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Committee for Medicinal Products for Human Use (CHMP)

Ziagen

(abacavir sulfate)

Procedure No. EMEA/H/C/000252/P45/075

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

**Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted**

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.



INTRODUCTION

On 3 October 2008, the MAH submitted the clinical overview and report on **study PACTG Protocol 1052** for Ziagen (*Abacavir pharmacokinetics during chronic therapy in HIV-infected adolescent and young adults*), in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

Study PACTG P1052 was a phase I, open-label, age-stratified pharmacokinetic study of a single oral 300 mg dose of abacavir administered to HIV-infected adolescents aged ≥ 13 to <18 (stratum 1) and young adults aged ≥ 18 to < 25 years (stratum 2).

The MAH has reviewed the results of this study and has concluded that they are in accordance with the approved Global Data Sheet and that no changes to the Product Information are considered necessary.

SCIENTIFIC DISCUSSION

Clinical aspects

1. Introduction

As a reminder, Ziagen is indicated in adults and children from 3 months of age. The recommended dose in children aged 12 years and more is the adult dose i.e. 600 mg daily given as 300 mg BID or 600 mg QD.

For children less than 12 years, a dosing according to weight bands is recommended for Ziagen tablets and a dosing of 8 mg/kg BID (up to a maximum of 600 mg daily) is recommended for Ziagen oral solution.

Results from a previous study PACTG P1018 (a single dose PK study of an 8 mg/kg dose in children and adolescents 9 to <19 years of age) showed that the PK parameters in adolescents were more similar to children than to adults, indicating that using a 300 mg dose in adolescents may result in under-dosing.

Study PACTG P1052 was designed to address the question whether adolescents and young adults being given adult doses were achieving adequate plasma concentrations.

2. Clinical study(ies)

➤ Description

Study PACTG P1052 was a phase I, open-label, age-stratified pharmacokinetic study of a single oral 300 mg dose of abacavir administered to HIV-infected adolescents aged ≥ 13 to <18 (stratum 1) and young adults aged ≥ 18 to < 25 years (stratum 2).

➤ Methods

- Objective(s)

Primary objective:

To determine ABC PK parameters in a cohort of HIV-1 infected adolescents and young adults receiving the current recommended dose for comparison with previously published data for young children and adults

Secondary objective:

To examine the possible relationships between subject characteristics (age, body size, race/ethnicity and gender) and ABC PK parameters (oral clearance, AUC and half-life).

- Study design

Open-label, single-dose, PK study.

Enrolment was stratified by age (≥ 13 to <18 years and ≥ 18 to < 25 years).

- Study population /Sample size

Patients who had participated in P1018 were not eligible.

HIV-1 infected patients should have $CD4 > 100$ cells/mm³ and viral load $< 100\ 000$ cp/mL.

Patients had to be on abacavir for at least 8 weeks.

- Treatments

Subjects were given an observed 300 mg dose of ABC prescribed as part of the subject's current ARV treatment regimen.

- Outcomes/endpoints

PK parameters were assessed for Abacavir, its carboxylate metabolite and its glucuronide metabolite.

- PK modelling

Blood samples for PK parameters were drawn at pre dose, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 hours post-dose. Additional blood was drawn at pre dose and 4.0 hours post dose for assessing PK phenotype.

Blood samples were shipped from each site to St. Jude Core Pharmacology Laboratory for processing. One compartment absorption models were fit to each subject's data. Parameters were estimated using maximum likelihood with variance model parameters consistent with the variability of the assay allowing for measurable concentrations in pre dose samples. AUCs for abacavir estimated from the models were used for analysis. AUCs for abacavir metabolites were calculated using a trapezoidal rule.

- Statistical Methods

Because a number of the distributions of the PK parameters were skewed, medians and inter-quartile ranges and non-parametric Wilcoxon rank sum tests were used to compare distributions by age stratum, gender and race/ethnicity (reduced to two categories because of small numbers). Spearman correlations based on ranks were used to calculate correlations. Some comparisons with previously published data were done using means and standard deviations.

Median regression (least absolute residuals) lines were superimposed on scatter plots as visual summaries rather than normal linear regression lines as this technique is less sensitive to outliers. The multiple regression models were fit using linear regression, carefully checking residual plots to ensure no violation of assumptions.

➤ Results

- Recruitment/ Number analysed

15 subjects were enrolled into each stratum at 10 sites between August 2004 and December 2004. All 30 subjects completed the one day study and had evaluable PK data for analysis.

- Baseline data

53% of patients were male. 57% of patients were Black, non Hispanic.

Median CD4 count was 565 cells/mm³ and median CD4% was 27%.

52% of patients had CV < 400 cp/mL.

The majority of patients (n=24) received Trizivir alone (n=15) or with another ARV drug (n=9).

Table 6: Antiretroviral treatment regimen

Regimen	Age stratum				Total	
	<18 yrs		>=18 yrs		N	%
	N	%	N	%		
triz	6	40.0	9	60.0	15	50.0
triz,efv	0	0	3	20.0	3	10.0
triz,tdf	0	0	2	13.3	2	6.7
triz,apv	1	6.7	0	0	1	3.3
triz,tdf,efv,kal	1	6.7	0	0	1	3.3
triz,tdf,kal	2	13.3	0	0	2	6.7
abc,d4t,kal	2	13.3	0	0	2	6.7
abc,3tc,efv,nfv	1	6.7	0	0	1	3.3
abc,d4t,nfv,sqv	1	6.7	0	0	1	3.3
abc,d4t,tdf	0	0	1	6.7	1	3.3
abc,d4t,ddi,apv	1	6.7	0	0	1	3.3
Total	15	100.0	15	100.0	30	100.0

- Efficacy results

Non applicable

- Safety results

Non applicable

- PK results

Pre dose abacavir concentrations were undetectable in 11 subjects, <1000 mg/ml in 18 subjects, and 1230 mg/ml in one subject. Eight (8) subjects reached their maximum post-dose concentration by 0.5 hours, 9 by 1 hour, 9 by 2 hours and 4 by 3 hours. The distribution of Ka (the first order absorption rate constant) from the first order model is summarized in Table 11.

Table 11: Distribution of Ka from 1st order model

	N	Mean	Std	Min	P25	Median	P75	Max
<18 yrs	15	3.3	2.09	0.7	0.7	3.6	5.0	6.7
>=18 yrs	15	2.5	1.67	0.6	0.7	2.6	4.0	5.0
All	30	2.9	1.90	0.6	0.7	3.0	5.0	6.7

Summary statistics for PK parameters are shown overall in the table 12 (appendix).

Summary statistics for PK parameters by age group, gender and race are given in tables 13 to 15 (appendix). The last column in the tables shows the significance values for Wilcoxon rank sum tests comparing distributions in the 2 groups. **There were no statistically significant differences in any of the PK parameters by age group or gender.** Hispanics had marginally higher median glucuronide AUCs than Blacks (p=0.044).

Spearman correlations (based on the ranks) of the PK parameters with age (years), weight (kg), weight-for-age-and-gender z-scores, height (cm), height z-scores, BMI, BMI z-scores, body surface area (BSA) and dose adjusted for weight and surface area are shown in Table 17, with significance values for testing the hypothesis that the correlations are equal to 0 in Table 18 (starred values show correlations statistically significant at the p=0.05 level). Although there were no statistically significant differences in any PK outcomes by age group, abacavir volume of distribution adjusted for weight or BSA were significantly negatively correlated with age as was clearance adjusted for body weight. Clearance adjusted for body weight was also significantly negatively correlated with weight, BMI, BSA and positively correlated with dose adjusted for weight or BSA.

Rapporteur's comment:

There is no statistically significant difference in abacavir PK parameters between patients aged ≥ 13 to <18 years and those aged ≥ 18 to < 25 years. Therefore, there is no concerning signal suggesting that adolescents might be under-dosed compared to adults with the currently recommended dose of abacavir.

- Comparison of P1052 PK results with previous published values

Published summary statistics are available from 2 studies (Hughes et al, 1999 for children aged 3 months to 13 years and Kumar et al, 1999 for adults aged 13-55 years) and from P10189. Comparisons are provided in table 19 (see below).

References:

Hughes W, McDowell JA, Shenep J, Flynn P, Kline MW, Yogev R, Symonds W, Lou Y, Hetherington S. (1999) Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. *Antimicrobial Agents and Chemotherapy*, **43**:609-615.

Kumar PN, Sweet DE, McDowell JA, Symonds W, Lou Y, Hetherington S, LaFon S. (1999) Safety and pharmacokinetics of abacavir (1592U89) following oral administration of escalating single doses in human immunodeficiency virus type 1-infected adults. *Antimicrobial Agents and Chemotherapy*, **43**:603-608.

Table 19: Comparison of single dose abacavir parameters (4 studies)

Parameter	study	agegrp	N	Median	Mean	CV	
Abacavir AUC (model)	P1018 <13yr*	<=13 yrs	15	7.14	7.66	53	
		4 mg/kg	.	.	2.82	48	
		8 mg/kg	.	.	8.09	37	
	P1018	13-<18 yrs	7	9.84	10.30	43	
	P1052	13-<18 yrs	15	6.59	7.35	40	
		>=18 yrs	15	7.01	7.61	32	
	adult**	300 mg	.	.	6.00	46	
		600 mg	.	.	15.70	48	
	Abacavir Cmax	P1018 <13yr*	<=13 yrs	15	3.41	3.39	40
			4 mg/kg	.	.	1.69	37
8 mg/kg			.	.	3.94	28	
P1018		13-<18 yrs	7	3.87	3.82	34	
P1052		13-<18 yrs	15	2.74	2.79	41	
		>=18 yrs	15	2.58	2.94	43	
adult**		300 mg	.	.	2.87	44	
		600 mg	.	.	4.73	31	
Abacavir cl/f (ml/min/kg)		P1018 <13yr*	<=13 yrs	15	18.00	22.67	63
			4 mg/kg	.	.	27.35	37
	8 mg/kg		.	.	18.88	41	
	P1018	13-<18 yrs	7	13.60	16.74	71	
	P1052	13-<18 yrs	15	12.10	13.03	41	
		>=18 yrs	15	9.80	10.43	39	
	adult**	300 mg	.	.	13.40	41	
		600 mg	.	.	10.20	41	
	Abacavir half life (hr)	P1018 <13yr*	<=13 yrs	15	1.22	1.25	36
			4 mg/kg	.	.	0.98	35
8 mg/kg			.	.	1.13	21	
P1018		13-<18 yrs	7	1.51	1.49	21	
P1052		13-<18 yrs	15	1.34	1.23	24	
		>=18 yrs	15	1.22	1.14	23	
adult**		300 mg	.	.	1.18	14	
		600 mg	.	.	1.74	31	

* AAC 43:609 1999: aged 3 months to 13 years

** AAC 43:603 1999: aged 13 to 55 years

Rapporteur's comment:

Based on historical comparison, abacavir Cmax and AUC were similar in patients from study P1052 than in adult patients receiving the same dose of 300 mg. Therefore, there is no trend indicating a decrease in abacavir PK parameters in adolescents compared to adults.

RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Study PACTG P1052 was designed to address the question whether adolescents and young adults being given adult doses were achieving adequate plasma concentrations.

There is no statistically significant difference in abacavir PK parameters between patients aged ≥ 13 to <18 years and those aged ≥ 18 to < 25 years. Therefore, there is no concerning signal suggesting that adolescents might be under-dosed compared to adults with the currently recommended dose of abacavir.

Based on historical comparison, abacavir C_{max} and AUC were similar in patients from study P1052 than in adult patients receiving the same dose of 300 mg. Therefore, there is no trend indicating a decrease in abacavir PK parameters in adolescents compared to adults.

Overall, the Rapporteur concurs with the MAH that no changes to the Product Information are considered necessary and that no further action is required regarding this submission

➤ Recommendation

Fulfilled:

No further action required

Not fulfilled:

ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable

Table 12: PK summaries overall

Parameter	N	Median	25%ile	75%ile	Min	Max	Mean	SE	CV
Abacavir 6 hour conc	29	180.00	151.00	284.00	90.00	892.00	259.48	34.17	70.92
Abacavir AUC (model)	30	6.72	5.46	9.59	3.53	12.24	7.48	0.48	35.21
Abacavir Cmax (mg/ml)	30	2620.00	2020.00	3700.00	988.00	5890.00	2864.27	217.89	41.67
Abacavir cl/f (l/hr)	30	44.70	31.30	54.90	24.41	85.00	45.44	3.08	37.13
Abacavir cl/f (ml/min/kg)	30	10.60	8.60	13.90	3.30	22.50	11.73	0.88	41.29
Abacavir cl/f (ml/min/m2)	30	390.50	331.00	579.00	161.00	829.00	437.77	30.77	38.49
Abacavir half life (hr)	30	1.23	1.00	1.39	0.51	1.65	1.19	0.05	23.63
Abacavir v/f (l)	30	71.55	49.07	96.90	28.10	199.10	77.84	6.99	49.18
Abacavir v/f (l/kg)	30	1.05	0.80	1.60	0.40	2.80	1.19	0.11	50.51
Abacavir v/f (l/m2)	30	40.60	30.00	59.40	14.70	110.60	45.00	4.02	48.96
Carb:ABC ratio 6hr conc	29	0.71	0.50	0.95	0.34	1.67	0.77	0.06	45.31
Carb:ABC ratio AUC	30	0.54	0.47	0.77	0.31	1.26	0.63	0.04	36.14
Carboxylate 6 hour conc	30	150.00	91.00	230.00	33.00	446.00	166.97	16.83	55.20
Carboxylate AUC	30	3.87	3.46	4.77	2.60	9.97	4.26	0.28	35.62
Carboxylate Cmax (mg/ml)	30	1365.00	1180.00	2060.00	884.00	3540.00	1611.00	119.01	40.46
Gluc:ABC ratio 6hr conc	29	1.75	1.37	2.20	0.98	8.74	2.13	0.28	69.62
Gluc:ABC ratio AUC	30	1.05	0.89	1.37	0.53	4.96	1.32	0.15	63.32
Glucuronide 6 hour conc	30	370.00	268.00	599.00	105.00	1320.00	466.03	56.03	65.85
Glucuronide AUC	30	7.56	6.43	9.66	4.52	16.62	8.56	0.60	38.48
Glucuronide Cmax (mg/ml)	30	2285.00	1600.00	3020.00	215.00	5040.00	2355.20	215.14	50.03

Table 13: PK summaries by age group

Parameter	Age stratum	N	Median	25%ile	75%ile	Min	Max	Mean	SE	CV	p-value*
Abacavir 6 hour conc	<18 yrs	14	197.50	151.00	414.00	118.00	892.00	311.93	63.22	75.84	0.4641
	>=18 yrs	15	177.00	144.00	274.00	90.00	472.00	210.53	26.40	48.56	
Abacavir AUC (model)	<18 yrs	15	6.59	4.94	11.07	3.53	11.99	7.35	0.75	39.52	0.5797
	>=18 yrs	15	7.01	5.47	9.59	3.91	12.24	7.61	0.63	31.91	
Abacavir Cmax (mg/ml)	<18 yrs	15	2740.00	2020.00	3700.00	988.00	4980.00	2788.53	297.92	41.38	0.9180
	>=18 yrs	15	2580.00	1960.00	3940.00	1670.00	5890.00	2940.00	327.27	43.11	
Abacavir cl/f (l/hr)	<18 yrs	15	45.50	27.10	60.80	25.00	85.00	47.47	5.04	41.12	0.6079
	>=18 yrs	15	42.80	31.30	54.90	24.41	76.80	43.40	3.65	32.56	
Abacavir cl/f (ml/min/kg)	<18 yrs	15	12.10	8.60	19.30	5.50	22.50	13.03	1.37	40.75	0.2718
	>=18 yrs	15	9.80	8.00	13.30	3.30	18.00	10.43	1.06	39.26	
Abacavir cl/f (ml/min/m2)	<18 yrs	15	399.00	337.00	680.00	231.00	829.00	481.60	49.74	40.00	0.2806
	>=18 yrs	15	382.00	330.00	494.00	161.00	670.00	393.93	34.25	33.68	
Abacavir half life (hr)	<18 yrs	15	1.34	1.00	1.50	0.62	1.65	1.23	0.08	24.03	0.3177
	>=18 yrs	15	1.22	0.97	1.32	0.51	1.46	1.14	0.07	23.29	
Abacavir v/f (l)	<18 yrs	15	73.50	52.80	109.30	34.23	199.10	82.91	11.35	53.03	0.6813
	>=18 yrs	15	67.10	45.90	96.90	28.10	136.10	72.77	8.36	44.48	
Abacavir v/f (l/kg)	<18 yrs	15	1.10	1.00	1.70	0.60	2.80	1.35	0.17	47.98	0.1932
	>=18 yrs	15	0.90	0.60	1.60	0.40	1.90	1.04	0.14	51.24	
Abacavir v/f (l/m2)	<18 yrs	15	41.70	33.40	63.90	27.10	110.60	50.56	6.35	48.62	0.2158
	>=18 yrs	15	37.80	20.60	59.40	14.70	71.30	39.45	4.73	46.40	

* Wilcoxon rank sum test

Table 13: PK summaries by age group (cont.)

Parameter	Age stratum	N	Median	25%ile	75%ile	Min	Max	Mean	SE	CV	p-value*
Carb:ABC ratio 6hr conc	<18 yrs	14	0.74	0.43	0.86	0.34	1.58	0.73	0.09	45.55	0.5602
	>=18 yrs	15	0.69	0.50	1.07	0.44	1.67	0.81	0.10	46.01	
Carb:ABC ratio AUC	<18 yrs	15	0.68	0.41	0.77	0.31	1.26	0.64	0.06	38.37	0.8211
	>=18 yrs	15	0.53	0.47	0.79	0.39	1.10	0.62	0.06	34.90	
Carboxylate 6 hour conc	<18 yrs	15	162.00	92.00	239.00	33.00	446.00	176.33	26.65	58.53	0.4368
	>=18 yrs	15	150.00	90.00	216.00	74.00	384.00	157.60	21.22	52.14	
Carboxylate AUC	<18 yrs	15	3.77	3.26	4.59	2.73	7.11	4.06	0.30	28.78	0.6516
	>=18 yrs	15	4.20	3.46	5.24	2.60	9.97	4.47	0.47	40.80	
Carboxylate Cmax (mg/ml)	<18 yrs	15	1280.00	1180.00	2140.00	904.00	2280.00	1543.40	129.54	32.51	1.0000
	>=18 yrs	15	1430.00	1000.00	2060.00	884.00	3540.00	1678.60	203.10	46.86	
Gluc:ABC ratio 6hr conc	<18 yrs	14	1.68	1.35	2.44	0.98	8.74	2.40	0.54	84.04	0.9827
	>=18 yrs	15	1.77	1.47	2.20	1.06	3.84	1.88	0.18	37.22	
Gluc:ABC ratio AUC	<18 yrs	15	1.21	0.89	1.81	0.80	4.96	1.55	0.28	70.71	0.2718
	>=18 yrs	15	1.04	0.86	1.28	0.53	2.13	1.09	0.09	33.63	
Glucuronide 6 hour conc	<18 yrs	15	407.00	268.00	806.00	105.00	1320.00	559.07	98.39	68.16	0.3277
	>=18 yrs	15	346.00	246.00	412.00	152.00	874.00	373.00	45.71	47.46	
Glucuronide AUC	<18 yrs	15	7.68	6.43	12.22	4.52	16.62	9.36	0.96	39.65	0.2897
	>=18 yrs	15	7.09	5.72	8.76	4.62	15.47	7.77	0.70	34.98	
Glucuronide Cmax (mg/ml)	<18 yrs	15	2480.00	1540.00	3260.00	215.00	5040.00	2514.20	359.27	55.34	0.4135
	>=18 yrs	15	2160.00	1600.00	2780.00	833.00	4250.00	2196.20	243.03	42.86	

* Wilcoxon rank sum test

Table 14: PK summaries by gender

Parameter	Gender	N	Median	25%ile	75%ile	Min	Max	Mean	SE	CV	p-value*
Abacavir 6 hour conc	Female	14	184.00	154.00	249.00	109.00	892.00	261.36	57.70	82.60	0.8626
	Male	15	176.00	141.00	388.00	90.00	606.00	257.73	40.38	60.68	
Abacavir AUC (model)	Female	14	6.50	5.47	11.27	3.60	11.99	7.60	0.75	36.71	0.8853
	Male	16	6.72	5.20	9.31	3.53	12.24	7.37	0.64	34.94	
Abacavir Cmax (mg/ml)	Female	14	2580.00	1960.00	3940.00	1130.00	4980.00	2805.00	307.65	41.04	0.8867
	Male	16	2700.00	2060.00	3660.00	988.00	5890.00	2916.13	316.13	43.36	
Abacavir cl/f (l/hr)	Female	14	46.45	26.50	54.90	25.00	83.40	44.62	4.40	36.90	0.9015
	Male	16	44.70	32.30	57.85	24.41	85.00	46.15	4.43	38.41	
Abacavir cl/f (ml/min/kg)	Female	14	11.05	8.00	13.90	5.50	19.30	11.54	1.09	35.49	0.8207
	Male	16	10.60	9.05	15.65	3.30	22.50	11.89	1.39	46.62	
Abacavir cl/f (ml/min/m2)	Female	14	399.50	334.00	579.00	231.00	772.00	437.21	39.78	34.05	0.9179
	Male	16	384.50	330.50	582.50	161.00	829.00	438.25	47.23	43.11	
Abacavir half life (hr)	Female	14	1.23	1.00	1.46	0.51	1.65	1.18	0.08	26.74	0.8528
	Male	16	1.23	1.00	1.37	0.62	1.58	1.19	0.06	21.45	
Abacavir v/f (l)	Female	14	73.10	37.70	96.90	28.10	199.10	77.95	12.31	59.11	0.7574
	Male	16	71.40	52.59	99.10	40.20	138.20	77.74	7.88	40.54	
Abacavir v/f (l/kg)	Female	14	1.05	0.70	1.70	0.40	2.80	1.21	0.17	54.09	0.9670
	Male	16	1.05	0.85	1.45	0.40	2.70	1.18	0.14	48.80	
Abacavir v/f (l/m2)	Female	14	40.80	31.10	62.60	14.70	110.60	46.35	6.74	54.42	0.9016
	Male	16	39.20	29.35	53.35	19.80	92.80	43.83	4.90	44.70	

* Wilcoxon rank sum test

Table 15: PK summaries by race/ethnicity

Parameter	Race/ ethnic	N	Median	25%ile	75%ile	Min	Max	Mean	SE	CV	p-value*
Abacavir 6 hour conc	White	2	107.00	90.00	124.00	90.00	124.00	107.00	17.00	22.47	0.6782
	Black	16	178.50	154.00	279.00	109.00	892.00	266.25	51.46	77.31	
	Hispanic	11	194.00	151.00	414.00	124.00	606.00	277.36	48.75	58.30	
Abacavir AUC (model)	White	2	4.66	3.91	5.40	3.91	5.40	4.66	0.75	22.63	0.4721
	Black	17	6.59	5.47	8.32	3.60	12.24	7.43	0.65	36.09	
	Hispanic	11	8.43	5.65	10.08	3.53	11.33	8.07	0.77	31.63	
Abacavir Cmax (mg/ml)	White	2	2205.00	1670.00	2740.00	1670.00	2740.00	2205.00	535.00	34.31	0.9442
	Black	17	2580.00	1960.00	3700.00	1130.00	5890.00	2957.65	319.03	44.47	
	Hispanic	11	2660.00	2060.00	3940.00	988.00	4730.00	2839.82	330.61	38.61	
Abacavir cl/f (l/hr)	White	2	66.20	55.60	76.80	55.60	76.80	66.20	10.60	22.64	0.5008
	Black	17	45.50	36.10	54.90	24.41	83.40	45.16	3.75	34.28	
	Hispanic	11	35.60	29.80	53.10	26.50	85.00	42.09	5.40	42.56	
Abacavir cl/f (ml/min/kg)	White	2	15.95	13.90	18.00	13.90	18.00	15.95	2.05	18.18	0.6252
	Black	17	10.20	8.00	13.30	3.30	19.60	11.05	1.10	40.98	
	Hispanic	11	10.00	9.50	16.50	3.70	22.50	12.01	1.65	45.53	
Abacavir cl/f (ml/min/m2)	White	2	624.50	579.00	670.00	579.00	670.00	624.50	45.50	10.30	0.5459
	Black	17	399.00	360.00	494.00	161.00	772.00	421.65	37.43	36.60	
	Hispanic	11	337.00	325.00	586.00	194.00	829.00	428.73	57.47	44.45	
Abacavir half life (hr)	White	2	1.37	1.23	1.50	1.23	1.50	1.37	0.14	13.99	0.2686
	Black	17	1.31	1.05	1.39	0.51	1.65	1.20	0.07	24.83	
	Hispanic	11	1.03	0.96	1.32	0.73	1.58	1.12	0.08	23.49	
Abacavir v/f (l)	White	2	128.15	120.20	136.10	120.20	136.10	128.15	7.95	8.77	0.4864
	Black	17	69.60	52.80	88.90	28.30	199.10	77.90	9.76	51.64	
	Hispanic	11	63.44	41.60	77.90	28.10	138.20	68.59	9.76	47.17	
Abacavir v/f (l/kg)	White	2	1.85	1.80	1.90	1.80	1.90	1.85	0.05	3.82	1.0000
	Black	17	1.00	0.90	1.30	0.40	2.80	1.14	0.14	52.22	
	Hispanic	11	1.00	0.80	1.43	0.40	2.70	1.16	0.19	54.26	
Abacavir v/f (l/m2)	White	2	73.22	71.30	75.13	71.30	75.13	73.22	1.92	3.70	0.7269
	Black	17	40.60	33.40	47.30	14.70	110.60	43.87	5.33	50.08	
	Hispanic	11	37.80	27.80	50.70	20.40	92.80	41.63	6.47	51.57	

* Wilcoxon rank sum test comparing Hispanic and Black groups only

Table 15: PK summaries by race/ethnicity (cont.)

Parameter	Race/ ethnic	N	Median	25%ile	75%ile	Min	Max	Mean	SE	CV	p-value*
Carb:ABC ratio 6hr conc	White	2	1.23	0.80	1.67	0.80	1.67	1.23	0.43	49.86	0.2564
	Black	16	0.58	0.50	0.79	0.34	1.31	0.67	0.07	39.20	
	Hispanic	11	0.79	0.46	1.07	0.39	1.58	0.84	0.11	44.00	
Carb:ABC ratio AUC	White	2	0.98	0.86	1.10	0.86	1.10	0.98	0.12	17.33	0.6923
	Black	17	0.53	0.47	0.70	0.31	0.96	0.58	0.04	30.27	
	Hispanic	11	0.53	0.41	0.79	0.39	1.26	0.64	0.08	41.04	
Carboxylate 6 hour conc	White	2	124.50	99.00	150.00	99.00	150.00	124.50	25.50	28.97	0.0642
	Black	17	139.00	86.00	200.00	33.00	446.00	152.94	24.77	66.78	
	Hispanic	11	162.00	154.00	236.00	92.00	384.00	196.36	23.67	39.98	
Carboxylate AUC	White	2	4.18	3.64	4.72	3.64	4.72	4.18	0.54	18.31	0.2688
	Black	17	3.52	2.90	4.96	2.60	7.11	4.03	0.33	33.63	
	Hispanic	11	4.10	3.53	4.77	3.46	9.97	4.63	0.56	40.05	
Carboxylate Cmax (ng/ml)	White	2	1900.00	1520.00	2280.00	1520.00	2280.00	1900.00	380.00	28.28	0.8521
	Black	17	1300.00	1030.00	2060.00	933.00	2990.00	1574.82	145.92	38.20	
	Hispanic	11	1280.00	1180.00	2060.00	884.00	3540.00	1614.36	234.58	48.19	
Gluc:ABC ratio 6hr conc	White	2	2.72	1.59	3.84	1.59	3.84	2.72	1.13	58.70	0.1005
	Black	16	1.52	1.31	2.07	1.06	3.02	1.69	0.14	32.59	
	Hispanic	11	1.89	1.62	2.67	0.98	8.74	2.66	0.66	81.99	
Gluc:ABC ratio AUC	White	2	1.77	1.40	2.13	1.40	2.13	1.77	0.36	29.01	0.2497
	Black	17	0.96	0.88	1.28	0.53	1.93	1.09	0.09	32.72	
	Hispanic	11	1.21	1.02	1.37	0.75	4.96	1.61	0.38	78.30	
Glucuronide 6 hour conc	White	2	271.50	197.00	346.00	197.00	346.00	271.50	74.50	38.81	0.0584
	Black	17	300.00	246.00	412.00	105.00	1220.00	396.76	65.76	68.34	
	Hispanic	11	435.00	343.00	874.00	234.00	1920.00	608.45	102.85	56.06	
Glucuronide AUC	White	2	7.34	7.01	7.68	7.01	7.68	7.34	0.33	6.43	0.0436
	Black	17	7.09	5.72	8.34	4.52	13.39	7.45	0.57	31.69	
	Hispanic	11	8.76	7.06	15.47	6.21	16.62	10.50	1.21	38.09	
Glucuronide Cmax (ng/mL)	White	2	2030.00	940.00	3120.00	940.00	3120.00	2030.00	1090.00	75.94	0.5157
	Black	17	2260.00	1700.00	2730.00	215.00	4330.00	2216.18	222.54	41.40	
	Hispanic	11	2780.00	990.00	4160.00	588.00	5040.00	2629.18	457.82	57.75	

* Wilcoxon rank sum test comparing Hispanic and Black groups only

Table 16: PK summaries by HIV-1 RNA detectability

Parameter	HIV-1	N	Median	25%le	75%le	Min	Max	Mean	SE	CV	p-value*
Abacavir 6 hour conc	<400	14	169.50	141.00	194.00	90.00	892.00	253.07	61.01	90.20	0.2606
	>=400	14	228.00	154.00	371.00	118.00	589.00	268.43	38.37	53.48	
Abacavir AUC (model)	<400	15	5.83	4.94	8.33	3.53	11.99	6.84	0.69	39.22	0.1734
	>=400	14	8.06	5.99	10.08	3.60	12.24	8.02	0.69	32.03	
Abacavir Cmax (mg/ml)	<400	15	2320.00	2020.00	3700.00	988.00	4730.00	2713.20	286.17	40.85	0.5895
	>=400	14	2700.00	1960.00	3180.00	1130.00	5890.00	2925.00	345.36	44.18	
Abacavir cl/f (l/hr)	<400	15	51.40	36.04	60.80	25.00	85.00	49.86	4.51	35.06	0.1670
	>=400	14	37.25	29.80	50.10	24.41	83.40	41.71	4.25	38.14	
Abacavir cl/f (ml/min/kg)	<400	15	13.30	10.20	18.00	3.70	22.50	13.75	1.32	37.21	0.0244
	>=400	14	9.35	7.80	12.10	3.30	19.30	9.71	1.02	39.35	
Abacavir cl/f (ml/min/m2)	<400	15	495.00	337.00	670.00	194.00	829.00	498.80	46.55	36.14	0.0741
	>=400	14	362.50	331.00	417.00	161.00	772.00	380.07	37.39	36.81	
Abacavir half life (hr)	<400	15	1.22	1.00	1.39	0.62	1.58	1.16	0.07	24.12	0.6973
	>=400	14	1.25	0.99	1.42	0.51	1.65	1.20	0.08	24.69	
Abacavir v/f (l)	<400	15	76.60	56.10	109.90	28.10	138.20	83.26	8.78	40.86	0.3560
	>=400	14	71.55	41.60	82.85	28.30	199.10	73.32	11.78	60.10	
Abacavir v/f (l/kg)	<400	15	1.30	0.90	1.80	0.40	2.70	1.36	0.15	43.83	0.0834
	>=400	14	0.95	0.70	1.10	0.40	2.80	1.03	0.16	59.25	
Abacavir v/f (l/m2)	<400	15	47.30	33.40	65.50	20.40	92.80	49.66	5.47	42.68	0.1734
	>=400	14	37.40	27.80	42.90	14.70	110.60	40.53	6.26	57.78	

* Wilcoxon rank sum test

Table 16: PK summaries by HIV-1 RNA detectability (cont.)

Parameter	HIV-1	N	Median	25%le	75%le	Min	Max	Mean	SE	CV	p-value*
Carb:ABC ratio 6hr conc	<400	14	0.82	0.68	1.20	0.39	1.67	0.93	0.10	42.01	0.0342
	>=400	14	0.50	0.44	0.74	0.34	1.06	0.62	0.07	39.32	
Carb:ABC ratio AUC	<400	15	0.70	0.53	0.86	0.41	1.26	0.74	0.06	32.43	0.0200
	>=400	14	0.49	0.39	0.68	0.31	0.85	0.53	0.05	32.07	
Carboxylate 6 hour conc	<400	15	154.00	99.00	236.00	33.00	446.00	178.73	26.13	56.63	0.4138
	>=400	14	140.50	90.00	200.00	74.00	384.00	155.29	23.29	56.12	
Carboxylate AUC	<400	15	4.10	3.62	4.96	2.73	9.97	4.60	0.47	39.33	0.1801
	>=400	14	3.51	2.90	4.59	2.60	5.89	3.87	0.30	29.50	
Carboxylate Cmax (mg/ml)	<400	15	1520.00	1250.00	2170.00	884.00	3540.00	1735.00	199.14	44.45	0.2659
	>=400	14	1240.00	1030.00	2000.00	933.00	2240.00	1427.50	123.82	32.45	
Gluc:ABC ratio 6hr conc	<400	14	1.95	1.59	2.67	1.08	8.74	2.62	0.53	75.72	0.0672
	>=400	14	1.58	1.30	1.85	0.98	3.02	1.65	0.14	32.67	
Gluc:ABC ratio AUC	<400	15	1.22	0.95	1.93	0.75	4.96	1.59	0.28	69.28	0.1273
	>=400	14	1.01	0.86	1.15	0.53	1.81	1.04	0.08	28.94	
Glucuronide 6 hour conc	<400	15	384.00	212.00	806.00	105.00	1320.00	513.27	99.33	74.96	0.7787
	>=400	14	328.00	268.00	599.00	218.00	874.00	417.64	57.03	51.10	
Glucuronide AUC	<400	15	7.71	6.21	12.22	4.52	16.62	9.11	0.97	41.27	0.2940
	>=400	14	7.08	6.43	7.92	4.62	15.47	7.79	0.73	35.12	
Glucuronide Cmax (mg/ml)	<400	15	2730.00	1760.00	3120.00	215.00	5040.00	2613.67	328.90	48.74	0.1433
	>=400	14	1765.00	1240.00	2480.00	588.00	3580.00	1942.93	241.10	46.43	

* Wilcoxon rank sum test

Table 17: Spearman correlations of PK parameters with subject characteristics

Parameter	Age (yrs)	Weight (kg)	Weight z-score	Height (cm)	Height z-score	BMI	BMI z-score	BSA	Dose (mg/kg)	Dose (mg/m ²)
Abacavir										
C _{max}	0.079	-0.143	-0.184	-0.251	-0.369	-0.003	-0.048	-0.256	0.068	0.256
6hr conc	0.016	-0.098	-0.069	-0.272	-0.403	0.110	0.051	-0.123	0.045	0.123
AUC (model)	0.206	-0.147	-0.204	-0.203	-0.352	-0.050	-0.131	-0.218	0.080	0.218
Vol dist	-0.169	0.223	0.267	0.338	0.481	0.048	0.159	0.294	-0.159	-0.294
Vol dist (/m ²)	-0.370	-0.071	0.042	0.055	0.204	-0.135	0.006	0.027	0.124	-0.027
Vol dist (/kg)	-0.389	-0.294	-0.184	-0.074	0.010	-0.334	-0.189	-0.185	0.300	0.185
Half life	-0.097	0.316	0.359	0.208	0.302	0.265	0.350	0.263	-0.272	-0.263
Clearance	-0.208	0.125	0.185	0.196	0.346	0.026	0.111	0.201	-0.063	-0.201
Clearance (/kg)	-0.379	-0.489	-0.381	-0.212	-0.162	-0.492	-0.356	-0.366	0.493	0.366
Clearance (/m ²)	-0.360	-0.183	-0.060	-0.045	0.102	-0.195	-0.069	-0.073	0.257	0.073
Carboxylate										
C _{max}	-0.059	-0.349	-0.347	-0.327	-0.371	-0.247	-0.225	-0.273	0.274	0.273
6hr conc	-0.094	-0.284	-0.308	-0.208	-0.360	-0.250	-0.283	-0.293	0.197	0.293
AUC (trap)	0.089	-0.430	-0.439	-0.349	-0.457	-0.313	-0.316	-0.403	0.384	0.403
Car:ABC AUC ratio	-0.195	-0.265	-0.251	-0.069	-0.026	-0.364	-0.295	-0.162	0.266	0.162
Car:ABC 6hr conc rat	-0.038	-0.267	-0.299	-0.014	-0.011	-0.376	-0.360	-0.243	0.197	0.243
Glucuronide										
C _{max}	-0.208	-0.444	-0.316	-0.614	-0.567	-0.097	-0.103	-0.499	0.381	0.499
6hr conc	-0.107	-0.204	-0.184	-0.233	-0.343	-0.081	-0.118	-0.233	0.137	0.233
AUC (trap)	-0.103	-0.426	-0.361	-0.558	-0.646	-0.082	-0.144	-0.511	0.386	0.511
Glu:ABC AUC ratio	-0.259	-0.286	-0.251	-0.277	-0.290	-0.139	-0.148	-0.280	0.262	0.280
Glu:ABC 6 hrconc rat	-0.120	-0.410	-0.392	-0.203	-0.200	-0.384	-0.351	-0.420	0.333	0.420

Table 18: P-values for Spearman correlations of PK parameters with subject characteristics

Parameter	Age (yrs)	Weight (kg)	Weight z-score	Height (cm)	Height z-score	BMI	BMI z-score	BSA	Dose (mg/kg)	Dose (mg/m ²)
Abacavir										
C _{max}	0.677	0.451	0.329	0.180	0.045*	0.988	0.801	0.172	0.722	0.172
6hr conc	0.934	0.614	0.722	0.154	0.030*	0.570	0.793	0.524	0.817	0.524
AUC (model)	0.274	0.439	0.280	0.282	0.056	0.792	0.489	0.248	0.673	0.248
Vol dist	0.371	0.236	0.154	0.068	0.007*	0.802	0.402	0.114	0.401	0.114
Vol dist (/m ²)	0.044*	0.711	0.826	0.772	0.279	0.477	0.977	0.886	0.514	0.886
Vol dist (/lg)	0.034*	0.115	0.332	0.698	0.956	0.071	0.317	0.328	0.108	0.328
Half life	0.609	0.088	0.052	0.271	0.105	0.157	0.058	0.160	0.146	0.160
Clearance	0.269	0.510	0.327	0.300	0.061	0.890	0.558	0.286	0.740	0.286
Clearance (/kg)	0.039*	0.006*	0.038*	0.261	0.394	0.006*	0.053	0.047*	0.006*	0.047*
Clearance (/m ²)	0.051	0.332	0.753	0.814	0.592	0.303	0.716	0.701	0.171	0.701
Carboxylate										
C _{max}	0.759	0.058	0.061	0.077	0.043*	0.189	0.232	0.144	0.142	0.144
6hr conc	0.620	0.128	0.097	0.271	0.051	0.182	0.129	0.116	0.296	0.116
AUC (trap)	0.639	0.018*	0.015*	0.058	0.011*	0.092	0.089	0.027*	0.036*	0.027*
Car:ABC AUC ratio	0.303	0.157	0.181	0.715	0.893	0.048*	0.114	0.394	0.155	0.394
Car:ABC 6hr conc rat	0.843	0.162	0.115	0.943	0.953	0.044*	0.055	0.203	0.307	0.203
Glucuronide										
C _{max}	0.270	0.014*	0.089	0.000*	0.001*	0.609	0.586	0.005*	0.038*	0.005*
6hr conc	0.574	0.278	0.329	0.214	0.063	0.671	0.534	0.215	0.471	0.215
AUC (trap)	0.586	0.019*	0.050*	0.001*	0.000*	0.666	0.448	0.004*	0.035*	0.004*
Glu:ABC AUC ratio	0.166	0.126	0.181	0.139	0.120	0.465	0.435	0.134	0.163	0.134
Glu: ABC 6hr conc rat	0.535	0.027	0.035*	0.290	0.298	0.040*	0.062	0.023*	0.077	0.023*