CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-003/SE1-002

21-004/SE1-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA : 21-003/21-004 (SE1-002)
TYPE : sNDA HBV Pediatric
DRUG : Lamivudine
SPONSOR: GlaxoSmithKline™

REVIEWER: Jen DiGiacinto, Pharm.D.
SUBMISSION DATE: 27FEB2001
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Purpose

The purpose of this sNDA (21-003 and 21-004) is to support labeling of Epivir-HBV™ Tablets and Oral Solution for the treatment of hepatitis B infection in pediatric patients between the ages of 2 and 17.

Background

This sNDA includes study reports for three studies NUCB2020, NUC30903, [redacted] NUCB2020 is a Phase II study designed to gain dosing and safety information that would facilitate the design of a Phase III trial in HBV-infected pediatric patients.

The results of NUCB2020 were first submitted in NDAs 21-003 and 21-004 and are included in this sNDA. Dr. Prabhu Rajagopalan reviewed these results initially and has a review on file.

The Sponsor designed NUC30903; a Phase III, double-blinded, placebo-controlled multi-centered study; to look at safety and efficacy in chronic HBV-infected pediatric patients ages ≥ 2 to < 18 years over a period of 52 weeks (N=286). The dose administered in this study was based on the results of NUCB2020.

[redacted]

NUCB2020

Study Design

This was a one-month dose-finding study with a 12-week follow up period conducted in pediatric subjects with HBV-infection. HBV-infection was defined as detectable HBV surface antigen (HBsAg) in the serum at screening and 6-months prior to screening, HBeAg and HBV DNA in the serum at screening, and ALT/AST below 3000 IU/L.

The subjects (age two years to twelve years) were randomized to receive one of the following 4 doses:

- 0.35 mg/kg po BID
- 1.5 mg/kg po BID
- 3.0 mg/kg po QD
- 4.0 mg/kg po BID

These 4 dosing regimens were administered to the subjects as the oral solution formulation. Subjects ages 13-17 years all received 100-mg po QD (the approved adult dose) as the tablet formulation.

The subjects were stratified by age, with 17 subjects in Stratum 1 (2-6 yo), 23 in Stratum 2 (7-12 yo), and 12 in Stratum 3 (13-17 yo).

Visits to the study site included screening days, day 1, days 14 and 28 during the treatment phase, and at week 4, 8, and 12 weeks after treatment completion.

Pharmacokinetic Blood and Urine Samples

Serial blood samples were collected on Day 1 and 28 at pre-dose and at 0.5, 1, 2, 4, 8, and 12 hours post dose. An extra blood sample was collected at 24 hours post-dose on Day 28. On Day 14, one blood sample was collected pre-dose for a trough comparison.

On Day 1 urine was collected at baseline, 0-6, and 6-12 hours for the 4-mg/kg BID dosing group.

Study Results

- N=53 As Treated Population
- N=52 Modified Intent to Treat Population- One subject did not have evidence of HBsAg for the entire six months prior to screening.

Regardless of formulation administered, Tmax, Cmax, and CL_f values generated were similar to data observed in previous HIV studies in similar patient populations. The exposure (AUC) was proportional to dose, except the 0.35 mg/kg BID group.

Oral clearance estimates were consistent with those seen in studies in HIV-infected pediatric patients, which show CL/F values peak at 2 years of age and decline with age to about 12 years, where values are similar to adults.

Study Results Continued

Table 1. Lamivudine Pharmacokinetic Parameters (Geometric Mean and 95% CI)

Parameter	Day	0.35 mg/kg BID N=8	1.5 mg/kg BID N=11	3 mg/kg QD N=11	4 mg/kg BID N=11	100 mg Tablet QD N=12
Tmax (hrs)	1	0.51 (0.51-1.02)	0.51 (0.51-2.03)	0.51 (0.51-2.03)	0.51 (0.51-4.07)	1.02 (0.51-4.07)
	28	1.02 (0.51-2.03)	1.02 (0.51-2.03)	0.51 (0.51-2.03)	1.02 (0.51-1.02)	1.02 (0.51-2.03)
Cmax ng/mL	1	257 (192-345)	971 (753-1253)	1573 (1173-2110)	2177 (1862-2546)	1392 (1073-1804)
	28	286 (166-492)	798 (637-999)	1855 (1440-2390)	2760 (2338-3259)	1496 (1233-1816)
AUC_{last}[b] ng•hr/mL	1	660 (491-886)	2296 (1969-2678)	4057 (3247-5068)	6399 (5788-7075)	4504 (3951-51330
	28	857 (708-1039)	2616 (2217-3085)	5784 (4899-6829)	7562 (6062-9432)	5414 (4656-6297)
AUC∞ ng•hr/mL	1	675 (503-905)	2353 (2019-2743)	4160 (3343-5177)	6540 (5911-7236)	4639 (4072-5286)
t½ (hrs)	1	2.09 (1.92-2.27)	2.16 (1.95-2.39)	2.14 (1.78-2.58)	1.95 ()1.75-2.17	2.70 (2.03-2.39)
	28[a]	3.40 (2.87-4.03)	2.985 (2.12-4.11)	7.56 (5.13-11.15)	2.52 (2.14-2.97)	6.45 (4.75-8.77)
Cmin[c] ng/mL	28	13 (9-36)	33 (24-58)	24 (13-73)	72 (59-203)	29 (26-37)
CL_{renal} mL/min	Day 1	NC	NC	NC	256 (205-318)	NC
R[d]	Day 28	1.32 (0.87-1.91)	1.17 (0.81-1.57)	1.19 (0.94-3.50)	1.19 (0.78-1.79)	1.11 (0.67-1.63)

[a] Day 28 values for t½ are greater when sampling is to 24 hours, i.e., in the QD regimen group
[b] AUC_{last} = AUC to last measured time point, i.e., 12 or 24 hours for BID or QD dosing schedules
[c] Median (range)
[d] Tmax and accumulation ratio, R, are shown as median (min-max)
NC = not calculated

- The adolescent group (13-17 years) had pharmacokinetic parameter estimates similar with those seen in previous adult studies.
- Trough values in all subjects were similar between Day 14 and Day 28.
- There were detectable lamivudine levels in all samples.

The median trough value for subjects in the 3-mg/kg QD regimen was 24 ng/mL (range [redacted]). *In vitro* experiments conducted in hepatoma cell lines have shown an extracellular concentration of ≥ 4-7 ng/mL is required to inhibit HBV by 50% (IC_{50}).

Pharmacokinetic/Pharmacodynamic Dose-Response in HBV-Infected Adults, Children and Adolescents

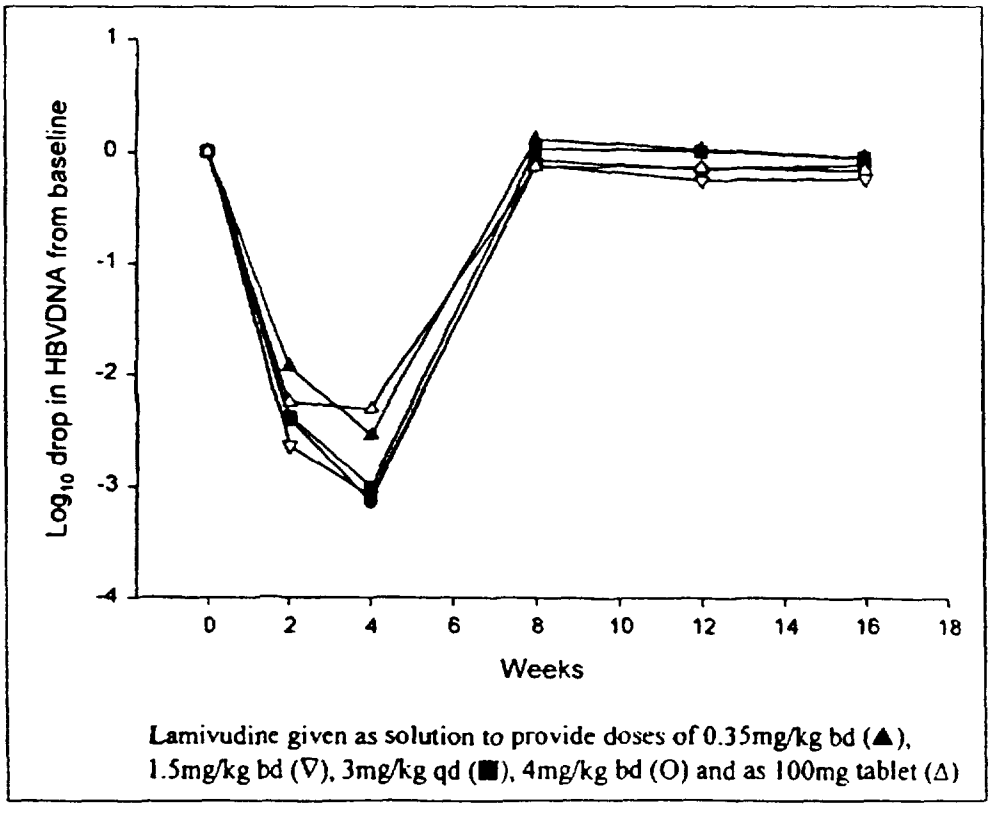
NUCB2002 and NUCA2003 were the first 1-month dose-ranging clinical studies conducted in HBV-infected adults in North America and Europe. These studies helped develop a pharmacokinetic-pharmacodynamic relationship for lamivudine in HBV-infected subjects. A relationship between lamivudine dose, AUC and reduction in the primary serological marker, serum HBV DNA exists. AUCτ (τ = 24 hours) correlates with a reduction in HBV DNA; however, an AUC above 4000 ng•hr/mL does not provide any further reduction in serum HBV DNA. The Sponsor offers the explanation that systemic exposure is directly linked to intrahepatocyte concentrations and tri-phosphate production and ultimately suppression of the virus in a dose-dependent manner.

The data from Study NUCB2002 were fit using a [redacted] The model demonstrates that doses of lamivudine that provides an AUC of 3300 ng•hr/mL will achieve an EC_{98}. Additionally, this model showed little gain in viral suppression for larger lamivudine doses. An adult dose of 100-mg QD provides a mean AUC of 4400 ng•hr/mL (Study NUCB2002) and provides 99% inhibition. However, the relationship between drug exposure and long-term efficacy is not known.

Children and Adolescents

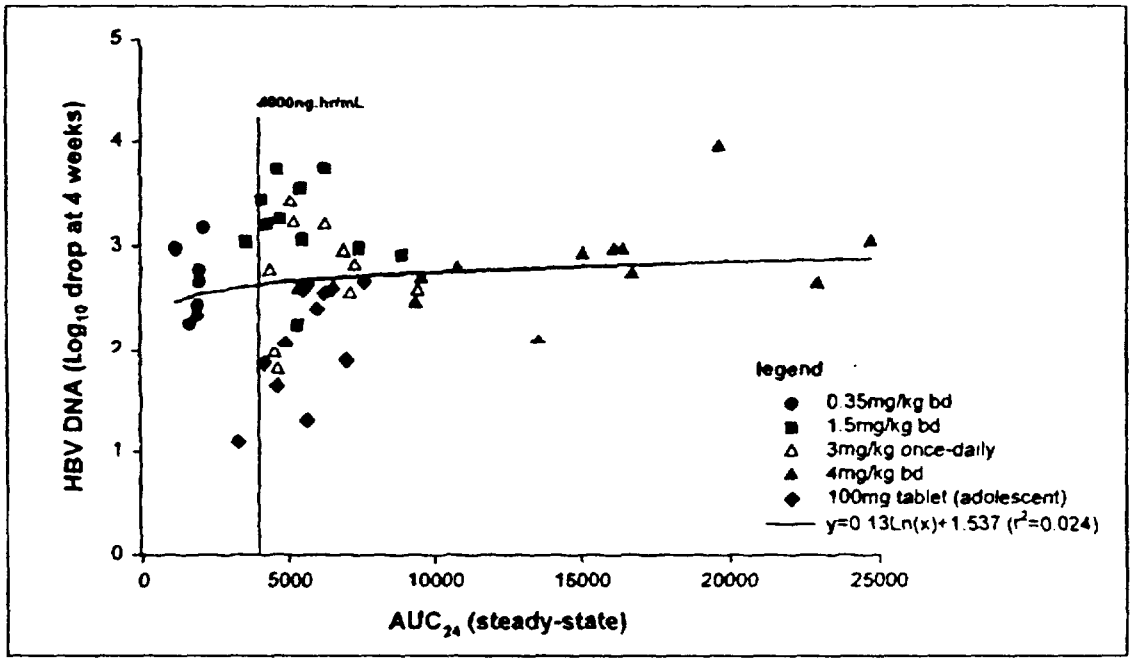
The pharmacokinetic/pharmacodynamic relationship was examined for NUCB2020.

Mean Change from Baseline in Log10 HBV DNA (pg/mL): Modified Intent to Treat Population (NUCB2020)



Lamivudine given as solution to provide doses of 0.35mg/kg bd (▲), 1.5mg/kg bd (▽), 3mg/kg qd (■), 4mg/kg bd (O) and as 100mg tablet (Δ)

HBV DNA Reduction [redacted] (log_{10} copies/mL) Versus Exposure at Steady State



Dose Justification in HBV-Infected Children and Adolescents

Younger pediatric patients have increased renal clearance and lower lamivudine bioavailability compared to adults. For this reason, children between the ages of 2-11 years should received 3-mg/kg/day of lamivudine administered once daily to achieve similar exposure as in adults receiving 100-mg QD. Adolescents (12-17 years and > 35 kg) have similar renal clearance values to adults and should follow the recommended adult dose of lamivudine (100-mg QD). These doses should provide a minimum daily AUC of approximately 4000 ng•hr/mL and trough concentrations > IC_{50} (5-7 ng/mL). The applicant evaluated lamivudine 3-mg/kg/day in children < 12 years old and 100-mg QD in adolescents in the safety and efficacy study NUC30903.

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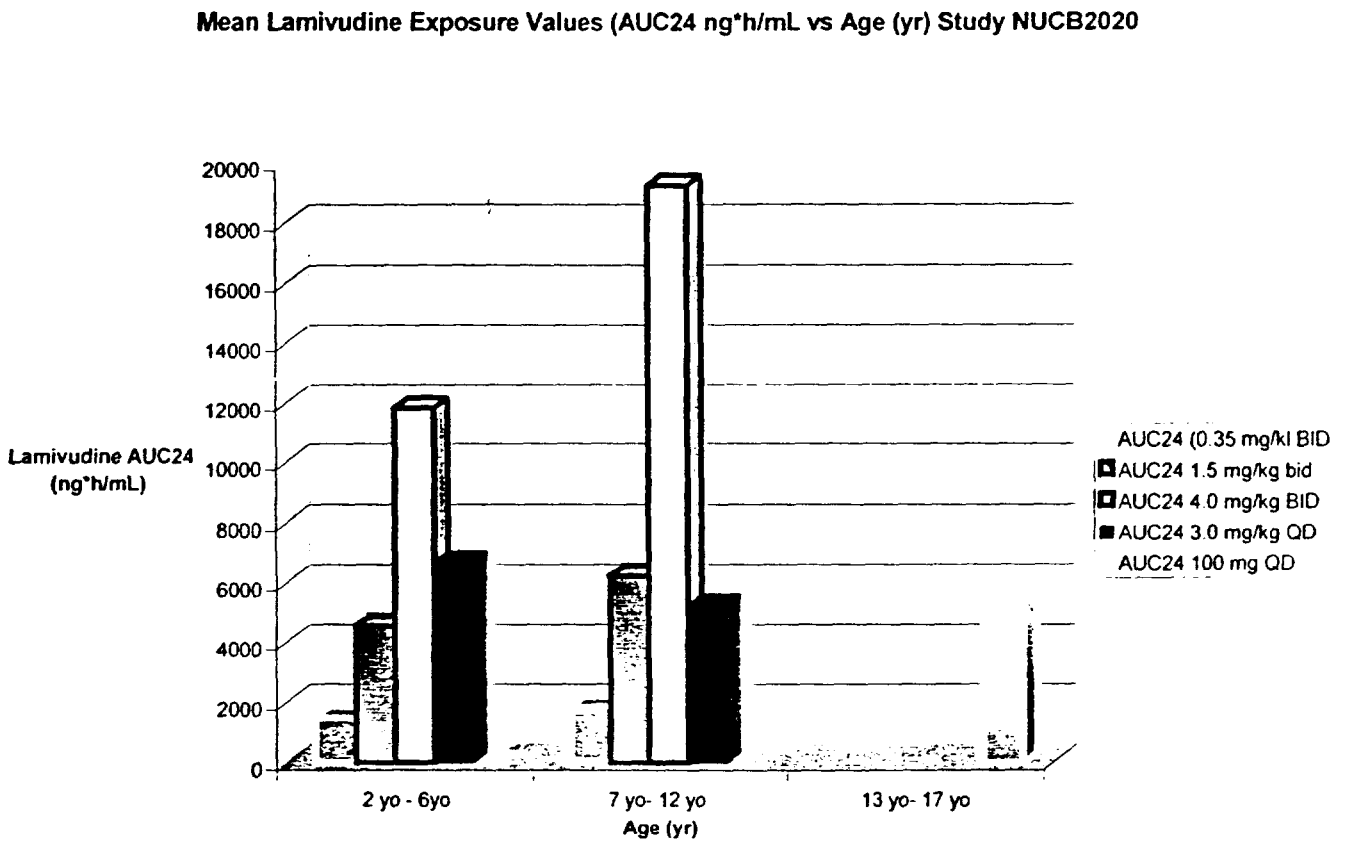
Mean Lamivudine Exposure Values vs. Age Graph for Lamivudine from NUCB2020



Assessment/Conclusion

The Sponsor provided pharmacokinetic data that support the evaluation of 3.0-mg/kg QD and 100-mg QD in children and adolescents for treatment of HBV-infection. The selected doses provide lamivudine exposures similar to the exposure in adults treated for HBV. Please refer to Dr. Melisse` Baylor's review for information regarding the safety and efficacy of lamivudine in the treatment of HBV-infection in the pediatric population.

/S/

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Concurrence: /S/ - 8-13-01

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