OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	20977 S-027, 20978 S-031, 20564 S-033, 20596 S-032
Submission Date	5/23/14
Name	ZIAGEN ® (abacavir sulfate) Epivir ® (lamivudine)
Clinical Pharmacology Reviewer	Su-Young Choi, Pharm.D., Ph.D
Pharmacometrics Reviewer	Fang Li, Ph.D
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D
Pharmacometrics Team Leader	Jeff Florian, Ph.D
OCP Division	Division of Clinical Pharmacology IV
OND Division	Division of Antiviral Products (DAVP)
Applicant	GSK
Formulation/Strength	ZIAGEN: Tablets (300 mg, scored) and oral solution (20 mg/mL) EPIVIR: Tablets (150 mg;scored, 300 mg) and oral solution (10 mg/mL)
Indication	ZIAGEN Adults: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily Pediatric patients aged 3 months and older: 8 mg/kg twice daily EPIVIR Adults: 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily. Pediatric patients aged 3 months and older: 4 mg/kg twice daily

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Executive Summary

Lamivudine (3TC;Epivir®) and abacavir (ABC;Ziagen®) are NRTIs (nucleos[t]ide reverse transcriptase inhibitors) approved for the treatment of HIV-1 infection. The sponsor submitted an efficacy supplement to support once daily dosing of abacavir and lamivudine in pediatric patients 3 months of age and older and to harmonize with the WHO treatment guidelines for dosing abacavir/lamivudine scored tablets in pediatric patients who weigh greater than or equal to 14 kg. In addition, Ziagen supplements were submitted to fulfill PREA PMRs that were established on August 2, 2004 with the approval of the once daily dosing in HIV-1 infected adults. The primary basis of approval for once daily dosing for both lamivudine and abacavir is efficacy and safety data from the ARROW study (see description below).

To support once daily dosing regimen of lamivudine and abacavir in pediatric patients, the sponsor submitted the following clinical study reports:

- ARROW (**A**nti**R**etroviral **R**esearch f**O**r **W**atoto) Randomization 3
    - ARROW (study COL105677) was a 5-year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric patients. HIV-1 infected, treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first line regimen containing ABC and 3TC, dosed twice daily according to WHO recommendations. Subjects on ART at least 36 weeks were eligible for participating Randomization 3, a fully powered comparison of once versus twice-daily dosing of abacavir and lamivudine (ABC+3TC) for the evaluation of efficacy and safety outcomes.
    - PK substudy 1: Pharmacokinetics of QD versus BID dosing of 3TC and ABC in subjects aged 3 years to 12 years who were taking abacavir and lamivudine scored tablets.
    - PK substudy 2: Relative bioavailability of scored tablets compared to oral solution formulations of 3TC/ABC in HIV-infected children when given in a drug regimen containing 3TC, ABC, zidovudine (ZDV), with or without nevirapine

- PENTA 13: Plasma pharmacokinetics of once versus twice daily lamivudine and abacavir-simplification of combination treatment in HIV-1 infected children (2 to 12 years old)
- PENTA 15: Plasma pharmacokinetics of once versus twice daily lamivudine and abacavir-simplification of combination treatment in HIV-1 infected children (3 to < 36 months old)
- PACTG1018: Single dose pharmacokinetic study of abacavir in HIV-1 infected children and adolescents
- PACTG1052: Abacavir pharmacokinetics during chronic therapy in HIV-1 infected adolescents and young adults
- Population pharmacokinetic analysis of pooled abacavir and lamivudine data from pediatric studies to support once daily dosing in HIV-infected children

In the ARROW trial (Randomization 3), the primary efficacy endpoint was viral load at 48 weeks after randomization to once or twice daily ABC+3TC. QD dosing of 3TC+ABC has been demonstrated to be non-inferior to BID dosing; proportions of subjects with plasma HIV-1 RNA less than 80 copies/mL in the QD and twice daily groups were 73% and 72%, respectively. In ARROW PK substudy 1 and PENTA15, ABC and 3TC AUC_{24hr} were comparable between QD and BID dosing regimens in pediatric patients.

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In ARROW PK substudy 2, 3TC plasma exposures following administration of the tablet were higher than those from the oral solution. Dose normalized C_{max} and AUC values were approximately 55% and 58% higher, respectively, following administration of the tablet formulation compared to the oral solution. (For both ABC and ZDV, dose-normalized AUC and C_{max} following administration of the tablet formulations were comparable to those following administration of the respective oral solution.) The clinical significance of this finding is yet to be determined.

Of note, PENTA13 was previously submitted to fulfill lamivudine postmarketing commitment 2 (issued on June 24, 2002) and reviewed by DAVP. PACTG 1018 and PACTG1052 do not directly support the proposed dosing regimen as the studies were conducted with an abacavir twice daily dosing regimen only. (Therefore, no individual study reviews were conducted for these three studies.)

Recommendation

The Office of Clinical Pharmacology has reviewed the submission and the sponsor's proposed labeling. The review team agrees that the ARROW study results support a once daily dosing regimen of 3TC and ABC in pediatric patients aged 3 months and older.

Post-Marketing Requirements (PMR)

The review team is considering issuing a (b) (4) . Discussions are ongoing at the time of this review and a final decision is still pending.

Summary of Important Clinical Pharmacology Findings

ARROW Randomization 3

Study Design

ARROW was an open-label clinical study conducted in Uganda and Zimbabwe, and had four fully powered randomizations, and two pharmacokinetic substudies. ARROW enrolled 1206 antiretroviral therapy (ART)-naïve pediatric patients from 3 months to 17 years of age. In Randomization 3, 669 subjects were randomized once they had completed at least 36 weeks of twice-daily ABC+3TC+either NRTI or NNRTI dosing in the main study (Randomization 1 and 2). The subjects were followed over at least 96 weeks for viral load, CD4 cell counts, disease progressions, safety outcomes, and adherence.

Results

Once daily dosing ABC+3TC+either NRTI or NNRTI was non-inferior to twice daily dosing with respect to virologic suppression through week 96. Virologic outcomes and safety outcomes between treatment arms were comparable across baseline characteristics (gender, age, or viral load at the beginning of Randomization 3).

Table 1. Proportions of subjects with HIV-1 RNA less than 80 copies at Baseline and Week 96

Subjects (%) with HIV-1 RNA < 80 copies/mL	ZIAGEN plus Lamivudine Twice-Daily Dosing	ZIAGEN plus Lamivudine Once-Daily Dosing

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	(n = 333)	(n = 336)
Baseline	250 (75%)	237 (71%)
Risk difference	-4.5% (95% CI -11% to 2%)	
Week 96	232 (70%)	226 (67%)
Risk difference	-2.4% (-9% to 5%)	

ARROW PK substudy Part 1

Study Design

This PK substudy compared the pharmacokinetics of ABC and 3TC QD and BID administration of scored tablets in 36 children aged 3 to 12 years on twice daily dosage regimens of the ARROW trial. After 36 weeks of a BID regimen, subjects were switched to a QD regimen. Serial PK samples were obtained at Week 36 (twice daily) and Week 40 (once daily).

Results

The results showed comparable 3TC and ABC AUC_{0-24} values between QD and BID dosing regimens. mean C_{max} values of 3TC and ABC were higher (approximately 76% and 64%, respectively) and C_{tau} values were lower in the QD dosing regimen (approximately 65%), compared to the BID dosing regimen.

PENTA15

Study Design

Children enrolled in the study were 3 to < 36 months old HIV-1 patients on a stable regimen containing ABC 8 mg/kg BID (with or without 3TC 4 mg BID). Serial PK samples were collected on Week 0 (BID). Following collection of these samples, children switched to ABC 16mg/kg QD (and 3TC 8mg/kg QD if applicable). Second pharmacokinetic sampling for the QD dosing regimen of ABC and 3TC was performed at Week 4.

Results

The results showed comparable 3TC and ABC AUC_{0-24} values between once and twice daily dosing regimens. The mean C_{max} values of 3TC and ABC were higher in the QD dosing regimen compared to the BID dosing regimen by approximately 2-fold.

ARROW PK substudy Part 2

Study design

This crossover study compared the PK of oral solutions and tablet formulations of ABC, 3TC, and zidovudine (ZDV) administered BID in HIV-infected children weighing 12 to 15kg who were ready to switch from liquid to solid formulations. Serial PK samples were obtained after at least 24 weeks on the oral solution formulation and 4 weeks after switching to the scored tablet formulations.

Results

3TC plasma exposures following administration of scored tablets (as Combivir) were higher than those from the oral solution. Dose normalized C_{max} and AUC values were approximately 55% and 58% higher, respectively, following administration of Combivir tablet formulation compared to the oral solution.
For both ABC and ZDV, dose-normalized AUC and Cmax following administration of the tablet formulations were comparable to those following administration of the respective oral solution.

Labeling Recommendations

The sponsor's original proposal and DAVP's recommendations are compared in the following tables. The key differences are highlighted in blue (sponsor's proposal) and in red (DAVP recommendation). The labeling language is still under discussion at the time this review was finalized.

ZIAGEN (Abacavir Sulfate)

2. Dosage and Administration

2.2. Pediatric patients

<table>
<tr><th>Sponsor's proposal</th><th>DAVP recommendations</th></tr>
<tr><td>The recommended oral dose of ZIAGEN oral solution in HIV-1-infected pediatric patients aged 3 months and older is 8 mg per kg twice daily (up to a maximum of 300 mg twice daily) or 16 mg per kg once daily (up to a maximum of 600 mg once in combination with other antiretroviral agents.</td><td>Acceptable</td></tr>
<tr><td>Table 1. Dosing recommendation for ZIAGEN scored tablets in pediatric patients
<table>
<tr><th rowspan="2">Weight (kg)</th><th rowspan="2">Once-Daily Dosing Regimen</th><th colspan="3">Twice-Daily Dosing Regimen</th></tr>
<tr><th>AM Dose</th><th>PM Dose</th><th>Total Daily Dose</th></tr>
<tr><td>14 to <20</td><td>1 tablet (300 mg)</td><td>½ tablet (150 mg)</td><td>½ tablet (150 mg)</td><td>300 mg</td></tr>
<tr><td>20 to <25</td><td>1½ tablets (450 mg)</td><td>½ tablet (150 mg)</td><td>1 tablet (300 mg)</td><td>450 mg</td></tr>
<tr><td>≥25</td><td>2 tablets (600 mg)</td><td>1 tablet (300 mg)</td><td>1 tablet (300 mg)</td><td>600 mg</td></tr>
</table></td><td>Acceptable</td></tr>
</table>

Reviewer comments: Current weight bands for scored tablets are 14 to < 21 kg, 21 to < 30 kg, and ≥ 30 kg. The sponsor proposed new weight bands to harmonize the WHO treatment guidelines for dosing abacavir scored tablets. As ARROW trial was conducted using WHO treatment guideline weight bands and demonstrated safety and efficacy, the proposal is acceptable. Pharmacometric analysis results by Dr. Fang Li also support the WHO weight bands (refer to pharmacometrics review).

12.3 Pharmacokinetics

Sponsor's proposal	DAVP recommendations
The pharmacokinetics of abacavir have been studied after either single or repeat doses of ZIAGEN in 169 pediatric subjects. Subjects receiving abacavir oral solution according to the recommended dosage regimen achieved plasma concentrations of abacavir similar to adults. Subjects receiving abacavir oral tablets achieved higher plasma concentrations of abacavir than subjects receiving oral solution because the weight-band–based dosing for the tablet formulation results in administration of higher mg per kg doses.	The pharmacokinetics of abacavir have been studied after either single or repeat doses of ZIAGEN in 169 pediatric subjects. Subjects receiving abacavir oral solution according to the recommended dosage regimen achieved plasma concentrations of abacavir similar to adults. Subjects receiving abacavir oral tablets achieved higher plasma concentrations of abacavir than subjects receiving oral solution (b) (6)

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The pharmacokinetics of abacavir dosed once daily in HIV-1-infected pediatric subjects aged 3 months through 12 years was evaluated in 3 trials (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]). All 3 trials were 2-period, crossover, open-label pharmacokinetic trials of twice- versus once-daily dosing of abacavir and lamivudine. These 3 trials demonstrated that once-daily dosing provides (b) (4) AUC_{0-24} to twice-daily dosing of abacavir at the same total daily dose for both the oral solution and tablet formulations. The mean C_{max} was approximately (b) (4)-fold higher with abacavir once-daily dosing compared with twice-daily dosing.	The pharmacokinetics of abacavir dosed once daily was compared to twice daily in HIV-1-infected pediatric subjects aged 3 months through 12 years in 3 clinical trials (b) (4) These 3 trials demonstrated that once-daily dosing provides comparable AUC_{0-24} to twice-daily dosing of abacavir at the same total daily dose. The mean C_{max} was approximately 1.6 to 2-fold higher with abacavir once-daily dosing compared with twice-daily dosing.

EPIVIR (lamivudine)

2. Dosage and administration

2.2 Pediatric patients

<table>
<tr><th>Sponsor's proposal</th><th>DAVP recommendations</th></tr>
<tr><td>The recommended oral dose of EPIVIR oral solution in HIV-1-infected pediatric patients aged 3 months and older is 4 mg per kg twice daily (b) (4) or 8 mg per kg once daily (up to a maximum of 300 mg once daily), administered in combination with other antiretroviral agents.</td><td>The recommended oral dose of EPIVIR oral solution in HIV-1-infected pediatric patients aged 3 months and older is 4 mg per kg twice daily (b) (4) or 8 mg per kg once daily (up to a maximum of 300 mg once daily), administered in combination with other antiretroviral agents.

(b) (4)</td></tr>
<tr><td>Table 1. Dosing recommendation for ZIAGEN scored tablets in pediatric patients

<table><tr><th rowspan="2">Weight (kg)</th><th rowspan="2">Once-Daily Dosing Regimen</th><th colspan="3">Twice-Daily Dosing Regimen</th></tr><tr><th>AM Dose</th><th>PM Dose</th><th>Total Daily Dose</th></tr><tr><td>14 to <20</td><td>1 tablet (b) (4)</td><td>½ tablet (b) (4)</td><td>½ tablet (b) (4)</td><td>(b) (4)</td></tr><tr><td>20 to <25</td><td>1½ tablets (b) (4)</td><td>½ tablet (b) (4)</td><td>1 tablet (b) (4)</td><td>(b) (4)</td></tr><tr><td>≥25</td><td>2 tablets (b) (4)</td><td>1 tablet (b) (4)</td><td>1 tablet (b) (4))</td><td>(b) (4)</td></tr></table></td><td>Acceptable (see ZIAGEN reviewer comments)</td></tr>
</table>

Reviewer comments
-Due to lower 3TC exposures in pediatric patients receiving the oral solution formulation, as compared to adult patients, it is unclear whether initiating treatment with a once daily dosing regimen using the solution would result in acceptable virologic and immunologic response in subjects with higher viral load or lower CD4 counts.
-ARROW Randomization 3 study results support switching regimens from BID to QD in subjects who have been on stable therapy for at least 36 weeks based on the study design. The results do not directly support treatment initiation with the QD dosing regimen for either 3TC or ABC. However, for ABC, the review team decided to allow treatment initiation with QD as ABC exposures observed in pediatric patients (regardless of age, weight bands, or formulations) were comparable to or higher than those observed in adult patients.

13.2 Pharmacokinetics

Sponsor's proposal	DAVP recommendations
The pharmacokinetics of lamivudine have been studied after either single or repeat doses of EPIVIR in 210 pediatric subjects. Subjects receiving lamivudine oral solution according to the recommended dosage regimen achieved (b) (4) Subjects receiving lamivudine oral tablets achieved (b) (4) (b) (4) . The absolute bioavailability of both EPIVIR tablet and oral solution are lower in children than adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown. The pharmacokinetics of lamivudine dosed once daily in HIV-1-infected pediatric subjects aged 3 months through 12 years was evaluated in 3 trials (PENTA-15 [n = 17], PENTA 13 [n = 19], and ARROW PK [n = 35]). All 3 trials were 2-period, crossover, open-label pharmacokinetic trials of twice- versus once-daily dosing of abacavir and lamivudine. These 3 trials demonstrated that once-daily dosing provides equivalent AUC_{0-24} to twice-daily dosing of lamivudine at the same total daily dose (b) (4) The mean C_{max} was approximately 80% to 90% higher with lamivudine once-daily dosing compared with twice-daily dosing. (b) (4)	The pharmacokinetics of lamivudine have been studied after either single or repeat doses of EPIVIR in 210 pediatric subjects. Subjects receiving lamivudine oral solution according to the recommended dosage regimen achieved slightly lower plasma concentrations of lamivudine compared to adults. Subjects receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults. The absolute bioavailability of both EPIVIR tablet and oral solution are lower in children than adults. The relative bioavailability of EPIVIR oral solution appears to be lower than tablets containing lamivudine by approximately 40% in pediatric patients despite there being no difference in adults. The mechanisms for the diminished absolute bioavailability of lamivudine and relative bioavailability of lamivudine solution are unknown. The pharmacokinetics of lamivudine dosed once daily was compared to twice daily in HIV-1-infected pediatric subjects aged 3 months through 12 years in 3 (b) (4) trials (b) (4) These 3 trials demonstrated that once-daily dosing provides comparable AUC_{0-24} to twice-daily dosing of lamivudine at the same total daily dose. The mean C_{max} was approximately 1.6 to 2-fold higher with lamivudine once-daily dosing compared with twice-daily dosing. (b) (4)

In addition, the sponsor proposed removing the following information from the current label. The proposed change is acceptable.

Pediatric Patients:

The absolute bioavailability of both EPIVIR tablet and oral solution are lower in children than adults. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Individual Trial Reviews

Title: Pharmacokinetic comparison of once vs. twice daily administration of abacavir and lamivudine scored tablets in HIV-infected African children (ARROW PK substudy 1).

Objective:

- To describe the plasma PK of lamivudine (3TC), zidovudine (ZDV) and abacavir (ABC) in HIV-infected children receiving tablet formulations with doses determined according to World Health Organization (WHO) weight bands.

- To compare plasma PK of twice versus once daily scored tablets of ABC and 3TC in HIV-infected African children.

Study Design

The study was designed to evaluate plasma exposures of 3TC and ABC following the switch from twice to once daily dosing in combination with efavirenz. PK samples were collected at Week 36 of the study when patients were taking twice daily regimens of ABC and 3TC (with or without ZDV) in combination with efavirenz. Immediately following completion of the PK sampling at Week 36, patients were switched from twice daily to once daily 3TC and ABC, taken in the morning, staying on the same WHO weight band (i.e. the same total daily dose). ZDV was dropped from the regimens of patients in Treatment Arm B per protocol. The second set of serial PK samples were collected at Week 40 (i.e., 4 weeks after switching to once daily antiretroviral therapy).

Subjects were admitted to the PK unit either the evening before the PK day or early in the morning. Serial blood samples were collected at Weeks 36 (0,1,2,4,6,8 and 12 hours post dose) and 40 (0,1,2,4,6,8,12, and 24 hours post dose). Actual date and time of each blood sample collection was recorded.

Key Inclusion Criteria

- Male or female between 3 and 12 years of age
- Enrolled in ARROW trial Arm A (ABC+3TC+NNRTI) or Arm B (ABC+3TC+ZDV+NNRTI for 36 weeks then ABC+3TC+NNRTI) and reached their 36 week visit
- Received 3TC, ABC, and EFV (with or without ZDV) at Week 36 with the expectation that the subject would remain on 3TC, ABC and EFV at Week 40
- Received whole or half scored tablets of 3TC and ABC (either single entities or Combivir+ABC).

Key Exclusion Criteria

- Having anemia.
- Having illnesses that could influence the pharmacokinetics of the antiretroviral drugs at week 36 or week 40; e.g., severe diarrhea, vomiting, renal or liver disease.
- Use of concomitant medications known to interact with the antiretroviral drugs.
- Missed doses of any antiretroviral drugs in the 3 days prior to the PK evaluation
- The subject was expected to change weight bands between weeks 36 and 40

Bioanalysis

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Plasma samples were analyzed for lamivudine, abacavir, and zidovudine using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) and higher limit of quantification (HLQ) for ABC and 3TC were 2.5ng/mL and 2500ng/mL, respectively. Quality Control samples (QC), prepared at 3 different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

Results

Subject disposition and demographics

Subject disposition and demographics are summarized in Table 1. 57%, 40%, and 3% of subjects received a total daily dose of 3TC 150 mg, 225 mg and 300 mg, respectively. 53%, 39%, and 8% of subjects received a total daily dose of ABC of 300 mg, 450 mg and 600 mg, respectively.

Table. 1 Subject disposition

	Age Group	Antiretroviral Drug		
		ABC	3TC	ZDV
Number of Subjects, n				
PK Concentration Population	Overall	41	41	41
PK Summary Population	Overall	41	41	17
PK Parameter Summary Population	Overall	36	35	15
	3-6 yrs	17	17	7
	7-12yrs	19	18	8
Age in Years, Mean (SD) *(PK Parameter Summary Population)*	Overall	7.27 ± 2.33	7.02 ± 2.06	7.21 ± 2.32
	3-6 yrs	5.28 ± 0.96	5.28 ± 0.96	5.33 ± 1.17
	7-12yrs	9.06 ± 1.60	8.67 ± 1.29	8.86 ± 1.72
Sex, Male, n (%) *(PK Parameter Summary Population)*	Overall	15 (42%)	14 (40%)	6 (40%)
	3-6 yrs	10 (59%)	10 (59%)	4 (57%)
	7-12yrs	5 (26%)	4 (22%)	2 (25%)
Weight, Mean (SD) *(PK Parameter Summary Population)*	Overall	19.8 ± 4.01	19.3 ± 3.48	20.1 ± 4.26
	3-6 yrs	16.6 ± 1.97	16.6 ± 1.97	16.6 ± 1.84
	7-12yrs	22.6 ± 3.10	21.9 ± 2.47	23.2 ± 3.18

*Subjects were excluded from the PK parameter population or PK parameter summary due to dosing error or unusual PK profiles (1 subject, very low concentrations for all samples collected)

Pharmacokinetic Results

Lamivudine (3TC)

3TC plasma pharmacokinetic parameters and statistical analyses are summarized in Table 2. AUC_{24hr} following once daily dosing were equivalent to those following twice daily dosing. As expected, C_{max} values were approximately 76% higher and C_{tau} values were approximately 65% lower in patients on the QD regimen as compared to patients on the BID regimen. No significant differences in 3TC exposures were observed between younger patients (3 to 6 years) and older patients (7 to 12 years) who received scored tablet formulations of lamivudine or Combivir. AUC values were slightly higher to adult historical data observed in NUCA3001, NUCA3002, AZL1002, and EPV1001 (9.2 to 11.6 µg·hr/mL).

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Table 2. Summary of plasma lamivudine pharmacokinetic parameters and statistical analyses following repeat dose administration

	QD	BID	GLS Mean ratio QD vs. BID [90% CI]
C_{max} (µg/mL)			
Overall (n=35)	3.17 (42)	1.80 (48)	1.76 [1.59-1.96]
3 to 6 years (n=17)	3.01 (35)	1.69 (44)	1.78 [1.50-2.11]
7 to 12 years (n=18)	3.34 (48)	1.91 (31)	1.75 [1.51-2.02]
$AUC_{0\text{-}24hr}$ (µg·hr/mL)			
Overall (n=35)	13.0 (38)	12.0 (33)	1.09 [0.98,1.20]
3 to 6 years (n=17)	12.3 (36)	11.1 (29)	1.10 [0.98,1.25]
7 to 12 years (n=18)	13.7 (46)	12.8 (36)	1.07 [0.89, 1.27]
C_{tau} (µg/mL)			
Overall (n=35)	0.084 (55)	0.052 (60)	0.35 [0.26-0.47]
3 to 6 years (n=17)	0.048 (65)	0.068 (49)	0.45 [0.28-0.73]
7 to 12 years (n=18)	0.057 (55)	0.103 (53)	0.28 [0.18-0.42]

*Data expressed as geometric mean (%CV)

Abacavir (ABC)

Abacavir plasma pharmacokinetic parameters and statistical analyses are summarized in Table 3. AUC_{24hr} following once daily dosing were comparable to those following twice daily dosing over all age groups. C_{max} values were approximately 64% higher and C_{tau} values were approximately 65% lower in patients on the once a day dose regimen compared to that of twice daily dose regimen. AUC values were approximately 30% and higher to adult historical data listed in the current USPI (12 µg·hr/mL).

Table 3. Summary of plasma abacavir pharmacokinetic parameters and statistical analyses following repeat dose administration

	QD	BID	GLS Mean ratio QD vs. BID
C_{max}(µg/mL)			
Overall (n=36)	6.84 (45)	4.18 (38)	1.64 [1.43-1.88]
3 to 6 years (n=17)	6.38 (45)	4.12 (38)	1.66 [1.39-1.99]
7 to 12 years (n=19)	6.85 (53)	4.23 (39)	1.62 [1.43-1.88]
$AUC_{0\text{-}24hr}$ (µg·hr/mL)			
Overall (n=36)	15.3 (42)	15.6 (40)	0.97 [0.89-1.08]
3 to 6 years (n=17)	15.0 (40)	15.6 (41)	0.96 [0.87-1.06]
7 to 12 years (n=19)	15.6 (45)	15.6 (39)	1.00 [0.84-1.19]
C_{tau} (µg/mL)			
Overall (n=36)	0.009 (117)	0.024 (97)	0.35 [0.26-0.47]
3 to 6 years (n=17)	0.010 (118)	0.021 (83)	0.45 [0.28-0.73]
7 to 12 years (n=19)	0.008 (121)	0.028 (108)	0.28 [0.18-0.42]

Reviewer comments
Overall, the magnitude of changes in PK parameters (i.e., comparable AUC values, ~ 65-75% increased Cmax values, and ~65% decreased Cmin values) upon switching from BID to QD dosing regimen were comparable to adult historical control data. These are expected results based on the linear PK of ABC and 3TC.
AUC and Cmax values were higher than adult historical control data, but the BID dosing regimen has been used for a long time and no appreciable exposure-dependent adverse events have been identified.

Conclusion

- For both ABC and 3TC, the AUC_{24hr} following once daily dosing were comparable to those following twice daily dosing over all age groups. C_{max} values were approximately 65-75% higher and C_{tau} values were lower by 65% in patients on the once a day dose regimen compared to that of twice daily dose regimen.

Title: Plasma pharmacokinetic study of once versus twice daily abacavir as part of combination antiretroviral therapy in children with HIV-1 infected aged 3 to < 36 months (PENTA15)

Objectives

- To compare plasma PK parameters of q24h versus q12h dosing of ABC (and 3TC) in HIV-1 infected infants and children aged 3 months to 36 months
- To compare age related differences in the PK parameters of q24h versus q12h dosing of ABC and 3TC in infants and children in three age groups (3 to <12 months, 12 to < 24 months and 24 to < 36 months)

Study Design

Children on a stable regimen containing ABC 8 mg/kg q12h (with or without 3TC 4 mg/kg q12h) were eligible for enrollment. At Study Week 0, serial PK samples were collected. Following collection of these samples, children switched to ABC 16mg/kg q24h (and 3TC 8mg/kg q24h). The same total daily dose of ABC and 3TC was given on the q24h regimen, as on the previous q12h regimen (within 25% to allow appropriate adjustment for growth). All children took q24h ABC (with or without 3TC) in the morning, until the week 4 visit, when a second PK sampling was performed.

Blood samples were taken at 0 (pre-dose), 1, 2, 3, 4, 6, 8 and 12 hours post-dose on the first PK day (q12h PK at steady-state) and at 0 (predose), 1, 2, 3, 4, 6, 8, 12 and 24 hours on the second PK day(q24h PK at steady-state). After the second PK sampling was completed, the intent was for children to remain on q24h ABC (with or without 3TC) dosing at least until week 12 of the study in order to assess HIV-1 RNA at week 12.

Key Inclusion Criteria

- Infants and children with confirmed presence of HIV-1 infection, aged 3 to 36 months
- Currently on combination ART including ABC oral solution with or without 3TC oral solution, for at least 12 weeks and expected to stay on this regimen for at least a further 12 weeks.
- Suppressed HIV-1 RNA viral load (i.e. <400 copies/ml) or non-suppressed, but low, HIV-1 RNA viral load (i.e. 400-20 000 copies/ml). The non-suppressed children should have had a stable or decreasing HIV-1 RNA viral load prior to study entry and should be considered to be still gaining benefit from the current regimen
- Stable or rising CD4+ cell percent

Key Exclusion Criteria

- Intercurrent illness
- Receiving concomitant therapy except prophylactic antibiotics
- Abnormal renal or liver function (grade 3 or above)

Bioanalysis

ABC and 3TC were extracted from 500 µL of human plasma by a solid phase extraction then analyzed by HPLC with UV detection at a wavelength of 260 nm. The lower limit of Quantification (LLQ) and the Upper Limit of Quantitation (ULOQ) were 0.015 mg/L and 5 mg/L for ABC. The LLOQ and ULOQ for 3TC were 0.05 mg/L and 5 mg/L, respectively. QC samples were prepared for abacavir and lamivudine in

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human plasma at three concentrations (0.1, 0.4 and 2 mg/L) which spanned the calibration range of the method. Individual QC results were deemed acceptable if the calculated concentration deviated by no more than 15% from the actual concentration. The analytical run was approved if no more than one-third of the QC results exceeded the acceptable limit.

Results

Subject disposition, demographics and baseline characteristics

18 children had evaluable PK samples. All 18 children were evaluated for ABC PK. and 17 children were evaluated for 3TC PK. The median (range) age was 23 (5-34) months. 10 (56%) were boys, median (range) weight was 11 (7-13) kg, height was 82 (74-87) cm. 14 (78%) children were black (African or other), 3 (17%) were white, and 1 (6%) was mixed black/white.

At screening, 8 (44%), 8 (44%), and 2 (11%) children had HIV-1 RNA <50, ≥50 to <400 and above 400 copies/ml, respectively. Median (IQR) CD4 count and percent at screening were 1899 (1344-3150) cells/mm^3 and 39 (35-45) %, respectively. Concomitant NNRTIs and PIs administered to the patients were lopinavir/ritonavir (44%) or nevirapine (56%). In one patient, emtricitabine was administered instead of 3TC. Two subjects received zidovidine and one subject received stavudine in addition to 3TC and ABC.

Pharmacokinetic Results

Lamivudine

ABC AUC_{24hr} values following once daily dosing were comparable to those following twice daily dosing over all age groups. The Cmax values were approximately two times higher on q24h dosing compared to q12h. AUC values observed in this study were slightly higher to adult historical data observed in NUCA3001, NUCA3002, AZL1002, and EPV1001 (9.2 to 11.6 μg·hr/mL). Mean C_{min} values were approximately 41% lower in patients on the once a day dose regimen compared to that of twice daily dose regimen (0.050 μg/mL in QD dosing and 0.086 μg/mL in BID doing).

Table 1. PENTA 15: Summary of steady-state plasma lamivudine pharmacokinetic parameters and statistical comparisons for once- and twice-daily administration of lamivudine oral solution

Plasma PK Parameter	Age Group	Lamivudine 8 mg/kg Once-Daily Dosing Geometric Mean (95% CI)	Lamivudine 4 mg/kg Twice-Daily Dosing Geometric Mean (95% CI)	Once- Versus Twice-Daily Dosing Comparison GLS Mean Ratio [90% CI]
AUC(0-24) (μg·h/mL)	Overall (N=17)	8.66 (7.46, 10.1)	9.48 (7.89, 11.40)	0.91 [0.79, 1.06]
	3-12 mo (N=4)	10.31 (6.26, 17.0)	9.24 (4.66, 18.3)	—[a]
	12-24 mo (N=6)	7.13 (5.84, 8.71)	9.54 (6.71, 13.6)	—[a]
	24-36 mo (N=7)	9.27 (7.11, 12.1)	9.58 (6.65, 13.8)	—[a]
Cmax (μg/mL)	Overall (N=16)[b]	1.87 (1.65, 2.13)	1.05 (0.88, 1.26)	1.78 [1.52, 2.09]
	3-12 mo (N=4)	2.37 (1.57, 3.57)	1.04 (0.76, 1.41)	—[a]
	12-24 mo (N=6)	1.71 (1.46, 2.02)	1.22 (0.82, 1.80)	—[a]
	24-36 mo[b] (N=6)	1.75 (1.39, 2.20)	0.92 (0.62, 1.35)	—[a]
CL/F/kg (L/h/kg)	Overall (N=17)	0.86 (0.74, 1.01)	0.79 (0.65, 0.96)	1.10 [0.95, 1.28]
	3-12 mo (N=4)	0.72 (0.42, 1.26)	0.79 (0.36, 1.73)	—[a]
	12-24 mo (N=6)	1.05 (0.88, 1.25)	0.80 (0.55, 1.18)	—[a]
	24-36 mo (N=7)	0.81 (0.61, 1.07)	0.77 (0.53, 1.12)	—[a]

Source data: PENTA 15 clinical study report, Table 6b, Table 7e, and Table 7f.
CI = confidence interval; GLS mean ratio = ratio of geometric least squares means; PK = pharmacokinetic.
a. For individual age groups, n is too small for meaningful once- versus twice-daily comparisons.
b. One child (≥24 to <36 months) excluded from Cmax summary due to a missing 1-hour plasma concentration on the first PK day

Abacavir

ABC AUC_{24hr} following once daily dosing were equivalent to those following twice daily dosing over all age groups. C_{max} was approximately two times higher on QD dosing compared to BID with no difference between age groups. Mean C_{min} values were approximately 58% lower in patients on QD dosing compared to those on BID dosing (0.011 μg/mL in QD dosing and 0.026 μg/mL in BID dosing).

Table 1. PENTA15: Summary of state-state plasma abacavir pharmacokinetic parameters and statistical comparisons for once- and twice daily administration of abacavir oral solution

Plasma PK Parameter	Age Group	Abacavir 16 mg/kg Once-Daily Dosing Geometric Mean (95% CI)	Abacavir 8 mg/kg Twice-Daily Dosing Geometric Mean (95% CI)	Once- Versus Twice-Daily Dosing Comparison GLS Mean Ratio (90% CI)
AUC(0-24) (µg·h/mL)	Overall (N=18)	11.6 (9.89-13.5)	10.9 (8.89-13.2)	1.07 (0.92-1.23)
	3-12 mo (N=4)	15.9 (8.86-28.5)	12.7 (6.52-24.6)	—[a]
	12-24 mo (N=6)	10.6 (7.68-14.6)	13.9 (10.4-18.5)	—[a]
	24-36 mo (N=8)	10.5 (8.87-12.5)	8.34 (6.27-11.1)	—[a]
Cmax (µg/mL)	Overall (N=17)[b]	4.68 (3.86-5.67)	2.29 (1.80-2.91)	2.04 (1.73-2.42)
	3-12 mo (N=4)	5.89 (2.83-12.3)	2.43 (1.37-4.31)	—[a]
	12-24 mo (N=6)	5.29 (3.70-7.56)	3.18 (2.24-4.52)	—[a]
	24-36 mo[b] (N=7)	3.69 (2.95-4.61)	1.67[e] (1.10-2.53)	—[a]
CL/F/kg (L/h/kg)	Overall (N=18)	1.38 (1.17-1.62)	1.47 (1.21-1.79)	0.94 (0.81-1.08)
	3-12 mo (N=4)	0.97 (0.52-1.81)	1.23 (0.61-2.48)	—[a]
	12-24 mo (N=6)	1.52 (1.11-2.09)	1.17 (0.94-1.46)	—[a]
	24-36 mo (N=8)	1.52 (1.29-1.78)	1.91 (1.44-2.53)	—[a]

Source data: PENTA 15 clinical study report, Table 6a, Table 7a, and Table 7b.
CI = confidence interval; GLS mean ratio = ratio of geometric least squares means; mo = months; PK = pharmacokinetic.
a. For individual age groups, n is too small for meaningful once- versus twice-daily comparisons.
b. One child (≥24-<36 months) excluded from Cmax summary due to a missing 1-hour plasma concentration on the first PK day.

Antiviral Activity

There was no indication of loss of virological control in this small group of children. At screening, 4, 8, 12, 24 and 48 weeks, 89%, 93%, 93%, 94%, 100% and 89% of children had HIV-1 RNA <400 copies/ml. There was also no indication of decreasing CD4 count or percent.

Conclusion

- In HIV-1–infected children aged 3 to 36 months, oral administration of 3TC as a solution at a dose of 8 mg/kg once daily provided similar AUC_{24hr} values as the 4 mg/kg twice-daily regimen. Cmax values on once-daily regimens were higher than those on twice-daily regimens by approximately 2-fold.

Title: ARROW PK Substudy 2: Relative Bioavailability of Scored Tablets versus Oral Solution Formulations of Lamivudine, Abacavir, and Zidovudine in HIV-Infected - African Children.

Objective: To describe the plasma PK of lamivudine (3TC), abacavir (ABC), and zidovudine (ZDV) when administered twice daily as oral solutions versus scored tablets of either 3TC, ABC, or COMBIVIR™ (ZDV + 3TC) to HIV infected African children weighing 12 to 15kg

Study Design
Patients receiving ABC, 3TC, and ZDV oral solution formulations (with or without nevirapine)], weighing 12 to 15 kg and expected to in the same weight band within the next 4 weeks of treatment were eligible for this PK substudy. The first serial PK sampling was performed after Week 24 of the trial, at the time when the child was about to be switched from liquid to solid ARV formulations. Immediately following completion of the first PK sampling, children were switched to solid formulations of all study drugs. The solid formulation dose was one-half tablet twice daily as recommended by the WHO. The second serial PK sampling was performed 4 weeks after switching to solid formulations.

On the days of PK sampling, blood samples were collected at 0, 1, 2, 4, 6, 8 and 12 hours post-dose.

Key inclusion criteria
- Male or female in the 12 to15kg weight band and expected to remain in the same weight band for at least 4 weeks.
- Received separate liquid formulations of 3TC, ABC, and ZDV (with or without nevirapine)
- Ready to switch to tablet formulations of 3TC, ABC, and ZDV.

Key exclusion criteria
- having anemia.
- having illnesses that could influence the pharmacokinetics of the antiretroviral drugs; e.g., severe diarrhea, vomiting, renal or liver disease or
- Use of concomitant medications known to interact with the antiretroviral drugs.
- Missed doses of antiretroviral drugs in the 3 days prior to either PK evaluation

Dosing Regimens
For PK Day 1
- ABC Oral Solution: 6mL (120mg) twice daily
- 3TC Oral Solution: 6mL (60mg) twice daily
- ZDV Oral Solution: 12mL (120mg) twice daily

For PK Day 2:
- ABC Scored Tablet: ½ tablet (150mg) twice daily
- COMBIVIR Scored Tablet: ½ tablet (75mg 3TC + 150mg ZDV) twice daily

Bioanalysis
Plasma samples were analyzed for lamivudine, abacavir, and zidovudine using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. The lower limit of quantitation of (LLQ) for lamivudine, abacavir, and zidovudine was 2.5ng/mL with a higher limit of

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quantification (HLQ) of 2500ng/mL. Quality Control samples (QC), prepared at 3 different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

Results

Subject disposition and demographics

Subject disposition and demographics are summarized in Table 1. Nine children were excluded from the PK Parameter Summary Population because they received the solution dose for the 10 to 12kg weight band on the first PK day. 3 subjects received concomitant nevirapine solutions.

Table 1. Subject disposition

Number of Subjects, n	
PK Concentration Population	28
PK Summary Population	28
PK Parameter Summary Population	19
Age in Years, Mean (SD) *(PK Parameter Summary Population)*	2.97 ± 0.631
Sex, Male, n (%) *(PK Parameter Summary Population)*	6 (32%)
Weight, Mean (SD) *(PK Parameter Summary Population)*	12.45 ± 0.34

Source Data: Table 9.1

Pharmacokinetic results

Lamivudine

For 3TC, plasma exposures were higher following the administration of the lamivudine/zidovudine combination tablet. After dose-normalization, C_{max} and AUC values were approximately 55% and 58% higher, respectively, compared to the lamivudine oral solution. The reason for this finding is unknown. Of note, a previous study in adult HIV-infected patients (NUCA1003) demonstrated equivalent 3TC plasma exposures between tablet and solution.

Table 1. 3TC pharmacokinetic parameters and GM ratio (after dose-normalization)

	Solution/60 mg (n=19)	Tablet/ 75 mg (n=19)	Dose-normalized geometric mean ratio (90% CI)
C_{max} (µg/mL)	1.05 (38)	2.03 (21)	1.55 [1.33-1.81]
AUC_{12hr} (µg·hr/mL)	4.16 (36)	8.20 (20)	1.58 [1.33-1.81]
C_{12hr} (µg/mL)	0.077 (33)	0.106 (30)	1.10 [0.97-1.25]

Data expressed as geometric mean (%CV)

PK parameters for oral solution were normalized to a 75 mg dose

Reviewer comments

- *There is a confounding factor that may limit the interpretation of results; relative bioavailability of 3TC solution and Combivir (ZDV + 3TC) tablet has not been directly assessed.*

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- *Similar study results have been reported using different FDC tablets containing lamivudine (compared to lamivudine solution; P1056 and P1069). In combination with 3TC PK data in pediatric patients from other trials, it is reasonable to conclude that the relative bioavailability of 3TC solution is lower compared to tablets (including various fixed-dose combination tablet products).*

- *One author has postulated that sorbitol (sweetener in ABC and NVP solutions) may cause reduced bioavailability of 3TC during co-administration (Garcia-Arieta, 2014; see "cross-study, cross-submission review for lamivudine exposures)*

Abacavir

For ABC, the plasma dose-normalized AUC and C_{max} values following administration of abacavir as a tablet were comparable to those following administration of abacavir oral solution. A lower C_{12hr} mean value was observed in tablets after dose normalization. However, interpretation is limited due to significant inter-individual variability observed in C_{12hr} (> 80% CV).

	Solution/120 mg (n=19)	Tablet/150 mg (n=19)	Dose-normalized geometric mean ratio [90% CI]
C_{max} (µg/mL)	4.94 (40)	6.3 (34)	0.96 [0.83-1.12]
AUC_{12hr} (µg·hr/mL)	11.9 (53)	14.2 (42)	1.02 [0.89-1.17]
C_{12hr} (µg/mL)	0.027 (96)	0.026 (82)	0.76 [0.55-1.06]

Data expressed as geometric mean (%CV)

PK parameters for oral solution were normalized to a 150 mg dose

Zidovudine

The sponsor conducted similar analysis for zidovudine in this study. Similar to abacavir, dose-normalized plasma exposures of ZDV were equivalent following administration of tablet and syrup.

Conclusion

- 3TC plasma exposures following administration of tablet were higher than those from the oral solution. Dose normalized Cmax and AUC values were approximately 55% and 58% higher, respectively, following administration of the tablet formulation compared to the oral solution. The cause is unknown.
- For both ABC and ZDV, dose-normalized AUC and Cmax following administration of the tablet formulations were equivalent to those following administration of the respective oral solution

CROSS-STUDY, CROSS-SUBMISSION REVIEW: Lamivudine PK

Although the purpose of the current submission was not related to re-evaluating the culamivudine doses in pediatric patients, the review team has had several in-depth discussions on re-evaluation of the adequacy of the current lamivudine dose in pediatric patients receiving oral solutions. The following QBR (question-based review) summarize key issues with respect to lower lamivudine exposures in pediatric patients. The review team is considering issuing a PMR to further evaluate the clinical consequences of lower lamivudine exposures in pediatric patients receiving solutions. Discussions are ongoing at the time of this review and a final decision is still pending.

1. Is lamivudine exposure lower in pediatric patients taking solutions as compared to adult patients?

Yes it is. As summarized in Table 1, across trials, pediatric patients taking solutions showed lower lamivudine exposures as compared to adults. Modeling and simulation results also showed similar results (refer to Dr. Fang Li's review). The sponsor stated that the exposures are comparable to adults based on EPV10001 study results. However, 3TC exposures in EPV10001 appear to be lower than those observed in HIV patients (AZL10002, NUCA 3001 and 3002) or other pharmacokinetic studies in healthy volunteers (Bruno et al, 2001., Johnson et al, 1999). In pediatric subjects receiving tablet formulations, regardless of ages, 3TC exposures were comparable to or slightly higher than those observed in adults.

Table 1. Summary of 3TC AUC24hr at steady-state in clinical trials

	Adult trials (150 mg BID)	**PENTA13 4 mg/kg BID**		**PENTA15 4 mg/kg BID**	**ARROW part 1 Tablets 3.8 to 5.9 mg/kg BID**		**ARROW Part 2 4 mg/kg BID**	**NUCA2002 and 2005 4 mg/kg BID[a]**		
Age		2 to < 6 y	6 to < 13 y	3 to 36 months	3 to < 6 y	6 to < 12 y	1.8 to 4 y (mean: 3)	< 2 y	2 to < 6 y	6 to 12 y
AUC_{24} (µg/mL *hr)	NUCA3001/ 3002 (n=396, popPK) **11.6** AZL10002[b] (n=12 **11.0** EPV10001[c] (n=60) **9.2**	All subjects (n=9) **7.6** Excluding one subject receiving tablet **7.0**	All subjects (n=9) **10.6** Solution (n=5) **9.3** Tablet (n=4) **12.4**	All subjects received solutions (n=17) **9.5**	All subjects received tablets (n=12) **12.0**	All subjects received tablets (n=23) **12.0**	(n=19) **8.3** Solution (n=19) **8.3** Tablet* (n=19) **13.2**	(n=5) **7 .2**	(n=27) **8.3**	(n=40) **10.1**

*Dose normalized to 4 mg/kg

a. Formulation information (tablet or solution) is not available.

b: HIV-infected patients

c: Healthy volunteers

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2. What is the cause of lower lamivudine exposure in subjects receiving oral solutions?

It appears that the relative bioavailability of 3TC solutions is lower compared to tablet formulations containing lamivudine in pediatric patients, but not in adults. Refer to Arrow substudy 2 individual review for detailed information. In a publication (*Garcia-Arieta 2014*), it was postulated that sorbitol, used as a sweetener in the solution formulations of both ABC and NVP, may have decreased the absorption of 3TC in pediatric patients. The effects of sorbitol in ABC oral solution on 3TC PK cannot be determined as almost all patients in PENTA13, PENTA15, and ARROW received concomitant ABC. In PENTA 15, lower 3TC AUC_{24hr} values were observed (8.0 µg/mL·hr) in patients receiving concomitant nevirapine solutions (n=10) compared to subjects not receiving nevirapine solutions (AUC_{24hr} 12.0 µg/mL·hr, n=7). This suggests sorbitol in concomitant medications may decrease 3TC lamivudine exposures. However, in NUCA2002 and 2005 where no subjects received NVP or ABC solutions, 3TC exposures were still lower in patients younger than 2 years old.

3. What is the exposure-response relationship for 3TC efficacy? Does the relationship suggest potential suboptimal efficacy of lamivudine in pediatric patients receiving solutions?

The dose-response relationship of 3TC for safety and efficacy was determined in pediatric patients (NUCA2002) receiving 1 -10 mg/kg/dose BID regimens for 24 weeks (n=89). The virologic response rates indicated that antiviral activities were seen most noticeably above 2 mg/kg/dose BID (Lewis et al, 1996). At the time of NDA review, it was concluded that 4 mg/kg/dose BIDwould provide the most adequate dose for both safety and efficacy (Clinical pharmacology review, 1995). Of note, pancreatitis was considered a serious adverse event of 3TC and a potential correlation between the dose and pancreatitis incidence prevented pursing higher doses for the approval in pediatric patients.

To the reviewer's knowledge, no information is available with respect to the plasma exposure-response relationship for 3TC efficacy. The sponsor stated that AUC would be correlated to efficacy rather than C_{max} or C_{min} as the active metabolite of 3TC (lamivudine-TP) has a long half-life in PBMC. While this is a reasonable speculation, no exposure-response relationship analysis results are available to confirm this hypothesis. There is a publication indicating a correlation between antiviral activity of 3TC and 3TC-TP concentrations in PBMC (Fletcher et al, 2000), but a correlation between lamivudine plasma concentrations and PBMC concentrations are largely unknown.

In summary, there are insufficient data to conclude whether lower 3TC exposures in pediatric patients receiving solutions can be potentially clinically relevant or not.

4. Are there any findings in subgroup analyses in the ARROW trial that indicate potential clinical relevance of lower lamivudine exposures?

Upon subgroup analyses, the review team identified that patients receiving oral solutions showed lower virologic response as compared to those received tablets at Week 0 (at the time of Randomization 3, patients have been on ARVs for at least 36 weeks) through Week 96 in both QD and BID groups (Table 2). In response to an FDA inquiry for the potential reasons for lower response rates in subjects receiving solutions (12/10/14 NDA 20977 SDN604), the sponsor stated that it is possibly due to the differences in 1) adherence or difficulty in measuring correct volumes of solutions or 2) age-related effects; subjects

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receiving solutions were younger (mean age: 2.9 years) than those receiving tablets (mean age: 6.8 years). Lower virological suppression rates and slower viral decay have been reported in younger pediatric patients and the observed response rates are comparable to historical data.

However, re-analysis in the youngest group showed lower response rates were still observed in the subgroup where the average age between tablet and solution groups were similar (Table 3), ruling out age-related effects. At this point, it is unclear whether lower response rates in subjects receiving solutions in ARROW is due to any baseline imbalance at the time of randomization 1 and 2 (at the time of ARV initiation, such as viral loads or the 3rd antiretroviral agent) or lower lamivudine exposures. Baseline characteristics at the time of randomization 1 and 2 and sparse PK data are not available.

Table 2. Subgroup analysis by formulations

	ABC+3TC Twice Daily HIV- RNA< 80 c/mL			**ABC+3TC Once Daily HIV- RNA< 80 c/mL**		
	SOLUTION	**TABLET**	**Total**	**SOLUTION**	**TABLET**	**Total**
Week 0	14/26 (53.9%)	236/307 (76.9%)	250/333 (75.1%)	15/30 (50%)	222/305 (72.8%)	237/335 (70.8%)
Week 48	14/26 (53.9%)	229/307 (74.6%)	243/333 (73.0%)	17/30 (56.7%)	223/305 (73.1%)	240/335 (71.6%)
Week 96	13/26 (50%)	222/307 (72.3%)	235/333 (70.6%)	17/30 (56.7%)	213/305 (69.8%)	230/335 (68.7%)

*Analyses conducted by Dr. Li (Pharmacometrics reviewer)

Table 3. Subgroup analysis by formulations in subjects less than 3 years old

	ABC+3TC Solution (n=37)	**ABC+3TC Tablet (n=37)**
Age (Median)	2.5 years	2.7 years
HIV-RNA < 80 c/mL		
Week 0	22/37 (59%)	29/37 (78%)
Week 48	21/36 (58%)	28/36 (78%)
Week 96	22/37 (59%)	25/36 (69%)

*BID and QD results were combined.

Conclusion

3TC solution PK in pediatric patients and its potential clinical implications were discussed. It is concluded that 3TC exposures are lower in pediatric subjects receiving solutions as compared to adults. Subgroup analyses in ARROW indicated lower virologic response rates in pediatric patients receiving solutions compared to those receiving tablets. However, at this time, it is unclear whether it is due to lower lamivudine exposures or baseline imbalance at the time of ARROW randomization 1 and 2.

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the exposure (e.g., AUC, C_{max}, C_{trough}) of abacavir and lamivudine support the proposed once-daily dosing regimen in children?

Yes, the AUC values of abacavir and lamivudine were similar between once-daily and twice-daily dosing of ABC + 3TC in children and adolescents. C_{max} for the once-daily regimen was higher while C_{trough} was lower, respectively, than the twice-daily dosing regimen for both compounds, as would be expected for a decrease in dosing frequency from twice-daily to once-daily. Of note, while most pediatric HIV-1 submissions rely on a comparison of PK exposures to determine the acceptability of proposed pediatric regimens, the current submission relies on this only as supportive information. Instead, the ARROW study, which included over 600 subjects split between twice-daily and once-daily dosing, is considered pivotal efficacy and safety information to support the approval of once-daily ABC+3TC and a change in dosing for twice-daily ABC+3TC to the WHO recommended dosing (i.e., the dosing utilized in ARROW).

Intensive PK substudy part 1 was conducted in 41 subjects in the ARROW study *Randomization 3* for once-daily dosing of ABC + 3TC versus twice-daily dosing after at least 36 weeks on antiretroviral treatment. The treatments include a control arm and two induction-maintenance arms for first line ART as shown in Table 1.

Population PK analyses for abacavir and lamivudine PK in children were conducted using data from two PK substudies in the ARROW study *Randomization 3* and four other clinical PK studies. Abacavir and lamivudine PK parameters (AUC, C_{max}, C_{trough}) were estimated with the developed models and simulations.

The ABC + 3TC dosing regimens were based on World Health Organization recommended weight bands as shown in Table 2. The total daily dose between the once-daily and twice-daily regimens was the same.

Table 1: Antiretroviral Treatment in the ARROW Study

Treatment Arm	Dosing regimen
Arm A (standard)	NNRTI + ABC + 3TC
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)

Table 2: Once- and Twice-Daily Pediatric Abacavir Dosage Regimens by WHO-Recommended Weight-Band Approach (2010) (Lamivudine Dosage Regimen is Half the Listed Total Dose in all Cells)

≥3 months of age	Dosing Regimen			
	Oral Solution: 8 mg/kg twice daily (maximum 300 mg twice daily) or 16 mg/kg once daily (maximum 600 mg once daily)			
Weight Range	**Scored Tablet – Twice or Once Daily**			
	Once-Daily Dosing	**Twice-Daily Dosing**		**Total Daily Dose**
		AM Dose	**PM Dose**	
14 to <20 kg	1 tablet (300 mg)	0.5 tablet (150 mg)	0.5 tablet (150 mg)	300 mg
≥20 to <25 kg	1.5 tablets (450 mg)	0.5 tablet (150 mg)	1 tablet (300 mg)	450 mg
≥25 kg	2 tablets (600 mg)	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Predicted lamivudine and abacavir AUC after once-daily and twice-daily dosing of ABC + 3TC are summarized in Table 3 and Table 4, respectively. The two dosing regimens demonstrated similar AUC values in children across all weight bands between once daily and twice-daily dosing. Of note, lower overall lamivudine exposures were observed regardless of regimen in pediatrics <14 kg compared to other pediatric weight bands. These lower exposure is hypothesized to be due to lower bioavailability of the lamivudine solution and is discussed in more detail in Section 4 of this review. As an additional comparison, previously reported AUCs for the approved doses in adults are also shown in the tables. Both the predicted AUC of both lamivudine and abacavir exceed those in adults after administration of the approved QD and BID doses. The pediatric AUC exposures in all weight bands for both QD and BID regimens are higher than that observed previously in adults with the exception of lamivudine QD or BID in pediatrics <14 kg. In this category, the lamivudine exposures were slightly lower (5-15%) lower than adults. While higher pediatrics exposures were observed compared to adults, the pediatrics exposures observed from the QD and BID regimens are considered acceptable as: 1) twice-daily dosing regimen evaluated in ARROW is similar to the already approved regimens (see Question 1.4) which have acceptable exposures, and 2) as the efficacy and safety information (see Question 1.2 and 1.3) are considered pivotal in this submission.

The C_{max} of once-daily dosing for both drugs was higher than twice-daily dosing, while C_{trough} of both drugs are lower in once-daily dosing. These are expected PK changes for a comparison of once-daily dosing versus twice-daily dosing. The increased C_{max} is not anticipated to be related with any safety concerns, which will be discussed below, and a lower C_{trough} is not believed to be clinically relevant based on efficacy data in adults and from the current study.

Table 3: **Predicted PK Parameters of Lamivudine in HIV-1-Infected Children on Once and Twice Daily Regimens of Oral Solution (Children < 14 kg) or Scored Tablets (Children ≥ 14 kg) Based on World Health Organization Recommended Total Daily Dosages and Weight Bands**

Lamivudine Parameter Median (90% CI)	**Once-daily**			**Twice-daily**		
	AUC_{0-24} (µg.h/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{0-24} (µg.h/mL)	C_{max} (µg/mL)	C_{trough} (µg/mL)
<14 kg	7.9 (4.5-14.6)	1.8 (0.9-3.4)	0.05 (0.02-0.13)	7.4 (4.1-13.8)	0.94 (0.49-1.75)	0.07 (0.02-0.23)
14 to < 20 kg	11.6 (6.3-21.9)	2.8 (1.4-5.4)	0.05 (0.02-0.14)	11.1 (5.9-20.9)	1.45 (0.75-2.74)	0.07 (0.02-0.32)
20 to < 25 kg	13.8 (7.3-26.2)	3.4 (1.7-6.4)	0.05 (0.02-0.14)	12.8 (7.2-22.3)	2.27 (1.14-4.31)	0.08 (0.02-0.44)
≥25 kg	13.6 (7.0-26.5)	3.4 (1.6-6.7)	0.05 (0.02-0.14))	13.1 (7.0-26.5)	1.76 (0.88-3.43)	0.07 (0.02-0.36)
Obs. Adult 300 mg total daily dose*	8.4 (7.0-11.7)	2.0 (1.3-3.0)	0.041 (0.025-0.067)	9.0 (7.3-12.4)	1.2 (0.9-1.7)	0.09 (0.06-0.14)

*historical adult data: EPV10001 (n=61 QD and n=61 BID)

Source: adapted from Table 16 on page 79 of sponsor's population PK report for lamivudine (2013n181170)

Table 4: **Predicted PK Parameters of Abacavir in HIV-1-Infected Children on Once and Twice Daily Regimens of Oral Solution (Children < 14 kg) or Scored Tablets (Children ≥ 14 kg) Based on World Health Organization Recommended Total Daily Dosages and Weight Bands**

Abacavir Predicted Parameter Median (90% CI)	**Once-daily**			**Twice-daily**		
	AUC_{0-24} (μg.h/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)	AUC_{0-24} (μg.h/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)
<14 kg (Oral solution)	13.8 (5.3-34.2)	5.0 (2.1-11.3)	0.03 (0.001-0.22)	13.2 (5.0-32.1)	2.6 (1.1-5.8)	0.05 (0.01-0.33)
14 to < 20 kg	16.9 (6.3-42.1)	6.6 (2.8-14.8)	0.021 (NQ-0.18)	16.4 (6.3-40.4)	3.3 (1.4-7.6)	0.04 (0.01-0.29)
20 to < 25 kg	19.9 (7.5-49.9)	7.9 (3.3-17.9)	0.02 (NQ-0.17)	19.3 (7.6-45.4)	5.4 (2.3-12.0)	0.03 (0.003-0.22)
≥25 kg	19.3 (7.1-50.4)	7.9 (3.2-18.5)	0.01 (NQ-0.13)	18.7 (6.8-47.6	4.0 (1.6-9.4)	0.03 (0.003-0.23)
Obs. Adult 600 mg total daily dose*	9.3 (4.6-14.8)	4.3 (2.1-6.0)	NQ (NQ-0.03)	8.1 (4.0-15.0)	1.8 (1.1-3.4)	0.02 (NQ-0.05)

*historical adult data: EPV10001 (n=61 QD and n=61 BID)

Source: adapted from Table 17 on page 72 of sponsor's population PK report for abacavir (2013n181066)

1.1.2 Do the Applicant's efficacy results support the proposed once-daily dosing of abacavir and lamivudine in children?

Yes, the once-daily dosing of ABC+3TC as part of antiretroviral therapy in children appeared similar to twice-daily dosing as evidenced by viral load suppression data in the ARROW study. Due to the similarities in the overall response rates for once-daily and twice-daily dosing and as it is unknown which lamivudine and abacavir PK parameter is determinant of efficacy, exposure-response analyses for efficacy were not conducted for this submission. A brief summary of the Applicant's efficacy results are provided below:

The sponsor submitted efficacy data from the pivotal ARROW study *Randomization 3* which compared the ability to maintain viral suppression between once-daily and twice

daily dosing of ABC+3TC. Following at least 36 weeks of treatment with ABC+3TC twice daily (plus other therapeutics), patients were randomized to either continue with ABC+3TC twice daily or to switch to the ABC+3TC once daily regimen (same total daily dose of twice-daily). The primary efficacy endpoint was viral load suppression of < 80 copies/mL at 48 weeks following the randomization. The non-inferiority martin was set at 12%. The proportion of subjects with viral loads < 80 copies/mL were found similar at Week 48 and Week 96 after randomization to once-versus twice-daily ABC+3TC (Table 5).

Table 5: **Number of Percentage of Subjects with viral load < 80 copies/mL at Randomization to Once- and Twice-Daily Dosing (week 0) and After 48 and 96 weeks of Once-and Twice-Daily Dosing of Abacavir and Lamivudine (Missing Data Points Excluded)**

Time Point Viral Load (Copies/mL)	Twice-Daily Dosing n (%)	Once-Daily Dosing n (%)	Total n (%)
Week 0[a]	331 (100)	335 (100)	666 (100)
<80	250 (76)	237 (71)	487 (73)
≥80	81 (24)	98 (29)	179 (27)
Risk difference (95% CI)	-4.8% (-11.5 – 1.9)		
Week 48[b]	331 (100)	330 (100)	661 (100)
<80	242 (73)	236 (72)	478 (72)
≥80	89 (27)	94 (28)	183 (28)
Risk difference (95% CI)	-1.6% (-8.4 – 5.2)		
Week 96[c]	326 (100)	331 (100)	657 (100)
<80	234 (72)	230 (69)	464 (71)
≥80	92 (28)	101 (31)	193 (29)
Risk difference (95% CI)	-2.3% (-9.3 – 4.7)		

Source: Table 12 on page 41 of sponsor's clinical overview report

1.1.3 Do the Applicant's safety results support the proposed once-daily dosing of abacavir and lamivudine in children?

Yes, the Applicant's analysis from the ARROW Study *Randomization 3* showed a similar safety profile based on AE rates in patients who received once-daily versus twice-daily dosing. While there was concern that increased C_{max} (1.6- to 2-fold) associated with once-daily dosing may impact safety, the increase in C_{max} did not appear to impact the incidence of all grade 3 and 4 AEs and SAEs between once- or twice-daily ABC+3TC. The proportions of subjects reporting Grade 3 and 4 AEs were similar in the twice-daily versus once-daily treatment groups (16.2% versus 17.0% of patients). The proportions of subjects with SAEs were also similar between the once-daily (9% of patients) and twice-daily ABC+3TC (11% of patients) treatment groups. There were numerically fewer deaths in the once-daily arm compared to twice-daily (4 versus 1), and none of the deaths were considered relating to ABC+ 3TC treatment. Finally, no subject discontinued study treatment because of AE and in either the once- or twice-daily group, no subjects in

Randomization 3 of the ARROW study experienced gastrointestinal clinical or laboratory grade 3 or 4 AEs leading to ART modification. Due to the similarities in the overall safety profiles for once-daily and twice-daily dosing, exposure-response analyses for safety were not conducted for this submission.

1.1.4 Is the dosing regimen based on WHO weight bands acceptable?

Yes, the predicted exposure of lamivudine and abacavir according to WHO weigh bands will produce similar or higher exposure than dosing according to current weight bands.

In the ARROW Study, drugs were provided as liquids, tablets and scored tablets and dosed according to WHO weight band tables. There are four weight bands in the dosing from both groups; however, the major difference between the FDA approved dosing and that recommended by WHO are in pediatrics with body weights of 20-21 kg, and 25-30 kg. Subjects weighing 25-30 kg would receive the adult dose with WHO dosing and 75% of the adult dose with the current FDA labeled dosing. Also, subjects weighting 20-21 kg will received 75% of the adult dose with WHO dosing while such subjects would receive 50% of the adult dose with the FDA labeled dose. As such, these two groups represent the only subjects who would have different exposures if the current labeled doses were changed to reflect WHO recommend dosing (and the dosing that was evaluated in ARROW).

The predicted AUC data of lamivudine according to current weight bands and the WHO weight bands are summarized in Table 6 and Table 7, respectively. For subjects weighing < 20 kg, 21 to 25 kg, and subjects ≥30 kg the exposure based on the two weight bands are the same as indicated by identical daily dose (mg/kg) and AUC values. For subjects in weight bands of 20-21 kg, and 25-30 kg, daily doses according to WHO bands will be higher than current weight bands and is projected to produce higher exposure for lamivudine and abacavir.

The increased exposure resulting from the WHO dosing regimen is considered acceptable as 1) the resulting AUC exposures while slightly higher overlap substantially with the exposure in other pediatric groups; and; 2) the safety and efficacy data from ARROW, which utilized WHO dosing, and was found acceptable, is considered pivotal for this submission. Therefore, a change of dosing according to current approved label to WHO recommended approach is acceptable.

Table 6: **Predicted Lamivudine AUC_{0-24} after Once-daily and Twice-daily Dosing of ABC + 3TC by Weight Band**

AUC_{0-24} (µg.h/mL) Mean(90% CI)							
Current Weight Bands				**WHO Weight Bands**			
Weight	**Pred. Once Daily**	**Pred. Twice Daily**	**Daily Dose (mg/kg)***	Weight	**Pred. Once Daily**	**Pred. Twice Daily**	**Daily Dose (mg/kg)***
<14 kg (Oral solution)	**7.9** (4.5-14.6)	**7.4** (4.1-13.8)	8.5 (7.8-9.3)	**<14 kg**	**7.9** (4.5-14.6)	**7.4** (4.1-13.8)	8.5 (7.8-9.3)
14 to 21 kg	**11.3** (6.1-21.6)	**10.8** (5.8-20.3)	8.7 (7.2-10.6)	**14 to < 20 kg**	**11.6** (6.3-21.9)	**11.1** (5.9-20.9)	9.0 (7.6-10.6)
>21 to < 30 kg	**12.8** (6.8-24.2)	**11.8** (6.6-20.9)	9 (7.8-10.7)	**20 to < 25 kg**	**13.8** (7.3-26.2)	**12.8** (7.2-22.3)	10.1 (9.0-11.2)
≥30 kg	**12.6** (6.7-24.3)	**12.1** (6.3-23.2)	8.4 (5.6-9.9)	**≥25 kg**	**13.6** (7.0-26.5)	**13.1** (6.7-25.4)	9.3 (5.6-11.8)

*Daily dose: median (range)

Table 7: **Predicted Abacavir AUC_{0-24} in Children after Once-daily and Twice-daily Dosing of ABC + 3TC by Weight Band**

AUC_{0-24} (µg.h/mL) Mean(90% CI)							
Current FDA Labeled Dosing				**WHO Dosing**			
Weight	**Pred. Once Daily**	**Pred. Twice Daily**	**Daily Dose (mg/kg)***	Weight	**Pred. Once Daily**	**Pred. Twice Daily**	**Daily Dose (mg/kg)***
<14 kg (Oral solution)	**13.8** (5.3-34.1)	**13.2** (5.1-32.1)	16.4 (15.8-17.3)	**<14 kg**	**13.8** (5.3-34.2)	**13.2** (5.0-32.1)	16.4 (15.8-17.3)
14 to 21 kg	**16.4** (6.2-41.8)	**15.9** (6.0-39.6)	17.5 (14.4-21.2)	**14 to < 20 kg**	**16.9** (6.3-42.1)	**16.4** (6.3-40.4)	17.9 (15.3-21.2)
>21 to < 30 kg	**18.1** (6.8-46.3)	**17.6** (6.9-41.9)	18.0 (15.5-21.3)	**20 to < 25 kg**	**19.9** (7.5-49.9)	**19.3** (7.6-45.4)	20.3 (18.0-22.5)
≥30 kg	**17.7** (6.6-45.5)	**17.2** (6.4-42.9)	16.7 (11.1-19.8)	**≥25 kg**	**19.3** (7.1-50.4)	**18.7** (6.8-47.6	18.5 (11.1-23.7)

*Daily dose: median (range)

1.2 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application from a clinical pharmacology perspective and recommends approval of once-daily dosing of abacavir and lamivudine for the treatment of children with HIV-1 infection in combination with other antiretroviral agents. The reviewer agrees with the sponsor's conclusions from the population PK analyses and simulations that once-daily dosing of ABC + 3TC would achieve similar exposure (AUC) as twice-daily dosing of ABC+3TC. Finally, given the pivotal efficacy study conducted with the WHO dosing regimen, the minor impact on exposures between FDA approved and WHO dosing regimens and currently approved dosing, and in the interest of harmonizing dosing recommendations, the reviewer recommends adopting the WHO dosing regimen for both once-daily and twice-daily dosing.

1.3 Label Statements

Please refer to the accompanying sections of the QBR

2 PERTINENT REGULATORY BACKGROUND

Abacavir sulfate (ABC; ZIAGEN®) and lamivudine (3TC, EPIVIR®) twice-daily have been approved for the treatment of HIV in adults and children. The once-daily dosing of abacavir and lamivudine has approved for use in adults but not in children. The current application is to seek approval of extending the once-daily oral administration of ABC and 3TC to HIV-1 infected pediatric patients aged 3 months and older, according to amended weight-band ranges.

The sponsor submitted safety, pharmacokinetic and efficacy data to support harmonization of the U.S. dosing weight bands with the World Health Organization (WHO) Treatment Guidelines for dosing of abacavir and lamivudine scored tablet in subjects ≥ 14 kg.

Supporting data in this submission consists of data on abacavir (with or without lamivudine) and lamivudine, including two PK substudies. The primary study is an open-label study ARROW (AntiRetroviral Research for Watoto), *a randomized trial of monitoring practice and induction maintenance drug regimens in the management of antiretroviral therapy in children with HIV infection in Africa; Once Daily versus Twice Daily Abacavir + Lamivudine*. The main safety and efficacy information supporting once-daily administration of abacavir and lamivudine comes from ARROW *Randomization 3*. In *the randomization,* 669 subjects were randomized once they had completed at least 36 weeks of twice-daily ABC+3TC dosing in the main study. The subjects were then followed for at least 96 weeks for viral load, CD4 cell counts, disease progressions, safety outcomes, and adherence.

Population PK studies for abacavir and lamivudine, respectively, were conducted utilizing data from six pediatric studies/substudies. Based on the final models, simulations were conducted to project exposure of once-daily exposure to support the proposed once-daily dosing regimen in children.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK for Abacavir

Objectives: 1) To develop a population PK model that characterizes the PK disposition of abacavir following oral administration to HIV-1 infected pediatric patients; 2) To evaluate the potential effect of selected subject covariates on key pharmacokinetic parameters of interest; 3) To use the final population PK model to simulate abacavir exposures and inform once daily dosing regimen in children of at least 3 months of age.

Data: Data from six clinical trials of abacavir in pediatric HIV-infected patients were included in the population PK analysis. ARROW (COL105677) PK Substudy Part 1, PENTA-13 (EPV40002), and PENTA-15(COL104929) compared abacavir PK once daily and twice daily dose regimens in children aged 3-12 years, 2-12 years, and 3-36 months, respectively, in combination with other antiretroviral therapy. ARROW PK Substudy Part 2 investigated the bioavailability of abacavir scored tablets relative to oral solution (in combination with lamivudine and zidovudine) in HIV-infected children weighing 12-15 kg. CNAA1013 (ACTG330) and CNAA1001 both investigated PK and safety of abacavir at oral solution doses of 4 mg/kg or 8 mg/kg twice daily in HIV-infected children aged 3 months to 12 or 13 years. Summary of demographic characteristics and dose by study and overall is demonstrated in Table 8.

Table 8: **Summary of Demographic Characteristics and Dose by Study and Overall**

Covariate	Summary Statistic[a] or Category	ARROW PK Substudy Part 1 (N=41)	PENTA-15 (N=18)	PENTA-13 (N=14)	CNAA1001 (N=22)	CNAA1013 (N=46)	ARROW PK Substudy Part 2 (N=28)[b]	Overall (6 studies) (N=169)
Age (y)	Median (range)	7.65 (3.58-12.6)	2 .0 (0.42-2.92)	5.13 (2.08-12.8)	2.41 (0.45-13.6)	6.0 (0.58-12.0)	2.82 (1.58-4.07)	4.08 (0.42-13.6)
Weight (kg)	Median (range)	20 (14-30)	11.75 (7.4-16.1)	19.2 (13.7-61.3)	11.9 (4.6-47.3)	20.7 (6.5-39.7)	12.3 (12-14)	15.9 (4.6-61.3)
Height (cm)	Median (range)	117 (93.6-142)	83.3 (65.0-98.0)	107.25 (88.5-164)	84.0 (54.0-146)	114 (65.0-151)	85.4 (71.8-95.2)	100 (54.0-164)
Sex	Female [N (%)]	24 (59%)	8 (44%)	8 (57%)	7 (32%)	22 (48%)	18 (64%)	87 (51%)
	Male [N (%)]	17 (41%)	10 (56%)	6 (43%)	15 (68%)	24 (52%)	10 (36%)	82 (49%)
Formulation	Solution [N (%)]	0 (0%)	18 (100%)	13 (87%)	22 (100%)	46 (100%)	28 (100%)	127 (75%)[b]
	Tablet [N (%)]	41 (100%)	0 (0%)	2 (13%)	0 (0%)	0 (0%)	28 (100%)	71 (42%)[b]
Daily Dose (mg)	Median (range)	300 (300-600)	190 (120-240)	320 (220-600)	156 (36-756)	220 (50-600)	270 (200-300)	300 (36-756)
Daily Dose (mg/kg)	Median (range)	20.0 (12.0-30.0)	16.0 (14.0-18.6)	16.4 (9.8-17.6)	8.2 (6.8-16.4)	15.4 (7.2-17.8)	20.7 (15.8-25.0)	16.2 (6.8-30.0)

Ethnicity/race not included in the dataset because this information was not collected in PENTA-13 and the majority (approximately 85%) of subjects in the other studies were Black.

a. For continuous variables, median (range) calculated across all treatments within each study (e.g. QD and BID, solution and tablets, multiple dose levels)

b. Subjects in ARROW Substudy Part 2 received both solution and tablet formulations hence sum of proportion of subjects receiving each formulation is >100%.

Source: Table 8 on page 33 of sponsor's population PK report for abacavir

Methods: Population PK model was developed using NONMEM software version 7.1.2 (ICON Development Solutions). The analyses were performed in a series of steps. First, model building was completed using data from 3 studies, including ARROW PK Substudy Part 1, PENTA-13, and PENTA-15, to confirm consistency of the structural model and covariate effects with a previously published pediatric population PK model. The 3-study model was used to predict abacavir PK parameters in HIV-infected subjects from ARROW PK Substudy Part 2, CNAA1001, and CNAA1003. Based on the results of

the external validation, a meta-analysis of all available pediatric data (6 studies) was conducted to re-estimate model parameters retaining the model structure obtained in the 3-study model. Following model refinement and performance evaluation, the final 6-study model was used to simulate different dosing scenarios of once daily versus twice daily oral administration of abacavir to children ages 3 months to 12 years.

Population PK Results

The pharmacokinetics of abacavir following oral administration were well-described by a 2-compartment model with first order absorption and elimination. Body weight had a significant effect on CL/F and V2/F with an exponential relationship fixed to the values obtained in the 3-study model. The final population PK parameter estimates are summarized in Table 9. The goodness of fits plots are shown in Figure 1. The visual predictive check of the final model is shown in Figure 2.

Table 9: **Final Population PK Parameter Estimates for Abacavir from the 6-Study Model**

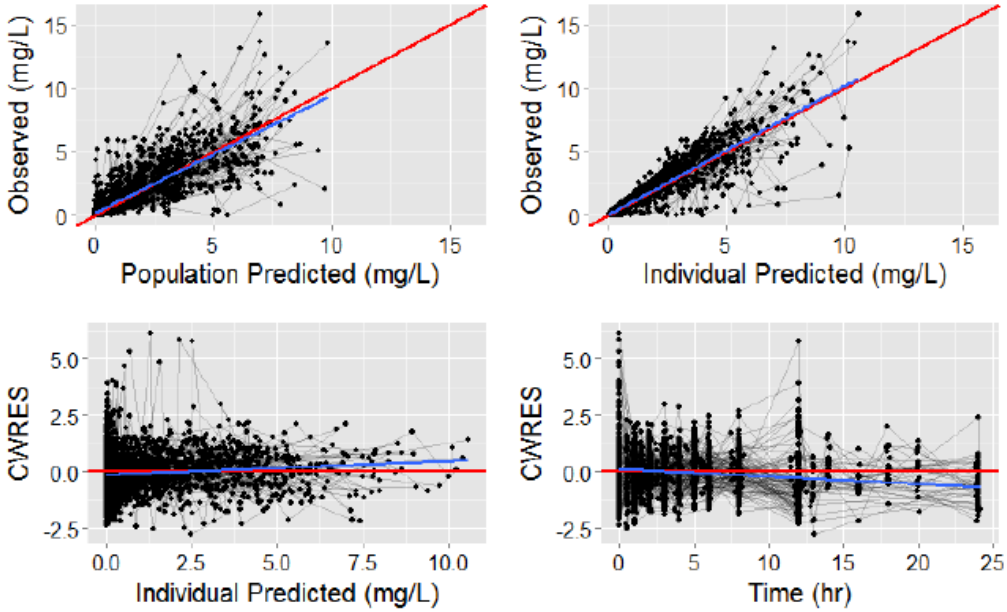
Parameter (unit)[a]	Notation	Population Estimate	RSE (%)	Bootstrap Mean (95% CI)
Absorption rate constant, Ka (1/h)	Θ1	0.85	2.31	0.85 (0.80-0.90)
Intercompartmental clearance, Q (L/h)	Θ2	1.69	7.87	1.69 (1.40-1.98)
Apparent central volume of distribution, V2/F (L) = Θ3*(WT/15.6)^ Θ7	Θ3	10.1	7.5	10.2 (8.5-11.7)
	Θ7	0.698 FIX		
Apparent peripheral compartment volume of distribution, V3/F (L)	Θ4	23.0	17.4	23.1 (14.7-31.3)
Apparent systemic clearance, CL/F (L/h) = Θ5x (WT/15.6)^θ6	Θ5	16.3	3.62	16.3 (15.1-17.5)
	Θ6	0.794 FIX		
Relative bioavailability, F1				
F1 tablet ARROW PK Substudy Part 2	Θ8	1.62	8.02	1.64 (1.36-1.88)
F1 solution ARROW PK Substudy Part 2	Θ9	1.75	8.23	1.75 (1.46-2.04)
Inter-individual variability		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
ηQ/F variance	Ω1	0.461 (67.9%)[b]	18.5	0.440 (0.229-0.694)
ηV2/F variance	Ω2	0.269 (51.9%)[b]	25.7	0.273 (0.110-0.429)
ηV3/F variance	Ω3	0.845 (91.9%)[b]	32.2	0.830 (0.261-1.43)
ηCL/F variance	Ω4	0.132 (36.3%)[b]	24.8	0.132 (0.067-0.198)
Inter-occasion variability		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
OCCCL	Ω5	0.085 (29.2%)[b]	24.9	0.085 (0.04-0.131)
Residual error		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
Proportional error (mg/L)	σ1	0.141 (37.5%)	7.3	0.141 (0.122-0.161)

Abbreviations: CI = confidence interval; CV = coefficient of variation, RSE = percent relative standard error, WT = body weight, Θ = PK parameter estimation; η = inter-individual variability; Ω, = inter-individual or inter-occasion variability in population PK parameter;σ= population variance

a. Population parameter point-estimates for the full two compartment model and 95% CI and %CV from a non-parametric bootstrap are presented
b. Value in parentheses represents either the inter-individual or inter-occasion variability of the PK parameters calculated as the square root of Ω x 100%

Source: Table 10 on page 43 of sponsor's population PK report for abacavir

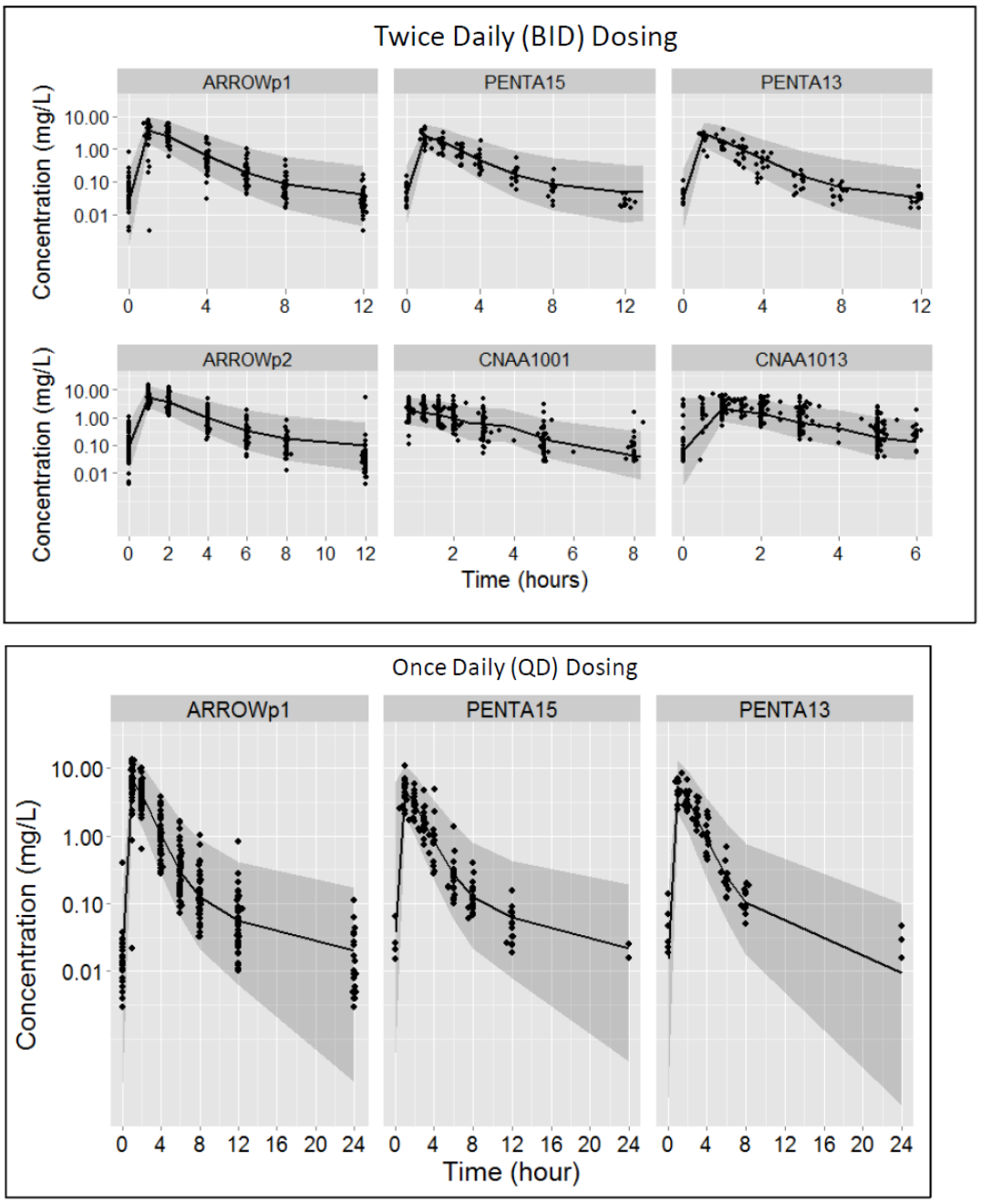
Figure 1: **Goodness-of-Fit Plots: Final Model (Final 6-Study Model)**



CWRES=Conditional weighted residuals

Source: Figure 32 on page 115 of sponsor's population PK report for abacavir

Figure 2: Visual Predictive Check (VPC) of the Final Abacavir Population PK Model (Final 6-Study Model)



Source: Figure 41 on page 128-129 of sponsor's population PK report for abacavir

Simulation Results

Simulations were based on oral solution and scored tablets dosages for the weight bands listed in the current ZIAGEN product label and in the World Health Organization (WHO)

2010 pediatric dosing recommendations. The simulation results using the final model are summarized in Table 10.

Table 10: **Predicted Abacavir AUC(0-24) in HIV-infected Children on Once and Twice Daily Regimens of Oral Solution (Children < 14 kg) or Scored Tablets (Children ≥ 14 kg) Dosed According to Weight Bands in the Current ZIAGEN Label or WHO 2010 Recommendations**

Simulation Based on Current Approved Weight Bands	Daily Dose (mg/kg)	AUC(0-24) (μg.h/mL)	
		Once Daily	Twice Daily
Overall	16.5 (11.1-21.3)	15.5 (5.79-40.2)	15.0 (5.61-37.7)
<14 kg	16.4 (15.8-17.3)	13.8 (5.29-34.2)	13.2 (5.07-32.1)
14 to 21 kg	17.5 (14.4-21.2)	16.4 (6.22-41.8)	15.9 (6.00-39.6)
>21 to <30 kg	18.0 (15.5-21.3)	18.1 (6.78-46.3)	17.6 (6.94-41.9)
≥30 kg	16.7 (11.1-19.8)	17.7 (6.58-45.5)	17.2 (6.40-42.9)
Simulation Based on WHO 2010 Recommendations	**Daily Dose (mg/kg)**	**AUC(0-24) (μg.h/mL)**	
		Once Daily	**Twice Daily**
Overall	16.7 (11.1-23.7)	16.1 (5.91-42.5)	15.6 (5.71-40.0)
<14 kg	16.4 (15.8-17.3)	13.8 (5.30-34.2)	13.2 (5.04-32.1)
14 to <20 kg	17.9 (15.3-21.2)	16.9 (6.32-42.1)	16.4 (6.30-40.4)
20 to <25 kg	20.3 (18.0-22.5)	19.9 (7.50-49.9)	19.3 (7.56-45.4)
≥25 kg	18.5 (11.1-23.7)	19.3 (7.07-50.4)	18.7 (6.83-47.6)
Observed Adult Data	**Daily Dose (mg/kg)**	**AUC(0-24) (μg.h/mL)**	
		Once Daily	**Twice Daily**
Study CAL102120	600mg	9.25 (4.56, 14.82)	8.06 (3.95, 15.04)
Study CNAA2001	600mg	—	11.66 (7.04, 18.01)

Dose presented as median (range). AUC(0-24) presented as median (90% CI).
Pediatric values represent results of 1000 trial replicates of 180 subjects per trial.

Source: Summary on page 14 of sponsor's population PK report for abacavir

3.2 Population PK for Lamivudine

Objectives: 1) To develop a population PK models that characterizes the PK disposition of lamivudine following oral administration to HIV-infected pediatric patients; 2) To evaluate the potential effect of selected subject covariates on key PK parameters of interest;3) To use the final population PK model to simulate lamivudine exposures and inform once daily dosing regimens in children of at least 3 months of age.

Data: PK data from six clinical studies of lamivudine in pediatric HIV-infected patients were included in this population PK analysis. ARROW (COL105677) PK Substudy Part 1, PENTA-13(EPA40002), and PENTA-15(COL104929) compared lamivudine PK once daily and twice daily dose regimens in children aged 3-12 years, 2-12 years, and 3-36 months, respectively, in combination with other antiretroviral therapy. ARROW PK Substudy Part 2 investigated the bioavailability of lamivudine scored tablets relative to oral solution (in combination with abacavir and zidovudine) in HIV-infected children weighing 12 to 15 kg. NUCA2002 evaluated the pharmacokinetics of intravenous and oral lamivudine (0.5 to 10 mg/kg BID) in HIV-infected children 3 months to 12 years of age, and NUCA2005 evaluated the pharmacokinetics of oral lamivudine at a dose of 4 mg/kg BID in combination with zidovudine and/or didanosine in HIV-infected children that were 2 to 19 years old. The demographics of the population data are summarized in Table 11.

Table 11: Summary of Demographic Characteristics and Dose by Study and Overall

Covariate	Summary Statistic[a] or Category	ARROW PK Substudy Part 1 (N=41)	PENTA-15 (N=17)	PENTA-13 (N=19)	NUCA2002[b] (oral) (N= 64)	NUCA2002 (iv) (N= 59)	NUCA2005 (N=40)	ARROW PK Substudy Part 2 (N=28)[b]	Overall, 6 studies (Oral dosing) (N=209)
Age (y)	Median (range)	7.66 (3.58-12.6)	2.0 (0.42-2.92)	5.83 (2.08-12.8)	7.33 (0.33-17.4)	7.42 (0.33-17.4)	9.42 (2.50-19.2)	2.84 (1.58-4.07)	5.97 (0.33-19.2)
Weight (kg)	Median (range)	20.0 (14.0-30.0)	11.5 (7.4-16.1)	22.2 (12.5-61.3)	20.7 (5.1-66.1)	19.8 (5.1-65.7)	23.5 (12.0-66.4)	12.3 (12.0-14.0)	18.3 (5.1-66.4)
Height (cm)	Median (range)	117 (93.6-142)	81.0 (65.0-98.0)	117 (88.5-164)	117 (61.0-181)	117 (61.0-181)	128 (89.6-177)	85.5 (71.8-95.2)	108 (61.0-181)
Creatinine Clearance (mL/min)	Median (range)	91.1 (40.8-145)	32.6 (14.0-51.6)	59.3 (28.8-160)	60.6 (9.28-205)	60.6 (9.28-205)	82.2 (29.7-181)	60.3 (39.3-85.4)	66.1 (9.28-205)
Sex	Female [N (%)]	24 (59)	7 (41)	10 (53)	27 (42)	26 (44)	16 (40)	18 (64)	102 (49)
	Male [N (%)]	17 (41)	10 (59)	9 (47)	37 (58)	33 (56)	24 (60)	10 (46)	107 (51)
Formulation	Solution [N (%)]	0 (0)	17 (100)	14 (74)	36 (57)	59 (100)	29 (72.5)	28 (100)	124 (59)[d]
	Solid[c] [N (%)]	41 (100)	0 (0)	5 (26)	27 (42)	NA	11 (27.5)	28(100)	112 (54)[d]
Daily Dose (mg)	Median (range)	150 (150-300)	90 (60.0-120)	190 (90.0-300)	156 (10.0-1100)	136 (15.2-1100)	188 (68.0-400)	150 (100-300)	150 (10.0-1100)
Daily Dose (mg/kg)	Median (range)	10.0 (7.3-15.0)	8.0 (7.0-9.3)	8.2 (4.9-9.8)	7.8 (1.0-21.8)	7.6 (1.0-21.0)	8.0 (3.8-8.8)	10.8 (8.0-24.0)	8.2 (1.0-24.0)

a. For continuous variables, median (range) calculated across all treatments within each study (e.g. QD and BID, solution and tablets, multiple dose levels)
b. NUCA2002: No oral formulation record for one subject hence sum of solution and tablet formulation is 63 instead of 64
c. Solid formulation refers to both scored tablet and investigational capsule formulations.
d. Subjects in ARROW PK Substudy Part 2 received both solution and tablet formulations; therefore, sum of proportion of subjects receiving each formulation is >100%..

Source: Table 8 on page 34 of sponsor's population PK report for lamivudine

Methods: Population PK model of lamivudine was developed using NONMEM software version 7.1.2 (ICON Development Solutions). The analyses were performed in a series of steps. First, model building was completed using data from 3 orally dosed studies, including ARROW PK Substudy Part 1, PENTA-13, and PENTA-15, to confirm consistency of the structural model and covariates effects with a previously published pediatric population PK model. The 3-study model was used to predict oral lamivudine PK parameters in HIV-infected subjects from ARROW PK Substudy Part 2, NUCA2002, and NUCA2005.

Based on the results of the external validation, a meta-analysis of all available pediatric data (6 studies) was conducted to re-estimate model parameters retaining the model structure obtained in the 3-study model. Following model refinement and performance evaluation, the final 6-study model was used to simulate different dosing scenarios of once daily versus twice daily oral administration of lamivudine to children ages 3 months to 12 years.

Population PK Results

The pharmacokinetics of abacavir following oral and intravenous administration were well-described by a 1-compartment model with first order elimination. Oral absorption was characterized by a first order absorption rate constant (Ka) with a lag time (ALAG1) and absolute bioavailability parameter (F1) estimates for oral solution and solid (tablet and capsule) formulations.

Body weight had a significant exponential relationship effect on the clearance (CL) and the volume of distribution (V). The final population PK parameter estimates of lamivudine are summarized in Table 12. The goodness of fits plots are shown in Figure 3. The visual predictive check of the final model is shown in Figure 4.

Table 12: Final Population PK Parameter Estimates of Lamivudine

Parameter (unit)[a]	Notation	Population Estimate	RSE (%)	Bootstrap Mean (95% CI)
Absorption rate constant, Ka (1/h)	Θ3	2.08	9.76	2.12 (1.57-2.59)
Lag time ALAG2 (h)	Θ4	0.297	12.1	0.299 (0.218-0.376)
Central compartment volume of distribution, V (L) = Θ2*(WT/18.5)^ Θ7	Θ2	23.1	4.68	23.2 (20.99-25.21)
	Θ7	0.677	8.98	0.68 (0.555-0.799)
Systemic clearance, CL (L/h) = Θ1 * (WT/18.5)^θ6	Θ1	9.16	4.49	9.17 (8.37-9.95)
	Θ6	0.758	7.07	0.758 (0.652-0.864)
Absolute bioavailability (F1) solution	Θ8	0.496	5.36	0.498 (0.445-0.547)
Absolute bioavailability (F1) tablet	Θ9	0.609	5.35	0.612 (0.544-0.674)
Inter-individual variability		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
ηCL variance	Ω1	0.082 (28.6%) [b]	20.2	0.081 (0.049-0.115)
ηV variance	Ω2	0.107 (32.7%) [b]	17.6	0.104 (0.071-0.143)
ηKa variance	Ω3	0.585 (76.5%) [b]	23.6	0.613 (0.265-0.907)
Inter-occasion variability		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
OCCCL	Ω4-6	0.062 (24.9%) [b]	14.9	0.062 (0.044-0.079)
OCCKA	Ω7-9	0.360 (60%) [b]	26.9	0.360 (0.129-0.591)
OCCV	Ω10-12	0.039 (19.7%) [b]	23.5	0.040 (0.021-0.056)
Residual error		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
Additive error (mg/L)	σ1	0.003	9.17	0.003 (0.002-0.004)
Weighting factor for residual error	Θ5	4.72	7.22	4.68 (4.06-5.38)

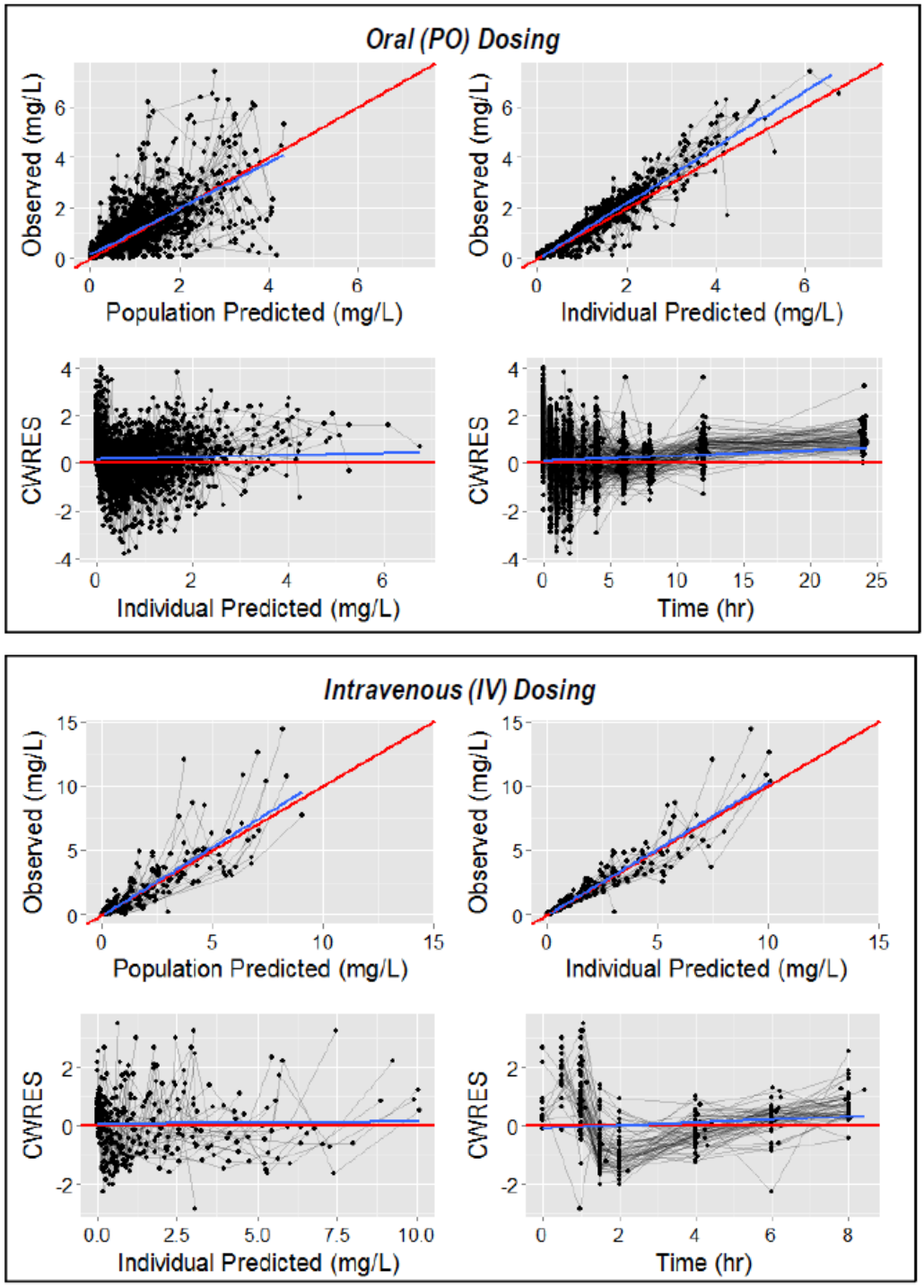
Abbreviations: CI = confidence interval; CV = coefficient of variation, RSE = percent relative standard error, WT = body weight, Θ = PK parameter estimation; η = inter-individual variability; Ω, = inter-individual or inter-occasion variability in population PK parameter; σ= population variance

a. Population parameter point-estimates for the full one compartment model and 95% CI and %CV from a non-parametric bootstrap are presented

b. Value in parentheses represents either the inter-individual or inter-occasion variability of the PK parameters calculated as the square root of Ω x 100%

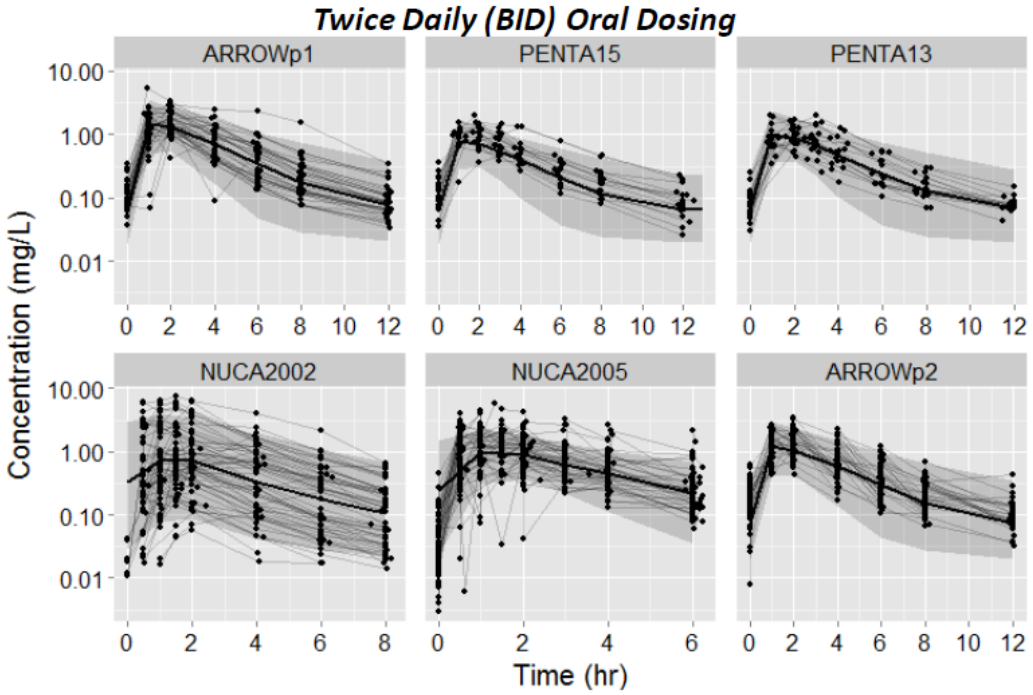
Source: Summary on page 13 of sponsor's population PK report for lamivudine

Figure 3: **Goodness-of-Fit Plots for Final Model (6-Study Model)**

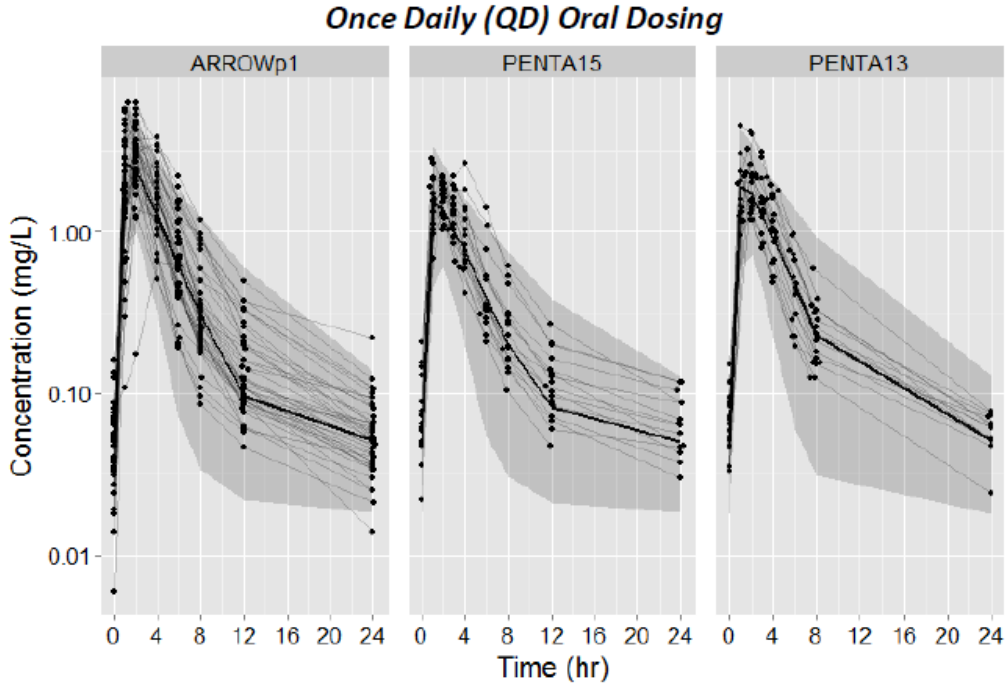


Source: Figure 30 on page 125 of sponsor's population PK report for lamivudine

Figure 4: **Visual Predictive Check (VPC) of the Final Lamivudine Population PK Model (Final 6-Study Model)**



Solid line represents median and shaded area represents 90% confidence intervals for predicted concentrations. Dots represented observed values.



Solid line represents median and shaded area represents 90% confidence intervals for predicted concentrations. Dots represented observed values.

Source: Adapted from Figure 39 on page 152 of sponsor's population PK report for lamivudine

Simulation Results

Simulations were based on oral solution and scored tablets dosages for the weight bands listed in the current EPIVIR product label and in the World Health Organization (WHO) 2010 pediatric dosing recommendations. The simulation results using the final model are summarized in Table 13.

Table 13: **Predicted lamivudine AUC(0-24) in HIV-Infected Children on Once and Twice Daily Regimens of Oral Solution (Children < 14 kg) or Scored Tablets (Children ≥ 14 kg) Dosed According to Weight Bands in the Current EPIVIR Label or WHO 2010 Recommendations**

Simulation Based on Current Approved Weight Bands	Daily Dose (mg/kg)	AUC(0-24) (µg.h/mL)	
		Once Daily	Twice Daily
Overall	8.5 (5.6-10.7)	9.90 (4.98-20.7)	9.35 (4.64-19.2)
<14 kg	8.5 (7.8-9.3)	7.94 (4.45-14.6)	7.42 (4.11-13.8)
14 to 21 kg	8.7 (7.2-10.6)	11.3 (6.11-21.6)	10.8 (5.76-20.3)
>21 to <30 kg	9.0 (7.8-10.7)	12.8 (6.84-24.2)	11.8 (6.58—20.9)
≥30 kg	8.4 (5.6-9.9)	12.6 (6.66-24.3)	12.1 (6.27-23.2)
Simulation Based on WHO 2010 Recommendations	**Daily Dose (mg/kg)**	**AUC(0-24) (µg.h/mL)**	
		Once Daily	**Twice Daily**
Overall	8.65 (5.6-11.8)	10.2 (5.03-22.2)	9.68 (4.66-20.9)
<14 kg	8.50 (7.8-9.3)	7.93 (4.46-14.6)	7.43 (4.11-13.8)
14 to <20 kg	9.0 (7.6-10.6)	11.6 (6.28-21.9)	11.1 (5.94-20.9)
20 to <25 kg	10.1 (9.0-11.2)	13.8 (7.34-26.2)	12.8 (7.15-22.3)
≥25 kg	9.3 (5.6-11.8)	13.6 (7.02-26.5)	13.1 (6.70-25.4)
Observed Adult Data	**Daily Dose (mg)**	**AUC(0-24) (µg.h/mL)**	
		Once Daily	**Twice Daily**
NUCB4001	300 (300-300)	NA	11.8 (8.84-18.8)
AZL10002	300 (300-300)	NA	10.2 (8.10-17.0)
EPV10001	300 (300-300)	8.44 (6.96-11.7)	8.99 (7.27-12.4)

Dose presented as median (range). AUC(0-24) presented as median (90% CI).
Pediatric values represent results of 1000 trial replicates of 180 subjects per trial.

Source: Summary on page 14 of sponsor's population PK report for lamivudine

Reviewer's Comments: The goodness-of-fit plots and visual predictive check (VPC) of the final model for abacavir and lamivudine indicate the observed data were adequately captured by the final models. The PK parameter estimates appear reasonable. Therefore, the sponsor's population PK analyses are acceptable.

The sponsor submitted data that compared the $AUC_{(0\_24)}$ of abacavir and lamivudine based on current approved weight bands and WHO-recommended weight bands; it would be more relevant to evaluate the difference of AUC for the same group of patients while dosing by current weight bands and WHO weight bands.

Independent analysis by the FDA reviewer was conducted for subgroup analysis of efficacy.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The Division of Pharmacometrics has reviewed the data and reports submitted in the population PK analyses as well as data in the ARROW study. The review team identified that in the ARROW study, subjects who received lamivudine oral solution had lower lamivudine exposure (AUC) and a lower response rate (HIV-1 RNA <=80 copies/mL) than subjects who received lamivudine tablets. The difference in response rate between formulation was evident at the beginning of *Randomization 3*: 51.8% (29/56) of oral solution subjects were suppressed, compared to 74.8%(458/612) of subjects who received tablets. The treatment difference was maintained over the course of *Randomization 3 and* was not impacted by dosing frequency (twice daily versus once daily), suggesting that, the difference, if any, was not a result of the dosing frequency, but may have been impacted by lower lamivudine exposures with the solution. Knowledge from previous discussion between the Agency and the sponsor and numerous publications (Kasirye P, 2012) indicated that lamivudine oral solution was associated with lower bioavailability compared with oral tablets (also refer Dr. Su-Young Choi's Clinical Pharmacology Review). There exists the potential that lower exposure of lamivudine may be associated with a lower response rate. An information request was then sent to the sponsor on November 12, 2014 to ask for clarification about this issue. The sponsor's response was summarized in Dr. Su-Young Choi's review. Briefly, no specific causes can be identified by the sponsor for the treatment difference between formulations, however, an impact of lower exposure of lamivudine on the response rate could not be ruled out.

Independent analyses were conducted by FDA pharmacometric reviewers to further explore the issue as discussed below.

4.2 Objectives

The objective of the analysis was to compare lamivudine exposure and efficacy in group of pediatrics patients administered oral solution or tablet.

4.3 Methods

4.3.1 Data Sets

The datasets used by the reviewer are population PK datasets and efficacy dataset submitted by the sponsor for PK/PD analysis of abacavir and lamivudine, respectively. Datasets used and their sources are summarized in Table 14.

Table 14. Analysis Data Sets

Study Number	Name	Link to EDR
Abacavir population PK (2013n181066)	nmgi265235pktotalv7 csv.txt	\\cdsesub1\evsprod\nda020977\0105\m5\datasets\2013n181066\analysis\legacy\programs
Lamivudine population PK (2013n181170)	nmgr109714pkarrowp entanucav7csv.txt	\\cdsesub1\evsprod\nda020977\0105\m5\datasets\2013n181170\analysis\legacy\programs

ARROW-Col105677	adeffout.xpt	\\cdsesub1\evsprod\nda020977\0105\m5\datasets\arrow-col105677\analysis\legacy\datasets\adeffout.xpt
ARROW-Col105677	vlpartc.xpt	cdsesub1\evsprod\nda020977\0105\m5\datasets\arrow-col105677\analysis\legacy\datasets\vlpartc.xpt
ARROW-Col105677	partb1r.xpt	cdsesub1\evsprod\nda020977\0105\m5\datasets\arrow-col105677\analysis\legacy\datasets\partb1r.xpt
ARROW-Col105677	ae34.xpt	cdsesub1\evsprod\nda020977\0105\m5\datasets\arrow-col105677\analysis\legacy\datasets\ae34.xpt

4.3.2 Software

NONMEM (Version 7.2) installed on a 48-core Linux cluster was used for the population PK analysis and simulations; SAS for windows 9.3 was used for all graphing and statistical analyses.

4.4 Results

4.4.1 Subgroup analysis for efficacy

The primary efficacy analysis in the ARROW study *Randomization 3* was explored by the reviewer. Proportions of subjects with HIV-1 RNA < 80 copies/mL were summarized in the table below.

As indicated, the response rate for virus suppression was lower in subjects administered with lamivudine oral solution, compared with subjects administered with tablet. The treatment difference was observed over the course of *Randomization 3*. The response rate does not appear to be affected by twice-daily versus once-daily dosing.

Table 15: Proportions of subjects with HIV-1 RNA < 80 copies/mL after Once-Daily versus Twice Daily Dosing of ABC + 3TC in combination with other ART Treatment in ARROW Study Randomization 3.

	ABC+3TC Twice Daily HIV- RNA< 80 c/mL			ABC+3TC Once Daily HIV- RNA< 80 c/mL		
	SOLUTION	TABLET	Total	SOLUTION	TABLET	Total
Week 0	14/26 (53.9%)	236/307 (76.9%)	250/333 (75.1%)	15/30 (50%)	222/305 (72.8%)	237/335 (70.8%)
Week 48	14/26 (53.9%)	229/307 (74.6%)	243/333 (73.0%)	17/30 (56.7%)	223/305 (73.1%)	240/335 (71.6%)
Week 96	13/26 (50%)	222/307 (72.3%)	235/333 (70.6%)	17/30 (56.7%)	213/305 (69.8%)	230/335 (68.7%)

Reviewer's Comment: Historical information in the literature and ARROW PK substudy results indicate that the oral solution of lamivudine is associated with lower exposure (AUC) than tablets in pediatrics, reportedly due to lower bioavailability. Lower response rate observed in treatment of oral solution in this study suggests that lamivudine exposure may be a contributing factor. Neither analysis by the sponsor nor the Agency could rule out such a possibility, therefore, a post-approval requirement (PMR) is being considered by the review team to explore whether higher lamivudine dose is needed when administered with oral solution.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
DM_PK_PD.sas	PK/PD analysis	~\Ongoing_Review\Abacavir_Lamivudine_NDA20977_20978_20564_20596\ER Analyses\Arrow
Nm_lamivudine.sas	Population PK for lamivudine	~\Ongoing_Review\NMBook\Ex15_Lamivudine\reviewer\popPK\run99

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/s/

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02/13/2015

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02/13/2015

SHIRLEY K SEO
02/13/2015