+3.5	0.82
Week 96	+59.7	-26.2	0.20

Source: Clinical Study Report

There were no statistically significant treatment arm differences between treatment arms for mean increase in CD4 cell counts since randomization at Week 48 or 96 (Table 43).

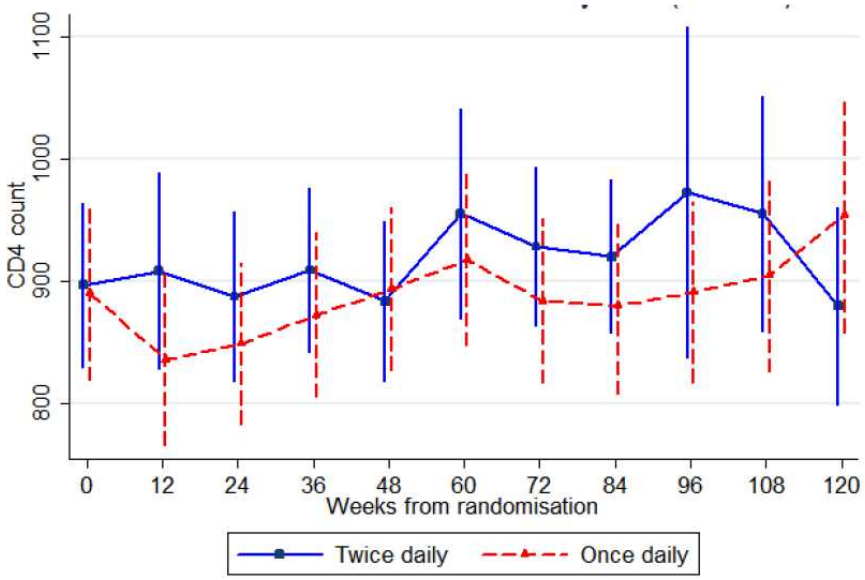
Figure 26 **Mean Change in CD4 Cell Count in Subjects who were >5 years of age (95% Confidence Interval) in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW**



The global significance test of difference in change from randomization was p=0.22.
Source: Clinical Study Report

The mean change in CD4 cell counts in subjects who were >5 years of age was also similar in the two treatment arms (Figure 26).

Figure 27 **Mean Absolute CD4 Count (95% CI) For Subjects >5 Years of Age in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW**



Source: Clinical Study Report

Mean absolute CD4 cell counts in subjects who were >5 years of age were also similar in the two treatment arms (Figure 27).

Table 44 WHO Stage 3/4 HIV Event or Death in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

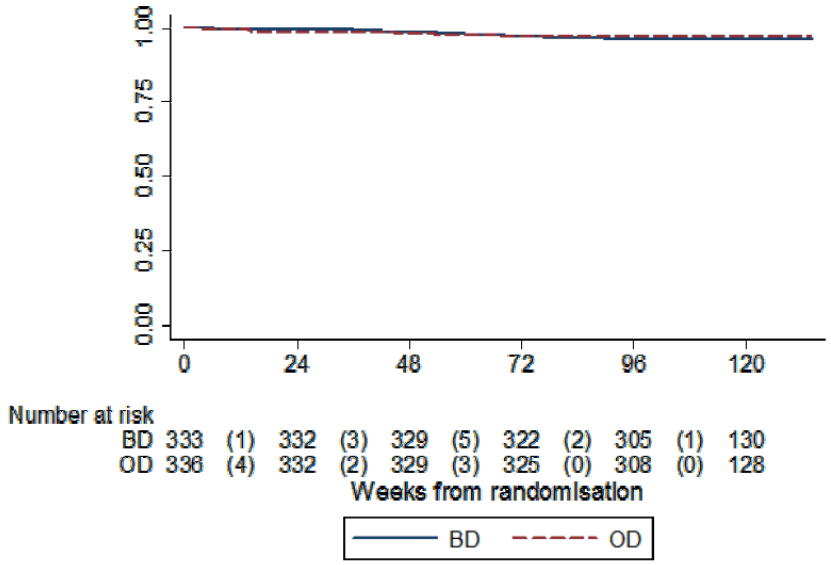
	Twice Daily N=333	Once Daily N=336	Total N=669
Randomised, n (%)	333 (100)	336 (100)	669 (100)
WHO Stage 3/4 HIV events	10	10	20
Died, n	4	1	5
WHO Stage 3/4 HIV events or death			
No. Events, n	14	11	25
No. Children, n (%)	12 (3.6)	9 (2.7)	21 (3.1)
Randomised, n	333	336	669
All WHO Stage 3/4 HIV events and deaths	14	11	25
<90 days	2	2	4
90 to 180 days	0	2	2
180 days to 2 years	12	7	19
>2 years	0	0	0
Total person years at risk	727	735	1462
Event rate (per 100 p/yrs)	1.9	1.5	1.7
<90 days	2.4	2.4	2.4
90 to 180 days	0.0	2.4	1.2
180 days to 2 years	2.4	1.4	1.9
>2 years	0.0	0.0	0.0

Source: Clinical Study Report

WHO Stage 3 and 4 HIV events are summarized in Table 44. Overall, 3% of the subjects experienced at least one WHO Stage 3/4 HIV event or died during the once daily versus twice daily randomization period. The total person-years at risk was 1462 years and the WHO Stage 3/4 event or death rate 1.7 events per 100 years.

The proportions of subjects reporting WHO Stage 3/4 HIV events were similar in the twice daily versus once daily treatment groups.

Figure 28 Time to First WHO Stage 3/4 HIV Event or Death in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW



Log-rank test for equality of survivor functions, p=0.51
Hazard ratio for once/twice daily 3TC and ABC = 0.75 (0.31, 1.77)
N.B. Log-rank test and estimated HR are unstratified due to very small event numbers.
Source: Clinical Study Report

Furthermore, the time to first reported WHO Stage 3/4 HIV event or death was similar between the two treatment groups (Figure 28).

Table 45 WHO Stage 3/4 HIV Events by Stage in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

	Twice Daily N=333	Once Daily N=336	Total N=669
Total, n (%)	10 (100)	10 (100)	20 (100)
Stage 4			
Severe malnutrition	2 (20.0)	0 (0.0)	2 (10.0)
Pneumocystis pneumonia	0 (0.0)	1 (10.0)	1 (5.0)
Oesophageal candidiasis	0 (0.0)	1 (10.0)	1 (5.0)
Ex. pulmonary cryptococcosis	1 (10.0)	0 (0.0)	1 (5.0)
Stage 3			
Pulmonary tuberculosis	4 (40.0)	6 (60.0)	10 (50.0)
Symptomatic lymphoid interstitial pneumonia	1 (10.0)	0 (0.0)	1 (5.0)
Moderate malnutrition	0 (0.0)	1 (10.0)	1 (5.0)
Tuberculosis lymphadenitis	1 (10.0)	0 (0.0)	1 (5.0)
Chronic diarrhoea	0 (0.0)	1 (10.0)	1 (5.0)
Chronic lung disease	1 (10.0)	0 (0.0)	1 (5.0)

Source: Clinical Study Report

Overall, five Stage 4 and 15 Stage 3 WHO Stage 3/4 HIV events were reported (Table 45). The most frequently reported WHO Stage 3/4 HIV event was pulmonary tuberculosis (10 events).

Table 46 WHO Stage 4 HIV Event or Death in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW

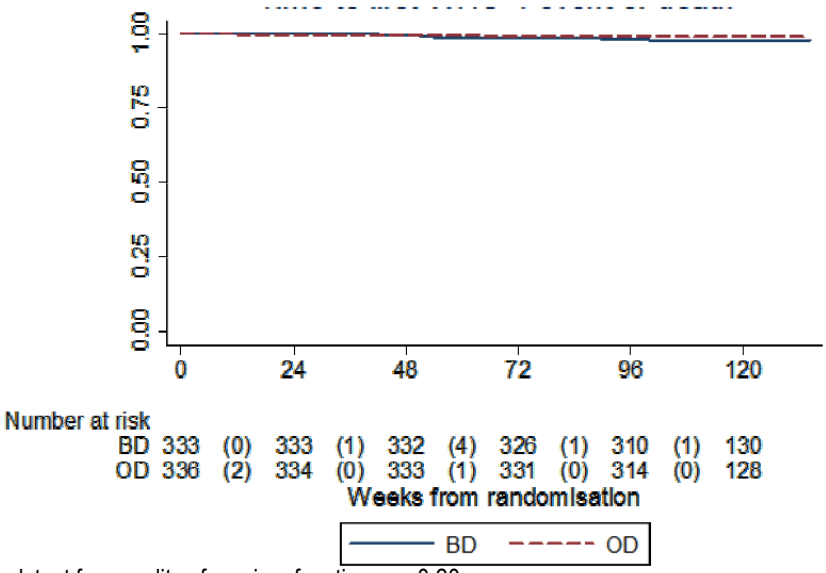
	Twice Daily	Once Daily	Total
Randomised, n (%)	333 (100)	336 (100)	669 (100)
WHO Stage 4 HIV events, n	3	2	5
Died, n	4	1	5
WHO Stage 4 HIV events or death			
No. Events, n	7	3	10
No. Children, n (%)	7 (2.1)	3 (0.9)	10 (1.5)
Randomised, n	333	336	669
All WHO Stage 4 HIV events and deaths	7	3	10
<90 days	0	1	1
90 to 180 days	0	1	1
180 days to 2 years	7	1	8
>2 years	0	0	0
Total person years at risk	727	735	1462
Event rate (per 100 patient years)	1.0	0.4	0.7
<90 days	0.0	1.2	0.6
90 to 180 days	0.0	1.2	0.6
180 days to 2 years	1.4	0.2	0.8
>2 years	0.0	0.0	0.0

Source: Clinical Study Report

Overall, a total of 10 subjects had a WHO Stage 4 HIV event or died during the study (Table 46) with the majority occurring in the BID arm within 180 days to 2 years and an additional three events occurring in the QD arm between <90 days and 2 years.

The corresponding time to event plot is shown in Figure 29.

Figure 29 **Time to First WHO Stage 4 HIV Event or Death in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW**



Log-rank test for equality of survivor functions, p=0.20
Hazard ratio (HR) for once/twice daily 3TC and ABC = 0.43 (0.11, 1.64)
N.B. Log-rank test and estimated HR are unstratified due to very small event numbers.
Source: Clinical Study Report

Table 47 Difference in Adherence between the Once Daily and Twice Daily Abacavir+Lamivudine Arms at Weeks 48 and 96 in ARROW

	Subjects Reporting Missing ART Pills in Last 4 Weeks		P-value[a]
	Twice Daily n/N (%)	Once Daily n/N (%)	
Week 0 (after 36 weeks on Treatment)	27/ 333 (8)	27/ 333 (8)	--
Week 48	29/ 330 (9)	32/ 336 (10)	0.74
Week 96	25/ 309 (8)	26/ 311 (8)	0.90

a. Chi-squared test

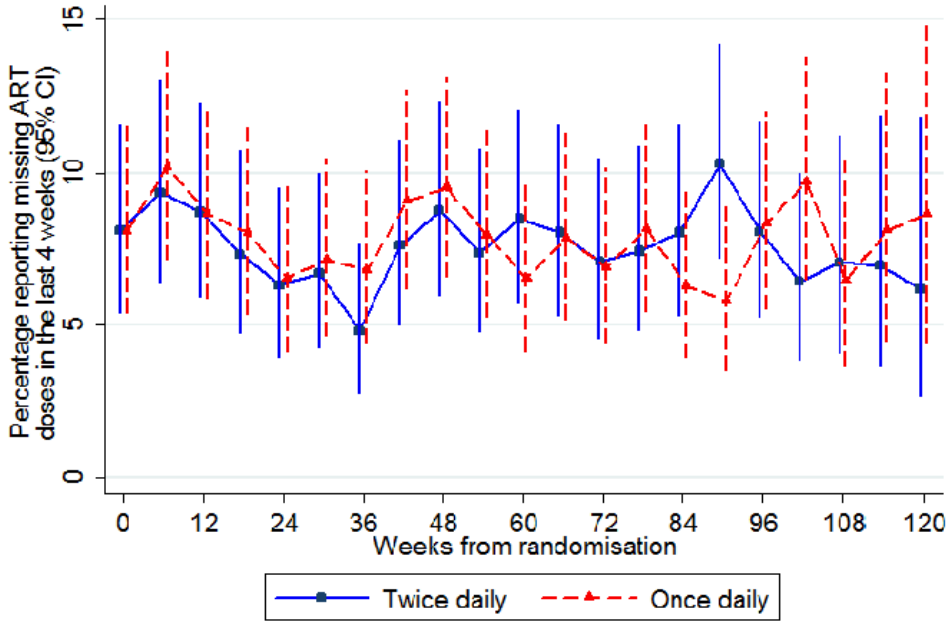
Note: most children were still receiving their ART regimen twice daily due to other drugs (NVP, ZDV) being dosed twice daily. Children had also been on ART for >36 weeks at randomization, so were not experiencing immediate challenges taking ART but were stable on treatment: overall adherence was therefore relatively high.

Source: Clinical Study Report

Adherence in both the once daily and twice daily arms was high. No significant differences in ART adherence between the once daily and twice daily treatment groups were observed (Table 47 and Figure 30).

The applicant noted that not all of the subjects in the once daily ABC+3TC arm were on a fully once daily regimen: those whose third drug was either NVP (Arms A and B) or ZDV (Arm C) would still receive this drug twice daily. Only those whose third drug was EFV once daily (Arms A and B) would be on a fully once-daily regimen in the once daily group.

Figure 30 **Carer Report of Missing ART Pills in the Last 4 Weeks in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW**



Global significance test of difference in change from randomization, p=0.93
Source: Clinical Study Report

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

/s/

FRASER B SMITH
02/13/2015

GUOXING SOON
02/18/2015