Medical Officer Review

Date	November 29, 2008
From	Yodit Belew, M.D.
Subject	Clinical Review
NDA Number **Supplement Number**	20-977
Applicant	GlaxoSmithKline
Date of Submission	June 21, 2008
PDUFA Goal Date	December 21, 2008
Proprietary Name/ **Established Names**	Ziagen (abacavir sulfate, ABC)
Dosage Forms/Strength	New proposed dosage form: scored 300 mg tablets Approved dosage forms: unscored 300mg tablets and oral solution (20mg/ml)
Proposed Indication(s)	Treatment of HIV infection
Recommendation	Approval

1. Recommendation

The submitted data support approval of this supplemental NDA (sNDA).

Ziagen is currently approved for use in children (from 3 months to 16 years) at a dose of 8 mg/kg twice daily for the treatment of HIV-1 infection. Ziagen is available as a 300 mg tablet (unscored) and oral solution. The purpose of the current supplemental NDA is to provide a score to the existing 300 mg tablet and dosing recommendations for HIV-1 infected pediatric population weighing 14 to ≥ 30 kg and who are able to swallow tablets. No actual study was conducted to evaluate the safety, tolerability and efficacy of the proposed doses using Ziagen scored tablet. However, the review relied on previous pediatric and adult safety, efficacy and pharmacokinetic (PK) data to link the currently proposed dose (exposure) with safety and efficacy outcomes. The sponsor submitted previously reviewed clinical and clinical pharmacology data, including actual and simulated exposure data in support of the proposed dosing regimen. Furthermore, the currently proposed scored tablet is identical to the currently approved, unscored 300mg tablet, with the exception of the score line. The efficacy and safety data from previous applications for Ziagen tablets and oral solution are thus acceptable for use in cross-reference to support this sNDA.

The primary objectives for evaluating dosing recommendations were to match the predicted exposures in children to historical PK data in children and adults to avoid under dosing and minimize over dosing.

This supplemental NDA contains predicted pharmacokinetics using the Monte Carlo simulation model and reanalysis of previous pediatric pharmacokinetic data to support dosing of Ziagen scored tablets (300 mg) for the treatment of HIV infection in pediatric patients 14 – ≥ 30 kg. Based on the Monte Carlo simulation model, the predicted pharmacokinetic profile for scored Ziagen tablets is comparable to the relevant historical pediatric and/or adult pharmacokinetic data. The existing pediatric pharmacokinetic, efficacy, and safety data were used to support dosing in weight bands where the predicted exposures from the scored Ziagen tablet deviated from the historical pediatric data.

Additionally, the sNDA was granted a priority review because the scored tablet provides an alternative for an oral solid formulation for children who are able to swallow solid oral formulations. A tablet formulation may improve patient adherence and may provide a more convenient dosing compared to larger volumes required with the oral solution.

2. Introduction/Background

The development of multiple antiretroviral therapies (ART) over the past decade has transformed human immunodeficiency virus (HIV) disease to a chronic condition in the developed world. The demand for access to antiretroviral treatment in resource poor settings has also increased, including access for infants and children. However, multiple challenges remain in the treatment of HIV infection in pediatric populations, such as development of appropriate pediatric formulations. Even when appropriate formulations (i.e. liquid) are available, challenges continue, including a requirement of larger volumes to deliver effective treatment, problems of palatability, storage, transport, and cost associated with liquid formulations. It is therefore preferred to give children solid formulations as soon as they are able to take them.

There have been increasing requests from organizations like the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF), for pharmaceutical industries to develop new dosage forms (i.e. scored tablets or dose proportional smaller tablets) for use by pediatric patients with HIV infection, particularly to facilitate treatment of children in resource-poor settings.

Ziagen was originally approved in December 1998 and is an important product for adults and pediatric patients receiving antiretroviral treatment for HIV-1 infection. In the US, ZIAGEN is available as a 300 mg tablets and as a 20mg/mL oral solution. The recommended oral adult dose of ZIAGEN is 600 mg daily, administered as either 300mg twice daily (BID) or 600mg once daily. The currently recommended oral dose of ZIAGEN for adolescents and pediatric patients 3 months to up to 16 years of age is 8mg/kg BID (up to a maximum of 300 mg BID). Once daily dosing is not approved for pediatric patients. The currently available unscored 300 mg tablets are not conducive to weight based dosing for many children. Therefore, although a child may be able to swallow a solid tablet, he or she is required to take the oral solution, which may necessitate a large volume to administer an effective dose. Volume and palitability issues have been shown to lead to non-adherence.

In order to improve adherence, ease of administration and storage, particularly in resource poor countries, the WHO had created slightly different dosing recommendations, which allows the use of tablets (albeit unscored) (Table 1) in patients 12 kg to < 40 kg. Many developing countries use this table as guidance for dosing.

Table 1: WHO Recommended dosing for abacavir, based on weight

Abacavir: Recommended dosing based on weight				
Weight range (kg)		Target dosing <16 years or <37.5 kg: 8 mg/kg/dose given twice daily Maximum dose >16 years or >37.5 kg: 300 mg/dose given twice daily	Dose (ml or tablets)	
Bottom	Top	Formulation	a.m.	p.m.
12	13.9	20 mg/ml syrup or 300 mg tablet	6 ml	6 ml
			0.5	0.5
14	16.9	300 mg tablet	0.5	0.5
17	19.9	300 mg tablet	0.5	0.5
20	24.9	300 mg tablet	1	0.5
25	29.9	300 mg tablet	1	1
30	34.9	300 mg tablet	1	1

On September 20, 2005, GlaxoSmithKline (GSK) met with WHO, UNICEF, Medecins Sans Frontieres (MSF), European Medicines Agency (EMEA) and the Food and Drug Administration (FDA) to discuss additional work that GSK could do to support scored tablet products. As follow up, a Parallel Scientific Advice meeting was held on June 13, 2006 with FDA, EMEA and GSK where discussions focused on the development of COMBIVIR® scored tablets, with the understanding that these discussions could be applied to the development program for scoring both EPIVIR® (lamivudine, 3TC) and ZIAGEN tablets. Scored tablets have received marketing approval in Europe for COMBIVIR, EPIVIR and ZIAGEN. The supplemental New Drug Application (sNDA) for EPIVIR scored 150mg tablets was approved in the United States (US) in January 2008. The proposed Ziagen pediatric dosing is as follows:

Weight (kg)	Dosage Using 150 mg Tablet		Total Daily Dose
	AM Dose	PM dose	
14 to 21	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21 to <30	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30	1 tablet ((b) (4) mg)	1 tablet ((b) (4) mg)	600 mg

The proposed Ziagen pediatric dosing would allow development of a scored (b) (4) tablet, as the weight bands proposed for Ziagen scored tablet are identical to the weight bands approved for Epivir scored tablet.

3. Clinical pharmacology

BACKGROUND:

The pharmacokinetics of ABC in children has been studied after single (4mg/kg, 8mg/kg) and repeat (4mg/kg, 8mg/kg) doses of ZIAGEN. Abacavir is rapidly and extensively absorbed from an oral solution administered to children, with peak plasma concentrations generally occurring within one hour. The PK parameter estimates of ABC are comparable among the various age-related subgroups of the pediatric population (from 3 months to 13 years) for each dose level. Abacavir is rapidly eliminated from the plasma of pediatric subjects with a half-life of 1 to 1.5 hours, which is comparable to values observed in adults. Plasma ABC exposures in pediatric patients is lower than adults at comparable doses based on body weight (mg/kg); therefore, pediatric subjects require higher doses (mg/kg) than adults to achieve similar exposure. A higher clearance in pediatric patients most likely contributed to lower exposure at a given dose when compared to adults. The mean oral clearance of ABC for adults was approximately 16mL/min/kg. The mean oral clearance value for pediatric patients ranged from approximately 26mL/min/kg in the 4mg/kg dose group to 18mL/min/kg in the 8mg/kg group. Although 4mg/kg BID in children was similar to the adult 300mg BID dose based on body weight, a higher dose (8mg/kg BID) was subsequently approved for marketing for treatment of pediatric patients with HIV-1 infection. The AUC and Cmax in children receiving 8 mg/kg BID is approximately 62% and 24% higher, respectively, than adults receiving 300 mg BID.

METHODS

First, we evaluated the percent difference in dose between the proposed regimen for the scored tablets and the currently approved regimen as shown in Table 4 below. More importantly, given the non linear pharmacokinetics of abacavir,

analysis of the predicted pharmacokinetics (exposure) was necessary to support the proposed dosing regimen. We therefore evaluated the predicted exposures from the scored tablets based on the Monte Carlo simulation. The Monte Carlo simulation is based on a well established and validated abacavir pharmacokinetic model. In addition, historical pediatric and adult exposure data from once daily, twice daily and thrice daily dosing regimens were used in our evaluation.

GSK also compared the predicted exposures from reanalysis of historical pediatric data but the Division did not rely on these findings because the analysis assumed linear PK. Please refer to Dr. Zhang's review for further details regarding the pharmacokinetic comparisons between the various methods evaluated.

In summary, the following data were used in the FDA evaluation.

Three pediatric studies (CNAA1001, ACTG 330/CNAA1013, and PENTA 13) provided PK data (AUC and Cmax) at 4-16mg/kg doses. These data were re-analyzed by GSK to estimate abacavir AUC and Cmax values from the proposed scored tablet dosing regimens.

Study CNAA1001 was a crossover, Phase I trial to evaluate the safety and PK parameters of single oral doses of ABC in HIV-infected children. Study ACTG 330 was a Phase I safety and PK study of ABC alone and in combination with other antiretroviral agents in infants and children with HIV infection. Study PENTA 13 is further described in Section 6. Tables 2 and 3 summarize the 3 studies.

Table 2: Summary of Studies CNAA1001, ACTG 330 and PENTA-13

Study	Age Range	Weight Range (kg)	ABC formulation/ dose/ frequency	N	PK Sampling Times
CNAA1001	3 months-13 years	3.9-44.3	Solution/ 4 and 8mg/kg/ single dose	22	0, 0.5, 1, 1.5, 2, 2.5, 3, 5, and 8h
ACTG 330	0.6-12 years	6.3-39.7	Solution/4mg/kg/BID and Solution/8mg/kg/BID	46	0, 1, 2, 3, and 5h
PENTA 13	2-12 years	13.7-60.5	Solution/8mg/kg/BID and Solution/16mg/kg/once daily	14	0. 1, 2, 3, 4, 6,8, and 12 (BID) or 24h (once daily)

N = number of subjects with ABC PK parameters reported
Source: GSK

Table 3: Summary of Number of Subjects with Reportable ABC PK Parameters by Study and Weight Band

	CNAA1001	ACTG330	PENTA-13	All studies
<14kg	13	11	2	26
14 to 21kg	3	12	6	21
>21 to <30kg	3	17	4	24
≥30kg	3	6	2	11
Total	22	46	14	82

Source: GSK

RESULTS:

The table below summarizes the percent difference between the proposed GSK doses and FDA approved dose.

Table 4: Percent differences in daily doses: Proposed GSK doses vs. FDA Approved Doses

Weight (kg)	Total daily dose (mg, based on 8mg/kg BID)	% difference (half tab BID, 300mg/day)	% difference (half tab [AM] and full tab [PM], 450mg/day)	% difference (full tab BID, 600mg/day)
14	224	33.9	100.9	167.9
15	240	25.0	87.5	150.0
16	256	17.2	75.8	134.4
17	272	10.3	65.4	120.6
18	288	4.2	56.3	108.3
19	304	-1.3	48.0	97.4
20	320	-6.3	40.6	87.5
21	336	-10.7	33.9	78.6
22	352	-14.8	27.8	70.5
23	368	-18.5	22.3	63.0
24	384	-21.9	17.2	56.3
25	400	-25.0	12.5	50.0
26	416	-27.9	8.2	44.2
27	432	-30.6	4.2	38.9
28	448	-33.0	0.4	33.9
29	464	-35.3	-3.0	29.3
30	480	-37.5	-6.3	25.0
31	496	-39.5	-9.3	21.0
32	512	-41.4	-12.1	17.2
33	528	-43.2	-14.8	13.6
34	544	-44.9	-17.3	10.3
35	560	-46.4	-19.6	7.1
36	576	-47.9	-21.9	4.2
37	592	-49.3	-24.0	1.4
38	600	-50.0	-25.0	0.0
39	600	-50.0	-25.0	0.0
40	600	-50.0	-25.0	0.0

The most daily percent decease that would result from the proposed dosing regimen is 6.3% (for the 20 kg child) and the highest dose increase is 33.9% (for 14 and 21 kg children). Given the non linear pharmacokinetics of abacavir, less significance was placed on percent difference in the daily dose. Evaluation of the acceptability of the proposed dosing regimen focused on the comparison between historical and predicted PK data as described below.

The table below compares the predicted abacavir exposure following the proposed scored ZIAGEN tablet dosing regimen to the historical pediatric and adult data. The predicted exposure is also compared to the data from the PENTA study. Please refer to the clinical section (Section 6) for further details on the PENTA study.

As discussed previously, there are three weight bands proposed for dosing: 14kg to 21 kg, >21kg to <30kg, and ≥30kg. The doses proposed for the lowest and highest weight bands give equal amount of abacavir both in the am and pm. For the middle weight band, the am and pm doses are unequal. Therefore, an additional q12 hr assessment has been done to evaluate potentially significant over exposure or underexposure.

Table 5: Comparison of Predicted ABC Exposure following the Proposed Scored ZIAGEN Tablet Dose Regimen to Historical Data in Adult and Pediatric Patients

Population	Pediatric	Pediatric	Pediatric	**Pediatric (PENTA)**	**Pediatric1**	**Adult2**	
Weight or age Range	14 to 21kg	>21 to <30kg	≥ 30 kg	**2-13 years**	**6.3-39.7kg**	**Not reported (age >13yrs)**	
Formulation Dose	Half Tab (150mg)	Half Tab (150mg) AM and Full Tab (300mg)	Full Tab (300mg)	**Solution 16 mg/kg**	**Solution 8mg/kg**	**Tablet 300mg**	**Tablet 600mg**
Frequency	q12h	q12h	q12h	**q24**	**q12h**	**q12h**	**q24h**
AUC(0-24), h.µg/mL, geometric mean(CV%)							
Observed	NA	NA	NA	**13.37 (11.80-15.15)**	**19.6 (47%)[1,3]**	**12.0 (29%)[2.3] 300mg BID**	**13.3 (16) [2,4] 600mg once daily**
Monte Carlo simulations	21.3 (32%)	21.9 (33%)	20.5 (30%)	**NA**	**NA**	**NA**	**NA**
Cmax, µg/mL, geometric mean (CV%)							
Observed	NA	NA	NA	**4.80**	**3.71 (37%)1**	**3.00 (30%)[2] 300mg BID**	**4.95 (23%)[2,5] 600mg once daily**
Monte Carlo simulations	3.69 (32%)	4.53 (37%)[6]	3.71 (31%)	**NA**	**NA**	**NA**	**NA**

1. ACTG 330 [RM1998/00100/00], values are mean (CV%), n=45 .
2. CNAA2001 [GM1997/00142/00], values are mean (CV%), n=20.
3. AUC(0-24), daily AUC, was calculated based on AUC(0-12) values reported in the original reports using the following formula: AUC(0-24) = 2 X AUC(0-12).
4. Based on reported AUC(0-τ) value from 600mg TID as there is no accumulation after multiple dose due to short half-life (~1.5hr).
5. Based on reported Cmax value from 600mg TID as there is no accumulation after multiple doses due to short halflife (~1.5hr).
6. Post evening dose (one full tablet).

Cmax:

Overall, the predicted Cmax for Ziagen scored tablet is acceptable across the 3 weight bands. The predicted Cmax are either supported by historical pediatric Cmax or historical adult Cmax.

According to the Monte Carlo simulation, for the 21-30kg weight band, the predicted Cmax is higher than the historical pediatric Cmax (Table 5). The predicted Cmax is 4.53, a 22% increase from historical pediatric Cmax but remains similar to the adult Cmax observed when 600mg is administered as once daily. Furthermore, the PENTA study provides supportive PK (safety and efficacy) data, where subjects received 16mg/kg/dose and the observed Cmax was 4.80 (range 4.04- 5.71), which is similar to the predicted Cmax for this weight band. Please refer to clinical section (Section 6) for details regarding comparison of activity and safety of once daily dosing in children and adults and the rationale behind the acceptability of using once daily dosing in children to support the proposed dosing regimen in the 21-30 kg weight band.

In summary, as the predicted Cmax values for all weight bands remain comparable to historical adult and/or pediatric values, no changes in acute toxicity reporting can be anticipated from Ziagen scored tablet administered as proposed.

AUC_{24}

Based on the Monte Carlo simulation prediction, the AUC_{24} for all 3 weight bands are similar to the historical pediatric AUC_{24} (Table 5).

However the exposures are higher than historical adult exposures. However, note that the original pediatric pharmacokinetic study of abacavir that led to its approval for use in children demonstrated clearance to be higher in younger children when compared to adults. As a result, a dose, which gave a 62% increase in AUC and 24% in Cmax was approved.

AUC_{12} for 21 to <30 kg weight Band

As discussed previously, the proposed dose for the middle weight band group (21- <30 kg) will lead to unequal dosing regimen (half tablet AM/whole tablet PM). To evaluate the potential impact of unequal dosing on the safety and efficacy profiles of ABC, plasma ABC exposures during each dosing interval, AUC_{12}, were estimated by Monte Carlo simulation.

As summarized in table below, subjects weighing >21 to <30kg are likely to have overexposure with the PM dose and underexposure with the am dose.

The average decrease in exposure with the AM dose is by 10% when compared to historical pediatric data but remains 36% higher than historical adult AUC_{12}.

Again, the goal of pediatric dosing is to achieve concentrations similar to adults. The predicted AUC_{12} is bracketed by the historical pediatric AUC_{12} and adult AUC_{12}. Furthermore, a 10% decrease in exposure is unlikely to have significant clinical consequences. For example, no dose adjustment is made for drug-drug interactions where the interaction leads to a 10% decreased exposure.

Table 6: Comparison of Monte Carlo Simulated Steady State ABC Exposures Post Morning and Evening Doses following BID Dosing in Children Taking Scored ZIAGEN Tablets

Study	Simulation	**Penta**	**Historical**			
Population	Pediatric	**Pediatirc**	**Pediatric1**	**Adults2**		
Range of weight (kg)	21 to 30		**6.3 to 39.7**	**>40**		
Formulation ABC Dose/ Frequency	Half tab 150mg AM and full tab/ 300 mg 12 h later	**Solution** **16mg/kg/day**	**Solution** **8mg/kg q12h**	**Tablet** **300mg q12h**	**Tablet** **600mg q24h**	**Tablet** **600mg tid**
N	1000	**14**	**46**	**20**	**20**	
Post Morning Dose						
AUCτ, h.µg/mL						
Geo Mean (CV%)	7.9 (33)	**6.7**	**8.8 (NR)**	**5.8 (NR)**		
Mean (CV%)	8.3 (33)		**9.8 (47)**	**6.0 (29)**	**6.65**	
Median	8.0		**9.0**	**5.8**		
Post Evening Dose						
AUCτ, h.µg/mL						
Geo Mean (CV%)	13.8 (33)	**6.7**	**8.8 (NR)**	**5.8 (NR)**		
Mean (CV%)	14.5 (32)		**9.8 (47)**	**6.0 (29)**	**6.65**	
Median	13.9		**9.0**	**5.8**		

NR = not reported
1. ACTG 330
2. CNAA2001
3. AUCτ was calculated as one-half of the $AUC_{(0-24)}$ values reported in Table 8.

With the PM dose, the predicted geometric AUC_{12} is 13.8 (>57% higher than historical pediatric AUC_{12} and 157% higher than adult AUC_{12}. The predicted mean AUC_{12} is 14.5 (>48% higher than historical pediatric AUC_{12} and 118% higher than adult AUC_{12}). See Clinical Section 6 for summary of data to support the proposed unequal dosing regimen (half tablet AM/whole tablet PM).

Individual weight analysis of the Predicted Pharmacokinetics (AUC, Cmax)

Dr. Zhang further evaluated the potential impact of unequal dosing (half tablet AM/whole tablet PM) on the safety and efficacy profiles of abacavir in children weighing >21 to <30kg. Plasma abacavir exposures during each dosing interval ($AUC_{0\text{-}12h}$ and $AUC_{12\text{-}24h}$) were re-estimated by the FDA with Monte Carlo simulations using the same PK model and same Trial Simulator methods as the applicant but with a weight band increment of 1 kg. The summary of predicted plasma abacavir exposure during each dosing interval ($AUC_{0\text{-}12h}$ and $AUC_{12\text{-}24h}$) and C_{max} from Monte Carlo simulations is presented in Table 7. Based on the calculated estimations, the following conclusions from Dr. Zhang's review are summarized as follows:

1. At the higher end of the (21 – 30 kg) weight band, the lowest mean $AUC_{0\text{-}12h}$ following administration of the half tablet in the morning was 7.0 h-μg/mL, about 30% lower than that of historical pediatric control ($AUC_{0\text{-}12h}$: 9.8 h-μg/mL at 8 mg/kg), but was slightly higher than the adults controls ($AUC_{0\text{-}12h}$: 6.0 h-μg/mL at 300mg BID. The $AUC_{0\text{-}24h}$ at 600 mg once daily in adults is 13.3 h-μg/mL. Because the half-life of abacavir is about 1-1.5 hours, with 600 mg once daily dosing, the $AUC_{12\text{-}24h}$ should be much less than 50% of the $AUC_{0\text{-}24h}$, i.e., the $AUC_{12\text{-}24h}$ value is much less than 6.7 h-μg/mL. Based on the similar efficacy observed in once daily and twice daily dosing in adults, the worst case scenario of 30% lower mean $AUC_{0\text{-}12h}$ receiving half tablet in the morning (7.0 h-μg/mL) is not expected to reduce efficacy.
   The approved dose regimens for adults are 300 mg BID and 600 mg QD. The approved pediatric dose regimen (8 mg/kg) has higher plasma exposures than those of adult dose regimens.

2. At the lower end of the (21 – 30 kg) weight band, the highest mean $AUC_{12\text{-}24h}$ following administration of the full tablet in the afternoon was 15.5 h-μg/mL, about 50% higher than that of historical pediatric control ($AUC_{12\text{-}24h}$: 9.8 h-μg/mL at 8 mg/kg), but was much lower than the adults controls ($AUC_{0\text{-}24h}$: 40.0 h-μg/mL at 600 mg TID). Based on the acceptable safety profile observed in adults receiving 600 mg TID dosing, the worst case scenario of 50% higher mean $AUC_{12\text{-}24h}$ receiving full tablet in the afternoon (15.5 h-μg/mL) is not expected to cause unacceptable safety issues.

Table 7: Monte Carlo Simulations of Abacavir Exposure in Pediatrics Data presented as median (10^{th} percentile to 90^{th} percentile)					
Dosing Regimen	Body Weight (kg)	$AUC_{ss,0-12}$ (μg h mL)	$AUC_{ss,12-24}$ (μg h mL)	$AUC_{ss,0-24}$ (μg h mL)	$C_{max,ss}$ (μg/mL)
Half tab/ (150 mg/q12)	14	12.8 (8.6-18.3)	12.6 (8.7-18.3)	25.5 (18.1-36.0)	4.2 (3.0-6.8)
	15	11.7 (8.4-17.8)	11.8 (8.5-17.9)	23.7 (17.4-35.0)	4.1 (2.9-6.3)
	16	11.6 (7.7-17.2)	11.3 (7.8-17.6)	22.3 (16.3-34.9)	4.1 (2.9-6.1)
	17	11.2 (6.9-16.0)	10.9 (7.0-15.8)	22.5 (14.0-31.5)	3.7 (2.6-5.3)
	18	10.4 (6.9-15.0)	10.5 (7.5-14.7)	20.6 (14.9-29.3)	3.8 (2.6-5.3)
	19	9.7 (6.6-12.9)	9.4 (6.6-13.3)	18.9 (13.9-25.4)	3.3 (2.3-4.9)
	20	9.4 (6.3-14.2)	9.5 (6.0-13.0)	18.9 (13.0-25.7)	3.4 (2.2-4.7)
	14-21				3.8 (2.6-5.8)
Half tab/ 150 mg AM and full tab/ 300mg 12h later	21	8.8 (6.2-12.4)	15.7 (10.3-21.8)	24.4 (18.0-34.1)	5.2 (3.4-9.7)
	22	8.5 (6.0-13.8)	15.5 (10.0-23.5)	24.0 (17.7-37.7)	5.2 (3.3-8.1)
	23	8.5 (5.6-12.3)	15.4 (10.5-21.8)	24.1 (16.7-33.8)	4.5 (2.9-7.3)
	24	8.1 (5.4-12.4)	14.3 (8.7-21.5)	22.4 (15.3-33.4)	4.4 (2.8-7.3)
	25	8.4 (5.5-11.5)	13.8 (8.8-21.1)	21.7 (15.0-30.9)	4.6 (3.0-7.2)
	26	7.9 (4.9-11.2)	13.0 (8.1-19.5)	21 (13.3-30.2)	4.2 (2.7-6.8)
	27	7.6 (5.0-10.9)	12.7 (8.6-18.5)	20.5 (14.3-28.4)	4.2 (2.9-6.3)
	28	6.9 (4.8-10.1)	12.4 (8.2-19.0)	19.1 (13.4-28.1)	4.1 (2.6-6.8)
	29	7.1 (4.6-9.7)	12.2 (7.8-17.1)	19.4 (13.3-25.8)	4.0 (2.6-6.0)
Full tab/ 300mg q12h	30	12.2 (7.7-17.6)	12.4 (8.2-18.0)	23.1 (18.2-34.4)	4.1 (2.8-6.0)
	31	11.5 (7.8-15.9)	11.3 (6.9-15.8)	22.4 (14.3-30.4)	3.9 (2.9-5.8)
	32	11.4 (7.9-15.4)	10.7 (8.0-14.9)	22.0 (16.4-30.5)	3.9 (3.0-5.3)
	33	11.2 (7.0-16.4)	10.4 (7.5-16)	21.2 (15.6-31.4)	3.9 (2.4-6.0)
	34	10.5 (6.5-15.5)	10.6 (6.5-15.8)	20.4 (15.5-31.3)	3.8 (2.6-5.6)
	35	10.4 (6.0-15.1)	11.0 (7.1-16.1)	21.4 (14.7-29.7)	3.7 (2.6-5.3)
	36	9.6 (7.0-14.4)	9.8 (6.6-13.8)	19.4 (14.0-28.7)	3.5 (2.7-5.1)
	37	8.8 (5.6-14.2)	8.7 (6.0-13.9)	17.6 (12.4-28.5)	3.4 (2.3-5.5)
	38	9.2 (5.6-13.9)	9.1 (5.8-13.4)	18.3 (11.6-26.6)	3.3 (2.3-4.6)
	39	9.3 (5.9-13.5)	9.7 (6.3-13.6)	19.0 (13.0-27.0)	3.4 (2.2-5.0)
	30-40	10.4 (6.5-15.3)	10.3 (6.7-15.4)	20.6 (14.1-29.9)	3.7 (2.5-5.5)
Pediatrics (8mg/kg) (Study ACTG 330)				Mean (%CV) 19.6 (47)	Mean (%CV) 3.7 (37)
Pediatrics (16 mg/kg q.d.) (Study PENTA 13)				GM (90%CI) 13.4 (11.8-15.1)	GM (90%CI) 4.8 (4.0-5.7)
Adults 600 mg t.i.d (Study CNAA2001)				Mean (%CV) 40.0 (25)	Mean (%CV) 7.0 (42)

Source: Dr Derek Zhang's Review

6. Clinical

6.1 Safety

Clinical studies with safety and PK data were important in supporting the currently proposed dosing regimen, particularly for those instances where a pediatric patient may receive higher exposure than what is currently approved.

The characteristics of abacavir have been well described. Abacavir has been extensively studied in adults at doses similar to or higher than the currently approved doses. Despite higher doses administered, the safety profile remained comparable among the adult clinical trials. In addition, although abacavir is

approved for children at a higher dose than the adult BID dose (i.e. when compared on a mg/kg basis), the safety profile in pediatrics remained similar to adults. Finally, when abacavir was administered to children at higher doses than the currently approved pediatric dose, no significant changes were noted in the adverse events profile. Below are discussions of the various studies conducted in adults and pediatrics.

Although limited experience is available for abacavir at higher dose (or exposure) than 8mg/kg BID in children, studies (with PK and safety data) are available on adults who received higher doses (exposures), providing insight into the safety profile that may be observed in children who are administered higher abacavir dose and include:

- Phase 2 adult clinical trial in which doses up to 600 mg TID were administered (12 week study) in adults, the adverse event profile remained similar to those reported with abacavir 300 mg BID. With exception of nausea and dizziness no significant increase in *frequency* of adverse events was seen.

- The adverse event profile has not changed significantly in adults after approval of 600 mg once daily.

- A study conducted in adults has shown that there is no exposure-safety relationship for abacavir. In fact nausea was the only adverse event slightly associated with a higher Cmax.

- The most serious adverse event associated with abacavir is hypersensitivity reaction. Hypersensitivity reaction is considered an idiosyncratic reaction. The lowest doses administered are likely to surpass the threshold required for triggering a reaction; therefore, an increased dose should not have bearing on incidence of hypersensitivity reactions. Furthermore, the Ziagen label has been recently updated to recommend HLA hypersensitivity skin testing prior to starting treatment with Ziagen.

Study CNAA3006 was used to support the original approval of abacavir in pediatrics. The study was a double-blind, randomized, multicenter trial to evaluate the safety and efficacy of the combination of abacavir/zidovudine/lamivudine vs. placebo/zidovudine/lamivudine in HIV-1 infected treatment experienced pediatric patients. Two hundred and five subjects (n=102 abacavir arm; n=103 placebo) between the ages of 6 months and 13 years were enrolled. At Week 48, the most common (all grades) AEs reported (for the abacavir containing arm, n=102) included nausea and vomiting (46%), cough (46%), fever (36%), diarrhea (20%), headache (21%) and skin rash (16%). Commonly reported Grade 3 and 4 laboratory toxicities were increased ALT and

AST (2%, 3%, respectively), hyperglycemia (2%), neutropenia (4%) and elevated amylase (4%). During the course of the 48 weeks period, 8 patients who received ABC/3TC/ZDV discontinued due to adverse events (4 due to nausea and/or vomiting, 3 due to fever, 2 due to rash). In addition, 4(3%) cases of possible ABC-related hypersensitivity reactions were observed during the 48 weeks and subsequent open-label treatment periods. Overall, the adverse events reported during this trial were similar to adults.

Two pediatric studies have been conducted using abacavir once daily dosing or doses higher than the currently recommended dose. These studies are summarized below.

The Pediatric European Network for Treatment AIDS (PENTA 13) published a study in Antiviral Therapy (2004) titled, "*Plasma pharmacokinetics of once-versus twice-daily Lamivudine and abacavir: simplification of combination treatment in HIV-1 infected children (PENTA-13)"*. The aim of the study was to compare the pharmacokinetics of abacavir/Lamivudine administered once-daily to twice daily. Twenty four subjects (aged 2 to 13 years) receiving combination treatment containing lamivudine and/or abacavir (8mg/kg) BID were enrolled into this single arm, open-label, crossover study. Subjects were followed for 24 weeks to evaluate safety and antiviral activity.

The safety of the q24h regimen appears to be similar to that of the q12h regimen. No subject discontinued the once-daily treatment during the 24 weeks of follow-up. One subject experienced grade 3 neutropenia (week 12) but the event resolved before week 24.

Additionally, a small GSK supported study (CNA30018) investigated high dose ABC solution at 12 mg/kg twice daily (maximum dose 600 mg) in combination with two or three other antiretroviral (ARV) drugs to treat HIV- associated encephalopathy in children. The dose of ABC used in this study was 50% higher than the approved 8 mg/kg BID dose of ABC in children. Seventeen children (59% female) between the ages of 30 months to almost 15 years (median 59 months/4.9 years; mean 6.3 years) were enrolled.

Overall, abacavir was well tolerated. A total of 79% had non serious AE. Among the common AEs were skin rash (non-hypersensitivity related) (50%), vomiting (28%), fever (28%), diarrhea (14%), anemia (14%), increased triglycerides or cholesterol (14%) and increased ALT or AST (14%). All AEs were mild to moderate except for one (pneumonia).Two children (11.8%) had a possible hypersensitivity reaction to abacavir and both withdrew from the study.

6.2 Efficacy

Based on the Monte Carlo simulation, the lowest predicted exposure is expected at the higher end of the 21 – <30 kg weight band following administration of the

half tablet in the morning (i.e. 7.0 h-μg/mL). The exposure is about 30% lower than that of historical pediatric control (AUC_{0-12h}: 9.8 h-μg/mL at 8 mg/kg), but remained higher than the adults controls (AUC_{0-12h}: 6.0 h-μg/mL at 300mg BID). Therefore, no significant change in efficacy is expected with the proposed dosing regimen.

Furthermore, a once daily dosing regimen has been approved in adults. The AUC_{24} at 600 mg once daily in adults is 13.3. The AUC_{12} is expected to be significantly lower than 50% of the AUC_{24}, as the half life of abacavir is only 1-1.5 hours. Therefore, one would predict the AUC_{12} value to be considerably less than 6.7. Nonetheless, the once daily dosing regimen in adults has been shown to be as effective as the BID regimen.

The PENTA study in the pediatric population also documented the effectiveness of once daily dosing in children older than 2 years of age. The study tried to enroll subjects who were on successful HAART regimen (i.e. viral load <100 copies/mL); the HARRT regimen had to include abacavir and/or lamivudine BID. The objective of the study included assessment of efficacy (i.e. to evaluate if subjects maintained viral load <100 copies/mL at week 24). At baseline, 16 out of the 20 children had a viral load < 100 copies/mL. At the end of the follow-up period, 17 out of the 19 children had viral load <100 copies/mL. The one child who missed the week 24 viral load measurement had undetectable viral load measurement throughout the study period.

Of note is the improved efficacy noted with the PENTA study when compared to the original pediatric study, CNAA 3006. The results from study CNAA 3006 provided limited evidence of the efficacy of abacavir when used in combination with lamivudine and zidovudine. The likely explanation of the unimpressive effectiveness demonstrated during CNAA 3006 is the suboptimal regimen. No PI or NNRTI was added to the treatment regimen. Rather, the two comparative regimens were 3 NRTIs vs. 2 NRTIs.

Based on the similar efficacy observed in once daily and twice daily dosing in adults (and pediatrics), the worst case scenario of 30% lower mean AUC_{12} that is expected when receiving half tablet in the morning is not expected to reduce efficacy.

7. Labeling

The following is the proposed dosing regimen by GSK. Based on the pharmacokinetic analysis, the proposed recommendations are acceptable.

Weight (kg)	Dosage Using 150 mg Tablet		Total Daily Dose
	AM Dose	PM dose	
14 to 21	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21 to <30	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30	1 tablet ((b) (4) mg)	1 tablet ((b) (4) mg)	600 mg

8. Recommendations/Risk Benefit Assessment

Abacavir has been approved since 1998. The safety, tolerability and efficacy of abacavir are well-established and considered a preferred nucleoside reverse transcriptase inhibitor for treatment-naïve pediatric patients by the DHHS treatment guidelines. The available data show similar safety profile and efficacy outcomes in pediatric and adult patients. No new efficacy data were submitted with this sNDA; safety and efficacy evaluation relied on our previous findings from the original approval and additional studies conducted by GSK or independent investigators. The predicted exposures from the proposed dosing regimen with Ziagen scored tablets appear to be similar to historical adult and pediatric data. Deviations from the historical exposure data do not appear to compromise efficacy or safety.

Considering the proposed scored tablet regimens, in most scenarios higher abacavir exposures are predicted; therefore, efficacy is not expected to be compromised. Even at the lowest dose or exposure, the predicted exposures remain higher than the adult. The primary objectives for evaluating dosing recommendations were to avoid under dosing and minimize over dosing. The goal was to match the predicted PK parameters to adults. Based on the review of the proposed dosing regimens and previous abacavir studies, no significant risks compromising the efficacy of abacavir in pediatric patients have been identified.

The total daily exposures are bracketed by existing historical pediatric and adult data and provide sufficient safety experience to support the proposed dosing recommendations. Although the daily exposures for all the weight bands do not lead to significant variation from previous pediatric data, the available safety data are limited from adults and children to support the predicted increase in exposures in children weighting 21-30 kg during the PM dose.
The following key points were considered when evaluating the increased exposures following the PM dose.

- The safety in adults and children appear similar despite the higher dose (in mg/kg) and exposure seen with the 8mg/kg dose in children compared to 300 mg bid in adults.

- No dose (exposure) – safety relationship has been established for abacavir. A study conducted in adults has shown that there is no exposure-safety relationship for abacavir. In fact nausea was the only adverse event slightly associated with a higher Cmax. For all weight groups (including the middle weight group), the Cmax was comparable to either adult or pediatric historical Cmax; therefore no increase in toxicity is expected with the currently proposed dose.

- Nausea is potentially minimized by administering the full tablet for the 21-30 kg group in the evening, as proposed by GSK. Furthermore, the predicted Cmax remained similar to the historical pediatric Cmax value (see Table 5).

- The safety of the q24h regimen from the PENTA study appears to be similar to the safety from the q12h regimen. More importantly, no significant changes in safety were reported from Study CNA30018 when the dose was increased by up to 50%.

- The most serious adverse event associated with abacavir is hypersensitivity reaction. Hypersensitivity reaction is considered an idiosyncratic reaction. The lowest doses administered are likely to surpass the threshold required for triggering a reaction; therefore, an increased dose should not have bearing on incidence of hypersensitivity reactions. In addition, Ziagen label has been recently updated to recommend HLA hypersensitivity skin testing prior to starting treatment with Ziagen.

- During the Phase 2 adult clinical trial, doses up to 600 mg TID were administered (12 week study) in adults. The adverse event profile remained similar to those reported with abacavir 300 mg BID. With exception of nausea and dizziness no significant increase in frequency of adverse events was seen.

- The adverse event profile has not changed significantly in adults after approval of 600 mg once daily. However, as reported in the abacavir sulfate label, higher incidences of severe drug hypersensitivity reactions and severe diarrhea were seen in one study where once daily treatment was administered.

Overall, the safety profile is similar between adults and pediatric subjects, with exception of reporting of more skin rash (not restricted to hypersensitivity rash). Although hypersensitivity is the most serious adverse event associated with abacavir, no dose response relationship is thought to exist. As stated previously, the currently Ziagen label recommends that patients be screened for HLA hypersensitivity prior to starting Ziagen.

Finally, patients are expected to transition to different weight bands as they grow, minimizing the length of any potential over-exposure. The availability of a tablet formulation for pediatric population is of significant importance as it relates to improved tolerance and compliance.

I recommend the approval of Ziagen scored tablet (300 mg) for the treatment of HIV-1 infection in pediatric patients weighing ≥14 kg. The dose recommendations are based on weight. These dose recommendations are anticipated to allow development for scored (b) (4) tablets. The submitted labeling has been reviewed and allows for the safe and effective use of the product. The labeling already includes important information regarding hypersensitivity reaction.

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/s/

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