# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA | 21797 S-18 and 21798 S-19 |
| Submission date | 9/20/3013 |
| Brand Name | Baraclude |
| Generic Name | Entecavir |
| OCP Division | DCP IV |
| OND Division | Division of Antiviral Products |
| Applicant | Bristol-Myers Squibb |
| Formulation | Tablet: 0.5 mg and 1.0 mg<br>Oral solution: 0.05 mg/mL |
| Indication | Treatment of chronic hepatitis B (CHB) infection |
| Dosage and Administration | Nucleoside-treatment-naïve with compensated liver disease: 0.5 mg once daily (adults and adolescents at least 16 years of age)<br>Lamivudine refractory or known lamivudine or telbivudine resistance mutations: 1.0 mg once daily (adults)<br>Decompensated liver disease: 1.0 mg once daily (adults)<br>Baraclude should be administered on an empty stomach. |
| Clinical Pharmacology Reviewer | Su-Young Choi, Pharm.D., Ph.D |
| Pharmacometrics Reviewer | Jeffry Florian, Ph.D |
| Clinical Pharmacology Team Leader | Shirley Seo, Ph.D |
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# Contents

# 1. Executive summary

Entecavir (Baraclude®) is approved for the treatment of chronic hepatitis B (CHB) infection who are treatment-naïve (0.5 mg once daily in adults and adolescents at least 16 years of age), are lamivudine refractory (or have known lamivudine or telbivudine resistance mutations; 1.0 mg once daily in adults), or have decompensated liver disease (1.0 mg once daily in adults).

The purpose of this supplemental NDA submission is to support the use of entecavir for the treatment of chronic hepatitis B infection in treatment-naïve pediatric patients at least 2 years of age and weighing at least 10 kg. The proposed dosing regimen is [redacted] (b) (4) 0.5 mg once daily. The applicant's proposed indication is limited to treatment-naïve pediatric patients due to the reduced efficacy and increased potential for emergent resistance in lamivudine-experienced adult patients. However, DAVP is currently reviewing whether an indication can be granted for lamivudine-experienced pediatric subjects who may not have an alternative option for HBV treatment.

To support approval, the applicant submitted the following study reports (AI463028 and AI463289). The proposed indication (CHB treatment in treatment-naïve pediatric patients) is primarily based on the study results from AI463289, the phase 3 trial comparing the efficacy and safety of entecavir to those of placebo. The results from AI463028 were used to determine the dosing regimen (0.015 mg/kg once daily up to a maximum dose of 0.5 mg) used in AI463289.

1. AI463028: Evaluation of the pharmacokinetics, safety, tolerability and efficacy of entecavir in pediatric subjects with chronic hepatitis B virus (HBV) infection who are HBeAg-positive.

The primary purpose of this study was to determine the doses of entecavir in pediatric patients that produce drug exposures comparable to those observed in adults. The pharmacokinetic results contained in the interim study reports were submitted previously and evaluated by the Office of Clinical Pharmacology (OCP). Upon review, The Division of Antiviral Products (DAVP) agreed that the proposed pediatric doses, [redacted] (b) (4) of 0.5 mg once daily for treatment-naïve pediatric patients and 0.030 mg/kg up to a maximum dose of 1 mg once daily for lamivudine-experienced patients were acceptable for further evaluation in Study AI463289. The study report in this submission is a 120-week report containing the safety, efficacy, and pharmacokinetic results. There are no new pharmacokinetic data since the last study report.

2. AI463289: A comparative study of the antiviral efficacy and safety of entecavir vs. placebo in pediatric subjects with chronic hepatitis B virus infection who are HBeAg-positive.

The primary purpose of this study was to determine safety and efficacy (combined primary endpoints of achieving HBV DNA suppression and hepatitis B e-antigen seroconversion at week 48) in pediatric patients. Although Study AI63028 included lamivudine-experienced patients, the applicant decided not to include lamivudine-experienced pediatric patients in this trial due to the reduced efficacy and increased potential for emergent resistance observed in lamivudine-experienced adult patients. In this trial, semi-intensive and sparse PK samples were obtained and used to confirm the appropriateness of the proposed doses and for population pharmacokinetic analyses.

## 1.1 Recommendation

From a clinical pharmacology perspective, we concur with the applicant's proposed dosing regimen with some changes to the final recommended dose for each body weight band.

- For the treatment of chronic hepatitis B infection in treatment-naïve pediatric patients at least 2 years of age and weighing at least 10 kg; (b) (4) 0.5 mg once daily.

The sponsor's original proposed dosing regimen for each weight band is listed in Table 1. While these weight bands and doses are reasonable from an exposure-matching perspective, the (b) (4) increment and non-integer body weight bands may reduce readability of the table and could potentially lead to a dosing error. Therefore, DAVP has provided two dosing options (Table 2) to the applicant and requested that they select one. Both of the dosing options are acceptable from a clinical pharmacology perspective. Also, as DAVP is currently reviewing whether an indication can be granted for lamivudine-experienced pediatric subjects who may not have an alternative option for HBV treatment, the tentative dosing schedule for lamivudine-experienced pediatric subjects was included in the revised table. DAVP is currently awaiting a response from the applicant.

**Table 1. Applicant's original proposed dosing schedule for pediatric patients**

| Body Weight | Recommended Once-Daily Dose of Oral Solution[a] |
|---|---|
| (b) (4) | |

**Table 2. Revised dosing schedule for pediatric patients**

| **Option 1: Dosing Schedule for Pediatric Patients** | | |
|---|---|---|
| | **Recommended Once-Daily Dose of Oral Solution (mL)** | |
| **Body Weight (kg)** | **Treatment-Naïve Patients[a]** | **Lamivudine-Experienced Patients[b c]** |
| 10 to 11 kg | 3 | 6 |
| greater than 11 to 14 kg | 4 | 8 |
| greater than 14 to 17 kg | 5 | 10 |
| greater than 17 to 20 kg | 6 | 12 |
| greater than 20 to 23 kg | 7 | 14 |
| greater than 23 to 26 kg | 8 | 16 |
| greater than 26 to 30 kg | 9 | 18 |
| greater than 30 kg | 10 | 20 |

| **Option 2: Dosing Schedule for Pediatric Patients** | | |
|---|---|---|
| | **Recommended Once-Daily Dose of Oral Solution (mL)** | |
| **Body Weight (kg)** | **Treatment-Naïve Patients[a]** | **Lamivudine-Experienced Patients[b c]** |
| 10 to 12 kg | 3.5 | 7 |
| greater than 12 to 14 kg | 4 | 8 |
| greater than 14 to 17 kg | 5 | 10 |
| greater than 17 to 20 kg | 6 | 12 |
| greater than 20 to 23 kg | 7 | 14 |
| greater than 23 to 26 kg | 8 | 16 |
| greater than 26 to 30 kg | 9 | 18 |
| greater than 30 kg | 10 | 20 |

[a] Children with body weight at least 32.6 kg should receive 10.0 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily.

[b] Children with body weight at least 32.6 kg should receive 20.0 mL (1.0 mg) of oral solution or one 1.0 mg tablet once daily.

[c] Baraclude should only be used in lamivudine-experienced pediatric patients who do not have other treatment options.

## 1.2 Phase IV Commitments

There are no post marketing commitments or requirements

## 1.3 Important clinical pharmacology and biopharmaceutics findings

This section describes key evidence that supports an indication for entecavir in treatment of chronic hepatitis B (CHB) in pediatric patients. The following two clinical trials were submitted for review.

**Trial AI463028**

This is an open-label study assessing the PK, safety, tolerability, and preliminary efficacy of entecavir in pediatric subjects (2 to < 18 years of age) with HBeAg-positive chronic HBV infection. The primary object of this study was to determine the doses of entecavir in pediatric CHB patients that produce drug exposures comparable to those observed in adults administered clinical doses (0.5 mg in treatment naïve adult patients and 1.0 mg in lamivudine-refractory adult patients). Subjects were enrolled into 3 age cohorts (2 to ≤ 6, 6 to ≤ 12, and 12 to ≤ 18 years of age) and 3 treatment groups (treatment-naïve, lamivudine-experienced, and patients with a history of treatment failure with any non-entecavir nucleosides). The tested doses in this study were 0.015 mg/kg up to a maximum dose of 0.5 mg once daily in treatment-naïve subjects and 0.030 mg/kg up to a maximum dose of 1.0 mg once daily in lamivudine-experienced subjects and subjects with a history of previous treatment failure. Intensive PK samples were collected at Week 2 and efficacy endpoints (plasma HBV DNA, ALT, HBeAg seroconversion) were determined through 96 weeks.

For the treatment-naïve group, the target exposure range for $AUC_{tau}$ was within ±30% (13.1-24.3 ng·hr/mL) of the median exposure ($AUC_{tau}$18.7 ng·hr/mL) estimated from the phase 2 population PK assessment (AI463027). As entecavir demonstrated linear PK up to a dose of 1.0 mg/kg, the target exposure range for the lamivudine-experienced group was 26.2 to 48.6 ng·hr/mL (±30% of 37.4 ng·hr/mL).

**Study results**

Study population

A total of 24 subjects in the treatment-naïve group and 19 subjects in the lamivudine-experienced group were enrolled as described in Table 3. PK sampling was optional for subjects with a history of treatment failure with any non-entecavir nucleosides and no pharmacokinetic sample was collected in this group.

**Table 3. Pharmacokinetic population in each age cohort and treatment group**

| | treatment-naïve,<br>0.015 mg/kg once daily<br>(maximum 0.5 mg) | Lamivudine-experienced<br>0.03 mg/kg<br>(maximum 1 mg) |
|---|---|---|
| Cohort I ≥2 to 6 ≤ yo | N=7 | N=3 |
| Cohort II >6 to ≤ 12 yo | N=9 | N=7 |
| Cohort III >12 to ≤ 18 yo | N=8 | N=9 |

Pharmacokinetic Results

The key pharmacokinetic parameters in each age cohort and adult historical data are summarized in Table 4. Overall, the doses of entecavir tested in pediatrics (0.015 mg/kg up to 0.5 mg once daily for treatment-

naïve patients and 0.030 mg/kg up to 1.0 mg once daily for lamivudine-experienced patients) delivered comparable exposures ($AUC_{tau}$) relative to adults. In both treatment groups, numerically lower entecavir exposures ($AUC_{tau}$) were observed in adolescent patients when compared to adult historical data but fell within the pre-defined target exposure. Higher $C_{max}$ values, approximately 1.5- to 2-fold higher relative to adults, were observed in the 2 to ≤ 6 and 6 to ≤ 12 years old cohorts. While it is unclear why the $C_{max}$ was increased in younger pediatric patients, it is unlikely to pose a significant safety concern based on the lack of an exposure-response relationship for the major adverse events.

**Table 4. Entecavir pharmacokinetic parameters observed in pediatric patients and adults (historical).**

| | **Treatment-naïve subjects** | | | **Lamivudine-experienced subjects** | | |
|---|---|---|---|---|---|---|
| | **AUCτ (ng·h/mL)** | **$C_{max}$ (ng/mL)** | **$C_{min}$ (ng/mL)** | **AUCτ (ng·h/mL)** | **$C_{max}$ (ng/mL)** | **$C_{min}$ (ng/mL)** |
| Cohort I 2 to 6 ≤ years | 17.0 (15.7-26.2) | 8.1 (24) | 0.24 (32) | 40.06 (33.5-56.3) | 16.0 (8) | 0.47 (17) |
| Cohort II > 6 to ≤ 12 years | 20.5 (14.1-25.8) | 6.3 (25) | 0.32 (22) | 43.91 (29.7-53.1) | 19.1 (15) | 0.49 (32) |
| Cohort III >12 to < 18 years | 15.4 (12.0-22.0) | 5.1 (27) | 0.27 (25) | 32.33 (26.0-51.4) | 11.3 (37) | 0.45 (24) |
| Adult[a] (Historical) | **18.7 (11.0-59.4)** | 4.2 | 0.3 | 37.4[b] (26.2-48.6) | 8.4 | 0.6 |

a: AI463017: population pharmacokinetic study results using adult trials.
b: Target exposure based on the linear pharmacokinetics between 0.5 mg and 1.0 mg doses.
AUC values are expressed as median (range). $C_{max}$ and $C_{min}$ values are expressed as geometric mean (%CV).

Efficacy and safety results

Key efficacy results at Week 48 are summarized in Table 5. At Week 48, 29% of the subjects in the treatment-naïve group and 16% of the subjects in the lamivudine experienced group met the protocol defined response (PDR) which is HBV DNA <50 IU/mL and HBeAg seroconversion on 2 sequential measurements drawn at least 2 weeks apart. 58% of the subjects in the treatment-naïve group and 47% of the subjects in the lamivudine-experienced group achieved HBV DNA <50 IU/mL. The mean change in HBV DNA from baseline to Week 48 was -5.86 and -5.36 $\log_{10}$ IU/mL in the treatment-naïve group and the lamivudine-experienced group, respectively.

Overall, entecavir was safe and well tolerated in the pediatric population. No deaths, discontinuations due to adverse events, malignancies or events of hepatic disease progression were reported. The safety profile was mostly consistent with the established safety profile in adults.

**Table 5. Key efficacy endpoints in treatment at Week 48 (NC=F)**

| Efficacy Endpoints | Number with Response/Number Evaluable (%) Group A LVD-naive N = 24 | Group B LVD-exp N = 19 |
|---|---|---|
| HBV DNA < 50 IU/ML | 14/24 (58.3) | 9/19 (47.4) |
| ALT NORMALIZATION (ALT <= 1.0 X ULN) | 20/24 (83.3) | 18/19 (94.7) |
| HBEAG SEROCONVERSION | 10/24 (41.7) | 3/19 (15.8) |
| PROTOCOL DEFINED RESPONSE (PDR) | 7/24 (29.2) | 3/19 (15.8) |
| MEAN LOG10 REDUCTION IN HBV DNA (IU/mL)*..... | - 5.86 | - 5.36 |

Source: Table S.5.1A

PDR is defined as confirmed HBV DNA < 50 IU/mL plus confirmed HBeAg seroconversion on 2 sequential measurements at least 14 days apart.
* HBV DNA by COBAS TaqMan - HPS assay.

**Trial AI463189**

**Study design**

This is a randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of entecavir in pediatric subjects with chronic hepatitis B infection who are HBeAg-positive and nucleos[t]ide naïve. Subjects of 2 to < 18 years of age were randomized 2:1 to entecavir: placebo for a maximum of 96 weeks with the primary endpoint at Week 48. 180 subjects were enrolled and the first 123 subjects were considered the study's primary cohort. The primary endpoint was the proportion of the subjects who achieved the protocol defined response, a combination of HBV DNA <50 IU/mL and HBeAg seroconversion at Week 48. Key secondary endpoints were the proportion of subjects with HBV DNA <50 IU/mL, with normalized ALT, with HBV DNA below the limit of quantitation (29 IU/mL), and with HBe seroconversion at Week 48. At week 2, semi-intensive (predose, 1, 2, and 4 hour post dose) pharmacokinetic samples were collected in a subset of subjects (n=10) to compare the exposure obtained in this study to study result AI463028. Sparse PK samples were collected at Weeks 4, 12, 24, 48 for population pharmacokinetic analyses.

**Results**

Semi-intensive pharmacokinetic study results

Semi-intensive pharmacokinetic samples were collected from ten subjects across the age cohorts (N= 4 in 2 to ≤ 6 years of age, N=2 in 6 to ≤ 12 years of age, N=4 in 12 to < 18 years of age). Individual pharmacokinetic parameters obtained in this study are listed in Table 6. Although a small number of subjects and time-points measured limits the data interpretation, time-concentration profiles and pharmacokinetic parameters obtained in this population appear to be comparable to the intensive PK results observed in AI463028 (Table 3).

**Table 6. Individual entecavir pharmacokinetic parameters in pediatric subjects (semi-intensive PK) in AI463189**

| Treatment | Subject | CMAX (ng/mL) | TMAX (h) | CMIN (ng/mL) |
|---|---|---|---|---|
| A | AI463189-12-8551 | 7.91 | 1.00 | 0.444 |
| | AI463189-17-8503 | 7.66 | 1.00 | 0.360 |
| | AI463189-17-8545 | 7.43 | 1.00 | 0.419 |
| | AI463189-59-8631 | 5.67 | 1.17 | 0.476 |
| B | AI463189-17-8504 | 5.68 | 1.00 | 0.355 |
| | AI463189-2-8532 | 8.64 | 0.98 | 0.337 |
| C | AI463189-17-8523 | 4.47 | 1.02 | 0.293 |
| | AI463189-23-8604 | 3.44 | 1.00 | 0.328 |
| | AI463189-47-8595 | 4.16 | 0.92 | 0.363 |
| | AI463189-7-8502 | 4.89 | 1.00 | 0.326 |

A: 2 to ≤ 6 years of age  B: 6 to ≤ 12 years of age  C: 12 to < 18 years of age

Efficacy and safety results

Key efficacy results are summarized in Table 7. The proportion of subjects who achieved the primary endpoint (combined HBV DNA <50 IU/mL and HBeAg seroconversion at Week 48) was significantly higher in the entecavir group than in the placebo group (24% vs. 2%, P=0.0049). In addition, the proportion of patients who achieved key secondary endpoints (HBV DNA <50 IU/mL, ALT normalization, HBV DNA <LOQ) was significantly higher in the entecavir group than the placebo group. The proportion of subjects who had HBeAg seroconversion was higher in the entecavir group (24%) than in the placebo group (12%), but the difference was not statistically significant.

Overall, entecavir was safe and well tolerated in the pediatric population in this study. No deaths, discontinuations due to adverse events, malignancies or events of hepatic disease progression were reported. The safety profile was mostly consistent with the established safety profile in adults. Most common drug-related adverse events were gastrointestinal events including nausea and vomiting.

**Table 7. Primary and key secondary endpoints at Week 48 – Primary cohort**

| Endpoint | Number with Response/Number Evaluable (%) ETV N = 82 | PBO N = 41 | Difference in Prop. (ETV - PBO) (95% CI) [P-value] |
|---|---|---|---|
| PRIMARY: HBV DNA < 50 IU/ML AND HBEAG SEROCONVERSION AT WEEK 48 | 20/82 (24.4) | 1/41 ( 2.4) | 20.2 (9.1, 31.4) [0.0049] |
| KEY SECONDARY: | | | |
| HBV DNA < 50 IU/ML AT WEEK 48 | 38/82 (46.3) | 1/41 ( 2.4) | 41.8 (29.4, 54.2) [<0.0001] |
| ALT NORMALIZATION AT WEEK 48 | 55/82 (67.1) | 9/41 (22.0) | 45.2 (29.2, 61.2) [<0.0001] |
| HBV DNA < LOQ AT WEEK 48 | 35/82 (42.7) | 1/41 ( 2.4) | 38.2 (25.9, 50.5) [<0.0001] |
| HBEAG SEROCONVERSION AT WEEK 48 | 20/82 (24.4) | 5/41 (12.2) | 12.1 (-1.5, 25.7) [0.11] |

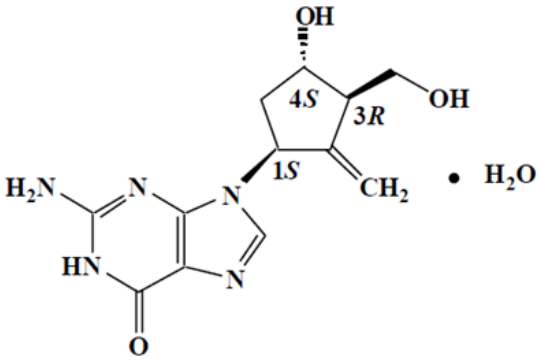
## 2. Question-Based Review

### 2.1 General Attributes

**2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?**

Drug substance

The chemical structure and structural formula of entecavir are shown below.




Molecular formula: $C_{12}H_{15}N_5O_3 \cdot H_20$
Relative molecular mass: 295.3

Formulations

Two strengths of entecavir film coated tablets (0.5 mg, 1.0 mg) are currently available on the market. The entecavir oral solution is manufactured in a strength of 0.05 mg/mL. It is ready-to-use, orange-flavored, clear, colorless to pale yellow aqueous solution packed in a 260 mL bottle. The bioequivalence between the tablet and the solution has been demonstrated in AI463035 and the study was reviewed at the time of NDA approval.

**2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?**

Entecavir is a guanosine nucleoside analogue with activity against HBV reverse transcriptase. It is efficiently phosphorylated to the active triphosphate form which has an intracellular half-life of 15 hours. Entecavir triphosphate inhibits HBV reverse transcriptase by competing with the natural substrate, deoxyguanosine triphosphate.

**2.1.3. What are the proposed dosage(s) and route(s) of administration?**

The proposed oral dose entecavir for the treatment of chronic hepatitis B infection in treatment-naïve pediatric patients from the age of 2 to 18 years is [redacted] (b) (4) 0.5 mg once daily. While the weight bands and doses originally proposed by the applicant are reasonable from an exposure-matching perspective, the [redacted] (b) (4) increment and non-integer body weight bands may reduce readability of the table and could potentially lead to a dosing error. Therefore, DAVP has provided two dosing options to the applicant. Please refer to section 1.1 for detailed information.

**Proposed dosing schedule for pediatric patients**


## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The following studies were used to support the indication and dosing.

**Trial AI463028**

This is an open-label study assessing the PK, safety, tolerability, and preliminary efficacy of entecavir in pediatric subjects (2 to < 18 years of age) with HBeAg-positive chronic HBV infection. The primary object of this study was to determine the doses of entecavir in pediatric HBV patients that produce drug exposures comparable to those observed in adults administered clinical doses (0.5 mg in treatment naïve adult patients and 1.0 mg in lamivudine-refractory adult patients). Subjects were to be enrolled into 3 age cohorts (2 to ≤ 6, 6 to ≤ 12, and 12 to ≤ 18 years of age). The tested doses in this study were 0.015 mg/kg up to a maximum dose of 0.5 mg once daily in treatment-naïve subjects and 0.015 mg/kg up to a maximum dose of 0.5 mg once daily and 0.030 mg/kg up to a maximum dose of 1.0 mg once daily in lamivudine-experienced subjects. Intensive PK samples up to 24 hours post-dose were collected at Week

2 and efficacy endpoints (plasma HBV DNA, ALT, HBeAg seroconversion) were determined through 96 weeks.

**Trial AI463189**

This is a randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of entecavir in pediatric subjects with chronic hepatitis B infection who are HBeAg-positive and nucleos[t]ide naïve. One eighty subjects of 2 to < 18 years of age were randomized 2:1 to entecavir: placebo for a maximum of 96 weeks with the primary endpoint at Week 48. The primary endpoint was the proportion of the subjects who achieved the protocol defined response, a combination of HBV DNA < 50 IU/mL and HBeAg seroconversion at Week 48. Key secondary endpoints were the proportion of subjects with HBV DNA < 50 IU/mL, with normalized ALT, with HBV DNA below the limit of quantitation (29 IU/mL), and with HBe seroconversion at Week 48. At week 2, semi-intensive (pre-dose, 1, 2, and 4 hour post dose) pharmacokinetic samples were collected in a subset of subjects (n=10) to compare the exposure obtained in this study to study result AI463028. Sparse PK samples were collected at Weeks 4, 12, 24, 48 for population pharmacokinetic analyses.

**2.2.2 What is the basis for selecting the response endpoints or biomarkers (and how are they measured in clinical pharmacology and clinical studies?**

The primary efficacy endpoint is a combination of HBV DNA <50 IU/mL and HBeAg seroconversion at Week 48. This is different from the entecavir adult trial primary endpoint: histologic improvement (more than 2-point decreases in the Knodell inflammatory score with no worsening of fibrosis at Week 48) which requires liver biopsy. At this time, DAVP does not recommend liver biopsy in pediatric HBV patients based on the risk vs. benefit assessment. Therefore, a combination of virologic and serologic endpoints was used as the primary endpoint in the trial AI463189.

Of note, it is unclear at this time whether the combined virologic and serologic endpoints in pediatric patients correlate with histologic improvement. Therefore, extrapolation of the adult efficacy results by matching exposures between the two populations is not currently accepted as the primary approach for an approval of HBV drugs for pediatric indications.

**2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Yes, entecavir is concentrations in human plasma were determined by validated using LC/MS/MS.

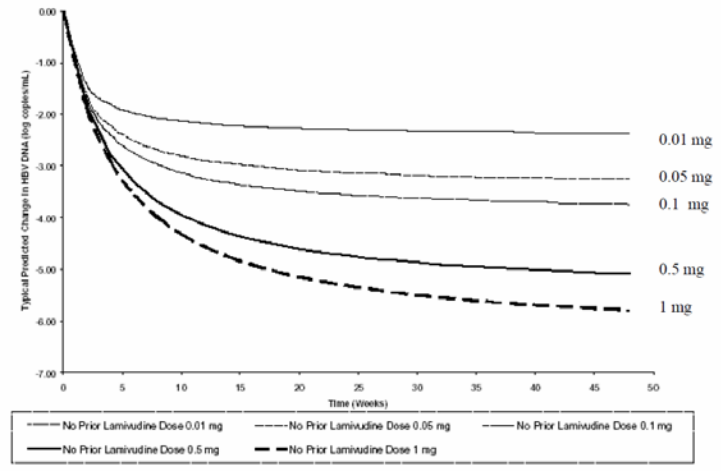
**2.4. Exposure-response**

**2.2.4.1 What are the characteristics of exposure-response relationships for efficacy?**

In adults, a dose-response relationship was demonstrated in the phase 2 dose-ranging studies (AI463004, AI463005, and AI463014) with 0.05 mg to 1 mg entecavir once daily regimen. Significantly greater and sustained viral suppression was demonstrated by the 0.5 mg and 1.0 mg doses in these trials as described in Fig 1. Because an increased incidence of CNS events was observed with the 1.0 mg dose in phase 2 studies, 0.5 mg was selected for nucleoside-naïve patients in Phase 3 trials. Due to the decreased sensitivity to entecavir, 1 mg was selected for lamivudine-refractory patients.

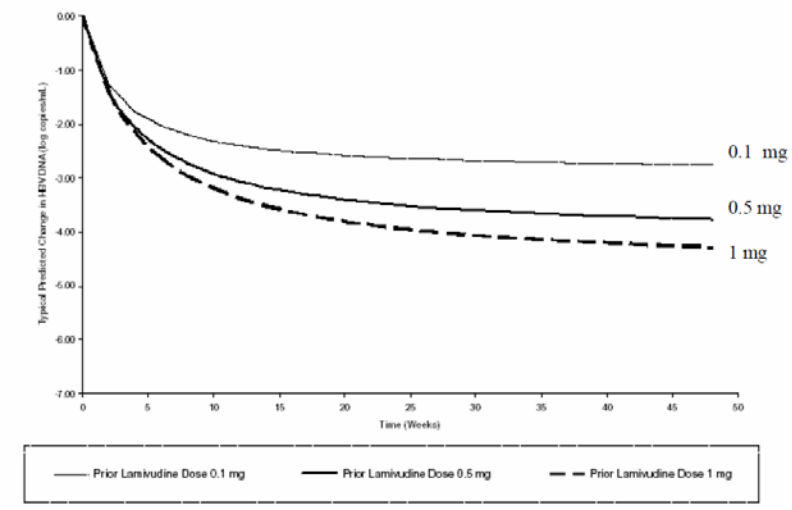
**Fig 1. Effects of entecavir doses on the time course of HBV DNA reduction in adults**

(a) Treatment-Naïve adult patients




Source:AI463027, population pharmacokinetic analysis using 3 dose ranging studies

(b) treatment-experience adult patients




In pediatric trials, dose–ranging studies were not conducted. With the doses used in two pediatric studies (0.015 mg/kg once daily up to a maximum dose of 0.5 mg once daily), there was no significant exposure response relationship between entecavir AUC and the endpoint of HBV <50 IU/mL at Week 48, supporting that higher entecavir exposures may not further improve the observed treatment response. Also, the overall hepatitis B viral time course and the exposure response relationship between entecavir AUC and viral load changes from the baseline were similar between pediatric and adult subjects. Please refer to the Question-Based Review in the pharmacometric review for further details (Appendix 4.2).

**2.2.4.2 What are the characteristics of exposure-response relationships for safety?**

In adults, the most common adverse reactions were headache and nausea (> 5% incidence). In some phase 2 trials, the incidence of pooled CNS events, including dizziness and insomnia, appeared to be increased with increasing entecavir doses, specifically with the 1.0 mg dose. However, population PK/PD analysis using data from all dose-ranging phase 2 trials (AI463004, AI463005, and AI463014), no clear relationships between the doses or exposures ($C_{max}$, $C_{min}$, and AUC) and the pooled adverse events were observed.

In pediatric patients, there were trends of increased vomiting and gastrointestinal adverse reactions with higher entecavir exposure. However, the overall incidence of grade 2 or higher events for vomiting and gastrointestinal adverse events was similar to the event rate reported in the label for adults (< 1% for vomiting, 2% for gastrointestinal adverse events, respectively). Please refer to the Question-Based Review in the pharmacometric review for further details (Appendix 4.2).

**2.2.5 What are the PK characteristics of entecavir?**

The following PK characteristics were observed in adults and are expected to be similar in the pediatric population**.**

Absorption

- Entecavir exposure was decreased by approximately 20% following administration with a high-fat or light meal compared to fasted conditions. Entecavir should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal) in adults. The same recommendation should be used for the pediatric population
- Entecavir is not a substrate of P-glycoprotein

Distribution

- The protein binding of entecavir in human plasma is low (approximately 13%).

Metabolism

- *In vitro* studies indicated that entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 enzyme system. Minor amounts of phase 2 metabolites (glucuronide and sulfate conjugates) were detected in urine and feces. These metabolites do not have pharmacological activity.

Elimination

- Renal excretion is the major route of elimination. Approximately 70% of the administered entecavir dose was excreted as unchanged drug in the mass-balance study in adults. Therefore entecavir clearance is decreased in subjects with renal impairment and dose adjustment is necessary in subjects with creatinine clearance less than 50 mL/min.

Drug interactions

- There were no significant pharmacokinetic interactions between entecavir and lamivudine, adefovir, or tenofovir. Entecavir is not expected to have significant drug interactions caused by induction or inhibition of hepatic drug metabolizing enzymes.

**2.3 Analytical Section**

**2.2.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

Entecavir was measured in plasma using liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS). The unchanged entecavir is the predominant circulating moiety in plasma and it is metabolized to a minor extent to an inactive glucuronide(s) and sulfate metabolite(s). Therefore, metabolites were not quantified for pharmacokinetic analyses.

**2.2.2 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

Total entecavir concentrations were measured in the trials as protein binding of entecavir is low (approximately 13%) and independent of concentration.

**2.2.3 What bioanalytical methods are used to assess concentrations?**

Plasma samples were analyzed for entecavir using validated method using solid phase extraction followed by LC/MS/MS detection. The detailed analytical performances are summarized in the individual study review (Appendix 4.1).

## 3. Labeling Recommendations

The label was updated by the applicant and DAVP reflecting the pediatric trial results. This section only shows the parts of the label relevant to clinical pharmacology. The text in blue shows the most recently proposed changes from DAVP. As of the date of this review, the applicant has not yet responded to the proposals.

**HIGHLIGHTS OF PRESCRIBINT INFORMATION**

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

# 4. Appendices

## 4.1 Individual study review

**AI463028**
**Title:** Evaluation of the pharmacokinetics, safety, tolerability and efficacy of entecavir in pediatric subjects with chronic hepatitis B virus infection who are HBeAg-positive (Phase 2b).

**Study initiation date:** June-2007
**Study completion date:** ongoing, cutoff date April 2013
**Study centers:** 19 study sites located in 8 countries

**Primary objects:** To determine the doses of entecavir in children and adolescents that produce drug exposures comparable to those observed in adults given the 0.5 mg and 1.0 mg doses.

**Study design**
***a. Study subjects***
Subjects are HBV-infected children and adolescents aged 2-18 years old (inclusive). A maximum of 64 evaluable subjects were enrolled into 3 dose groups and 3 age cohorts.

Age cohorts
- Cohort 1: 2 to ≤ 6 years old
- Cohort 2: 6 to ≤ 12 years old
- Cohort 3: 12 to < 18 years old

Treatment Groups
- Group A: Lamivudine-naïve subjects, at a starting dose of 0.015 mg/kg up to a maximum dose of 0.5 mg (8 subjects per each age cohort)
- Group B: Lamivudine-experienced subjects at a starting dose of 0.030 mg/kg up to a maximum of 1.0 mg (4 subjects in age cohort 1 and 8 subjects each in age cohorts 2 and 3)
- Group C: A maximum of 20 pediatric patients who failed previous treatment with any non-entecavir nucleos(t)ide analog. Pharmacokinetic assessment was optional for group C.

***b. Study duration***
All subjects were to receive a minimum of 48 weeks of study drug.

***c. Rationale for dose selection***
The sponsor selected 0.015 mg/kg up to a maximum dose of 0.5 mg once daily. This was expected to produce exposures comparable to exposures observed in adult trials. The target exposure in this study was within ±30 % (13.1-24.3 ng·hr/mL) of the median exposure (18.7 ng·hr/mL) obtained from the phase 2 population PK assessment. As entecavir demonstrated linear PK up to a dose of 1.0 mg/kg, the target exposure range for Group B and C was within 26.2 to 48.6 ng·hr/mL (±30 % of 37.4 ng·hr/mL).

***d. Study endpoint***

Pharmacokinetic endpoints

Entecavir pharmacokinetic parameters ($C_{max}$, $C_{min}$, $AUC_{tau}$, CL/F) at steady-state (at week 2) were derived from plasma concentration versus time data using Kinetica™ 5.0.

Efficacy/antiviral activity endpoints

The primary endpoint of the study was a combination of HBV DNA < 50 IU/mL and HBe seroconversion at Week 48. Antiviral activities were measured by the level of plasma HBV DNA by Roche COBAS ® Taqman HBV test through Week 48 and Week 96. Proportion of subjects with normalization of ALT through Week 48 and through Week 96 and proportion of subjects with hepatitis B e antigen loss and with HBe seroconversion through week 48 and Week 96 were also measured to determine antiviral efficacy.

***e. Dose and mode of administration.***

Entacavir 0.5 mg tablet, 1.0 mg tablet, or entecavir oral solution 0.05 mg/mL were administered orally.

**Bioanalytical methods**

Plasma samples were analyzed by (b) (4) Samples were received in frozen and were stored at – 20 ºC prior to analysis. The samples were analyzed with a validated method using liquid chromatography tandem mass spectrometry detection as summarized in Table 1.

Standards were accepted when predicted concentrations of at least three-fourth of the standards were within ± 15% of their individual nominal concentration values [± 20% for the lower limit of quantitation (LLOQ) standard]. Assays were accepted when the predicted concentrations of at least two-thirds of the analytical QC samples were within 15% of their individual nominal concentrations values and at least 50% QC samples were acceptable at each level. The results for the standard curves and analytical QC samples indicate that the method was precise and accurate for the analysis of entecavir in this study.

**Table 1. Summary of bioanalytical methods**

| | |
|---|---|
| **Matrix** | Plasma with $K_3$EDTA |
| **Sample volume** | 100 µL |
| **Internal standard** | [$^{13}$C, $D_2$]entecavir |
| **Extraction method** | Solid-phase extraction |
| **Calibration curve range (Lower limit of quantitation- Upper limit of quantitation)** | 0.05-20 ng/mL* |
| **Inter-Assay precision (% CV)** | ≤ 7.0% |
| **Inter-Assay accuracy (% Dev)** | ≤ 5.1 % |
| **$R^2$** | > 0.994 |
| **Room temperature stability** | Stable in plasma up to 24 hours |
| **Freeze-thaw stability** | Stable in plasma for 3 cycles at – 20º C |
| **Long-term stability** | Stable in plasma for at least 554 days at – 20º C. |
| **Reinjection reproducibility** | Stable up to 88 hours at room temperature |

* One sample was above ULOQ and reanalyzed after dilution.

*Reviewer comments*

*The original bioanalytical study report (07793ATCA_BPN) and the method validation report were submitted as an appendix in the 96 week interim study report. The current submission (Week 120 study report) contains the bioanalysis report for additional 7 samples. This is a combined review for both the original bioanalysis report (Week 96) and the current submission (Week 120).*

## Study results

### Population analyzed

A total of 64 patients were planned (Group A = 24, Group B = 20, Group C= 20) and a total of 48 subjects had initiated the study drug by the cutoff date for the report (Group A = 24, Group B = 20, Group C = 20). Plasma samples for pharmacokinetic analyses were collected for all subjects in group A and group B at week 2. No samples were collected in Group C as PK sampling was optional for this group. All subjects received entecavir for at least 48 weeks. The number of subjects with PK data available in each age cohort and treatment group is summarized in Table 2.

**Table 2. Pharmacokinetic population in each age cohort and treatment group**

| Age cohort/ Treatment Group | Group A<br>Lamivudine-naïve,<br>0.015 mg/kg once daily | Group B<br>Lamivudine-experienced<br>0.03 mg/kg |
|---|---|---|
| Cohort I ≥2 to 6 ≤ years | N=7 | N=3 |
| Cohort II >6 to ≤ 12 years | N=9 | N=7 |
| Cohort III >12 to ≤ 18 years | N=8 | N=9 |

### Demographics and baseline characteristics

The mean age was 9.9 years and the majority of subjects were male and Asian. The overall mean baseline HBV DNA by PCR was 7.85 $\log_{10}$ IU/mL. All subjects were HBeAg positive, HBeAb negative, and HBsAg positive.

### Pharmacokinetic results

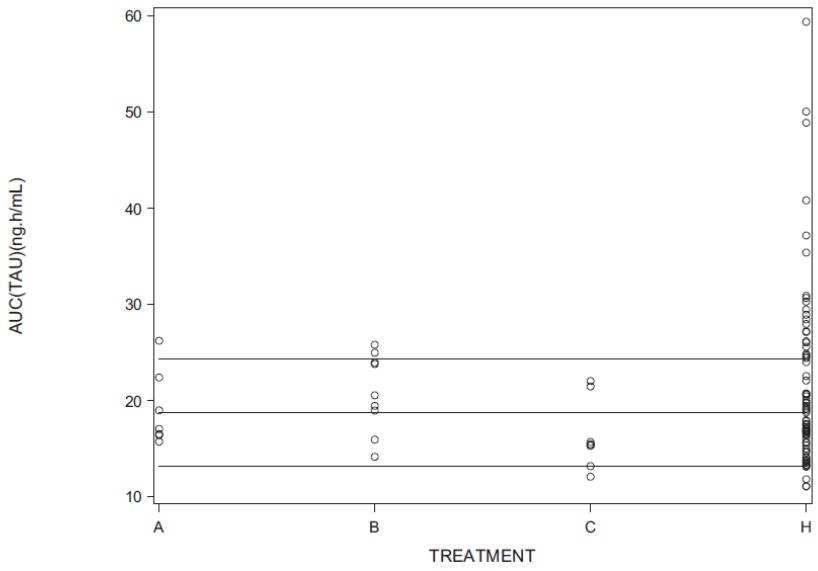
### Treatment-naïve subjects

Entacavir pharmacokinetic parameters in treatment-naive pediatric patients are summarized in Table 3. The scatter plot of entecavir AUC by age group versus historical adult data is presented in Fig 1. For each age group, the target exposure (AUCτ 18.7 ng*h/mL ± 30%) at steady-state was achieved after 2 weeks administration of entecavir 0.015 mg/kg with a maximum dose of 0.5 mg once daily. Therefore, the current dosing regimen produces entecavir exposure to those observed in adults given the 0.5 mg dose. Entecavir clearance increases as age increases and clearance normalized to body weight decreases as age increases, and BSA-normalized clearance is independent of age.

**Table 3. Summary of entecavir pharmacokinetic parameters in treatment-naïve pediatric patients**

| Age Group | Cmax (ng/mL) Geo. Mean (%CV) | Tmax (h) Median (Min-Max) | Cmin (ng/mL) Geo. Mean (%CV) | AUC(TAU) (ng•h/mL) Geo. Mean (%CV) | AUC(TAU) (ng•h/mL) Median (Min-Max) | CLT/F (L/h) Mean (SD) | CLT/F/BW (L/h/kg) Mean (SD) | CLT/F/BSA ($L/h/m^2$) Mean (SD) |
|---|---|---|---|---|---|---|---|---|
| 1 (N=7) | 8.07 (24) | 0.50 (0.5 - 1.0) | 0.244 (32) | 18.69 (21) | 17.00 (15.7 - 26.2) | 11.40 (2.564) | 0.814 (0.1436) | 19.5 (3.51) |
| 2 (N=9) | 6.29 (25) | 0.57 (0.5 - 2.0) | 0.320 (22) | 20.42 (20) | 20.51 (14.1 - 25.8) | 22.66 (6.134) | 0.656 (0.1232) | 19.5 (3.22) |
| 3 (N=8) | 5.11 (27) | 0.78 (0.5 - 1.0) | 0.271 (25) | 15.96 (22) | 15.37 (12.0 - 22.0) | 31.92 (6.429) | 0.499 (0.1139) | 18.8 (3.09) |

**Fig 1. Scatter plot of entecavir AUC by age group and historical adult data (AI463017)**




Treatment:
A- Entecavir 0.015 mg/kg (>= 2 - <= 6 yrs), B - Entecavir 0.015 mg/kg (>6 - <= 12 yrs), C - Entecavir 0.015 mg/kg (>12 - <= 18 yrs)
H - Predicted data from AI463017 Pop PK study with dose at 0.5mg
Note: Reference lines at 13.1 ng.h/mL, 18.7 ng.h/mL and 24.3 ng.h/mL under original scale

**Reviewer comments**

*1. The sponsor did not establish target $C_{max}$ or $C_{min}$ values in this study. The $C_{max}$ observed in the pediatric population in this study is higher than the $C_{max}$ in treatment-naive adult patients (median $C_{max}$ 4.2 ng/mL). In particular, an almost 2-fold higher $C_{max}$ was observed in the youngest cohort. This was also observed in Group B (lamivudine experienced population) of this study and in subjects that participated in the semi-intensive PK sampling in Study AI463289. Meanwhile, there was no significant difference in the $C_{min}$ between pediatric patients and adults (historical data; $C_{min}$ 0.3 ng/mL). A higher $C_{max}$ in younger pediatric patients could be potentially due to different gastrointestinal motility or different absorption profiles with the solution dosage form in the pediatric population. As there was no relationship between the $C_{max}$ and common adverse events in both the pediatric and adult populations, increased $C_{max}$ in the pediatric population is unlikely to pose a significant safety concern.*

*2. Numerically lower AUC was observed in adolescent patients. This appears to be driven by some obese patients. A trend of decreasing exposures with increasing body weight was observed with the fixed tablet dose (0.5 mg q.d.)in the adult population pharmacokinetic analyses. All subjects in this cohort (12 to 18 years old) received the maximum dose (0.5 mg daily) and exposures are still comparable to the adult exposures as described in Fig 2.*

*3. Entecavir clearance increases with age, clearance normalized to body weight decreases with age, and BSA-normalized clearance was independent of age. This was an expected result as renal excretion is the major route of elimination of entecavir.*

**Lamivudine-experienced patients**

Entecavir pharmacokinetic parameters in lamivudine-experienced pediatric patients are summarized in Table 4. For each age cohort, the target exposure (AUCτ within ±30% of 37.4 ng·h/mL) at steady-state was achieved after 2 weeks of administration of entecavir 0.030 mg/kg with a maximum dose of 1 mg once daily.

**Table 4. Summary of entecavir pharmacokinetic parameters in lamivudine-experienced pediatric patients**

| Age Group | Cmax (ng/mL) Geo. Mean (%CV) | Tmax (h) Median (Min-Max) | Cmin (ng/mL) Geo. Mean (%CV) | AUC(TAU) (ng•h/mL) Geo. Mean (%CV) | AUC(TAU) (ng•h/mL) Median (Min-Max) | CLT/F (L/h) Mean (SD) | CLT/F/BW (L/h/kg) Mean (SD) | CLT/F/BSA (L/h/m$^2$) Mean (SD) |
|---|---|---|---|---|---|---|---|---|
| 1 (N=3) | 16.03 (8) | 1.00 (0.5 - 1.5) | 0.468 (17) | 42.26 (27) | 40.06 (33.5 - 56.3) | 12.31 (3.102) | 0.722 (0.1576) | 17.6 (4.37) |
| 2 (N=7) | 19.01 (15) | 0.72 (0.5 - 1.0) | 0.497 (32) | 41.50 (21) | 43.91 (29.7 - 53.1) | 21.67 (6.940) | 0.660 (0.1412) | 19.3 (3.80) |
| 3 (N=9) | 11.32 (37) | 0.52 (0.5 - 1.0) | 0.455 (25) | 35.36 (24) | 32.33 (26.0 - 51.4) | 28.95 (6.496) | 0.478 (0.0405) | 17.3 (1.81) |

Source: Table S.8.2.3 of the Week 48 LVD-experienced CSR[7]

Treatment: 1 = ETV 0.03 mg/kg ETV (2 - 6 yrs)
2 = ETV 0.03 mg/kg ETV (> 6 - 12 yrs)
3 = ETV 0.03 mg/kg ETV (> 12 - 18 yrs)

**Efficacy and safety results**

Key efficacy endpoints at Week 48 are summarized in Table 5. At Week 48, 29% subjects in group A (treatment-naïve) and 16% subjects in group B (lamivudine-experienced) met the protocol defined response (PDR), HBV DNA < 50 IU/mL and HBeAg seroconversion on 2 sequential measurements drawn at least 2 weeks apart. 58% subjects in group A and 47% subjects in group B achieved HBV DNA < 50 IU/mL. The mean change in HBV DNA from baseline to Week 48 was – 5.86 and -5.36 $\log_{10}$ IU/mL in Group A and Group B, respectively. NC=F analysis were not conducted for Group C due to the limited number of subjects at the time of analyses (only 3 out of 5 subjects had reached the key efficacy time point). Overall, the efficacy results appear to be comparable to the results from AI463189 as well as adult historical data. For detailed efficacy review, please refer to Dr. Kimberly Martin's clinical review.

**Table 5. Key efficacy endpoints in treatment at Week 48 (NC=F)**

| Efficacy Endpoints | Number with Response/Number Evaluable (%) Group A LVD-naive N = 24 | Group B LVD-exp N = 19 |
|---|---|---|
| HBV DNA < 50 IU/ML | 14/24 (58.3) | 9/19 (47.4) |
| ALT NORMALIZATION (ALT <= 1.0 X ULN) | 20/24 (83.3) | 18/19 (94.7) |
| HBEAG SEROCONVERSION | 10/24 (41.7) | 3/19 (15.8) |
| PROTOCOL DEFINED RESPONSE (PDR) | 7/24 (29.2) | 3/19 (15.8) |
| MEAN LOG10 REDUCTION IN HBV DNA (IU/mL)*..... | - 5.86 | - 5.36 |

Source: Table S.5.1A

PDR is defined as confirmed HBV DNA < 50 IU/mL plus confirmed HBeAg seroconversion on 2 sequential measurements at least 14 days apart.
* HBV DNA by COBAS TaqMan - HPS assay.

**Safety results**

Entecavir was safe and well-tolerated in the pediatric populations. Overall, the frequency and nature of AEs was comparable between Groups A and B and consistent with those observed in clinical trials of entecavir in adults. According to the sponsor, no deaths, discontinuations due to AEs, malignancies, or events of hepatic disease progression were reported. Please refer to Dr. Martin's clinical review for detailed information.

**Conclusion**

Entecavir doses of 0.015 mg/kg up to 0.5 mg produced entecavir exposures (AUCτ) in treatment-naïve HBV pediatric patients comparable to exposures observed in adults receiving 0.5 mg once daily. Similarly, entecavir doses of 0.03 mg/kg up to1 mg produced entecavir exposures (AUCτ) in lamivudine-experienced HBV pediatric patients comparable to exposures observed in adults receiving 0.5 mg once daily. The efficacy was also comparable to the results observed in HBV infected adult patients. Entecavir was safe and well-tolerated in the pediatric populations. These doses are acceptable were further evaluation in the safety and efficacy trial AI463189.

**Individual study review (AI463189)**

**Title:** A comparative study of the antiviral efficacy and safety of entecavir versus placebo in pediatric subjects with chronic hepatitis B virus infection who are HBeAg-positive

**Study initiation date:** July 2010
**Study completion date:** ongoing, cutoff date April 2013
**Study centers:** 44 study sites located in North America, South America, Asia, and Europe

**Primary objects:** To compare the proportion of subjects in each treatment group who achieve a combination of HBV DNA suppression and hepatitis B e antigen seroconversion at Week 48

**Study design**
This is a comparative, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of entecavir in pediatric subjects with chronic hepatitis B infection who are HBeAg-positive and nucleos[t]ide naïve.

Subjects: Chronic HBV-infected children and adolescents (2 to < 18 years of age) were enrolled. Subjects were randomized 2:1 to entecavir or placebo for a maximum of 96 weeks with primary endpoint at Week 48. The randomization was stratified by age group (2 to ≤ 6 years; 6 to ≤12 years; 12 to < 18 years). A total of 228 subjects were enrolled and 180 subjects were randomized and treated (120 and 60 subjects in entecavir and placebo groups, respectively). The first 123 subjects were considered the study's "primary cohort" and the efficacy analysis in this interim report is based on the data from the primary cohort. The sponsor initially determined the sample size to be 123, which was expected to be able to detect the difference between the treatment group and placebo group; however, the number of subjects was later increased at the request of global regulatory authorities.

Efficacy endpoint
The primary endpoint was the proportion of subjects in the primary cohort who achieved a combination of 1) HBV DNA <50 IU/mL (using Roche COBAS® Taqman HBV test for use with the high pure system assay) and 2) HBeAg seroconversion at Week 48. Key secondary endpoints were proportion of subjects with HBV DNA <50 IU/mL, with normalized ALT, with HBV DNA below the limit of quantitation (29 IU/mL), with HBe seroconversion at Week 48.

**Pharmacokinetic assessments**
Sparse PK samples were collected at Weeks 4, 12, 24, 48. In a subset of subjects, semi-intensive PK samples were collected (at pre-dose, 1, 2, and 4 hour post-dost) at week 4 visit. Semi-intensive PK samples were analyzed and used to drive individual subject PK parameters by non-compartmental methods by Kinetica ™ 5.0.

**Bioanalytical methods**
Bioanalysis methods were validated and samples were analyzed by (b) (4)

The samples were analyzed with a validated method using liquid chromatography tandem mass spectrometry detection as summarized in Table 1. The validated method used samples containing $K_3$EDTA and the method was cross-validated with samples containing $K_2$EDTA.

Standards were accepted when predicted concentrations of at least three-fourth of the standards were within ± 15% of their individual nominal concentration values (± 20% for the LLOQ standard). Assays were accepted when the predicted concentrations of at least two-thirds of the analytical QC samples were within 15% of their individual nominal concentrations values and at least 50% QC samples were acceptable at each level. For all analytes at least two-thirds of incurred study sample repeat values must be within ± 20% of the average of the original and repeat values. The results for the standard curves and analytical QC samples indicate that the method was precise and accurate for the analysis of entecavir in this study.

**Table 1. Summary of bioanalytical methods**

| | |
|---|---|
| Matrix | Plasma with $K_2$EDTA |
| Sample volume | 200 µL |
| Internal standard | [$D_2$ $^{13}C$ $^{15}N$]entecavir |
| Extraction method | Solid-phase extraction |
| Calibration curve range<br>(Lower limit of quantitation- Upper limit of quantitation) | 0.05-20 ng/mL<br><br>QC: 0.15, 1.5, 7.5 and 15 ng/mL |
| Precision (% CV) | Intra-assay ≤ 6.6%<br>Inter-assay ≤ 3.3% |
| Accuracy (% Dev) | -1.3 to 0.8% |
| $R^2$ | > 0.994 |
| Room temperature stability | Stable in plasma up to 24 hours |
| Freeze-thaw stability | Stable in plasma for 3 cycles at – 20º C |
| Long-term stability | Stable in plasma for at least 554 days.<br>(Maximum time from collection to extraction in this study; 420 days) |

**Test products**
Entecavir 0.5 mg tablets and oral solutions (0.05 mg/mL) were used in this study.

**Summary of results**
Subject disposition and baseline demographic characteristics.
One eighty subjects had started study treatment. 7 subjects discontinued before Week 48. 123 subjects (defined as primary cohort by the applicant) reached Week 48. This interim analysis focuses on the safety and efficacy in the primary cohort. The majority of treated subjects were male and Asian or White. The mean age was 10.6 years (range: 2-17 years). The baseline HBV disease characteristics were comparable between the entecavir group and the placebo group as described in Table 2.

**Table 2. HBV characteristics at baseline in the primary cohort**

| | ETV N = 82 | PBO N = 41 | Total N = 123 |
|---|---|---|---|
| HBV DNA BY PCR (LOG10 IU/ML) | | | |
| N | 82 | 41 | 123 |
| MEAN (SE) | 8.06 (0.1121) | 7.83 (0.1399) | 7.98 (0.0883) |
| SD | 1.015 | 0.896 | 0.980 |
| MEDIAN | 8.17 | 7.96 | 8.06 |
| MIN, MAX | 4.9, 10.0 | 5.6, 9.2 | 4.9, 10.0 |
| HBV DNA CATEGORY - N (%) | | | |
| < 8 LOG10 IU/ML | 34 (41.5) | 23 (56.1) | 57 (46.3) |
| >= 8 LOG10 IU/ML | 48 (58.5) | 18 (43.9) | 66 (53.7) |
| HEPATITIS B SURFACE ANTIGEN - N (%) | | | |
| POSITIVE | 82 (100.0) | 40 (97.6) | 122 (99.2) |
| NEGATIVE | 0 | 1 ( 2.4) | 1 ( 0.8) |
| HEPATITIS B E ANTIGEN - N (%) | | | |
| POSITIVE | 82 (100.0) | 41 (100.0) | 123 (100.0) |
| HEPATITIS B E ANTIBODY - N (%) | | | |
| POSITIVE | 2 ( 2.4) | 0 | 2 ( 1.6) |
| NEGATIVE | 79 (96.3) | 41 (100.0) | 120 (97.6) |
| INDETERMINATE | 1 ( 1.2) | 0 | 1 ( 0.8) |
| HBV GENOTYPE - N (%) | | | |
| A | 15 (18.3) | 8 (19.5) | 23 (18.7) |
| B | 7 ( 8.5) | 7 (17.1) | 14 (11.4) |
| C | 23 (28.0) | 14 (34.1) | 37 (30.1) |
| D | 31 (37.8) | 10 (24.4) | 41 (33.3) |
| E | 2 ( 2.4) | 1 ( 2.4) | 3 ( 2.4) |
| F | 2 ( 2.4) | 0 | 2 ( 1.6) |
| INDETERMINATE | 2 ( 2.4) | 1 ( 2.4) | 3 ( 2.4) |
| INR | | | |
| N | 82 | 41 | 123 |
| MEAN (SE) | 1.136 (0.01882) | 1.069 (0.02036) | 1.113 (0.01450) |
| MIN, MAX | 0.88, 1.73 | 0.89, 1.52 | 0.88, 1.73 |

| | ETV N = 82 | PBO N = 41 | Total N = 123 |
|---|---|---|---|
| ALT (U/L) | | | |
| N | 82 | 41 | 123 |
| MEAN (SE) | 107.0 (6.572) | 100.5 (17.465) | 104.8 (7.248) |
| MIN, MAX | 38, 401 | 31, 764 | 31, 764 |
| ALT CATEGORY* - N (%) | | | |
| <= 2 x ULN | 14 (17.1) | 11 (26.8) | 25 (20.3) |
| >2 x ULN | 68 (82.9) | 30 (73.2) | 98 (79.7) |
| > 2 - 5 X ULN | 52 (63.4) | 27 (65.9) | 79 (64.2) |
| > 5 X ULN | 16 (19.5) | 3 ( 7.3) | 19 (15.4) |
| ROUTE OF TRANSMISSION - N (%) | | | |
| MOTHER-TO-CHILD | 50 (61.0) | 22 (53.7) | 72 (58.5) |
| HOUSEHOLD/CLOSE CONTACT | 6 ( 7.3) | 1 ( 2.4) | 7 ( 5.7) |
| TRANSFUSION | 5 ( 6.1) | 3 ( 7.3) | 8 ( 6.5) |
| UNKNOWN | 21 (25.6) | 15 (36.6) | 36 (29.3) |

**Pharmacokinetic results**

Semi-intensive pharmacokinetic samples were collected from ten subjects across the age cohorts (N= 4 in 2 to ≤ 6 years of age, N=2 in the 6 to ≤ 12 years of age, N=4 in 12 to < 18 years of age). Individual pharmacokinetic parameters obtained in this study are listed in Table 3. Although a small number of subjects and time-points measured limit the data interpretation, time-concentration profiles and pharmacokinetic parameters obtained in this population appear to be comparable to the intensive PK sampling observed in AI463028.

**Table 3. Summary of entecavir pharmacokinetic parameters by age cohorts**

| Treatment | Subject | CMAX (ng/mL) | TMAX (h) | CMIN (ng/mL) |
|---|---|---|---|---|
| A | AI463189-12-8551 | 7.91 | 1.00 | 0.444 |
| | AI463189-17-8503 | 7.66 | 1.00 | 0.360 |
| | AI463189-17-8545 | 7.43 | 1.00 | 0.419 |
| | AI463189-59-8631 | 5.67 | 1.17 | 0.476 |
| B | AI463189-17-8504 | 5.68 | 1.00 | 0.355 |
| | AI463189-2-8532 | 8.64 | 0.98 | 0.337 |
| C | AI463189-17-8523 | 4.47 | 1.02 | 0.293 |
| | AI463189-23-8604 | 3.44 | 1.00 | 0.328 |
| | AI463189-47-8595 | 4.16 | 0.92 | 0.363 |
| | AI463189-7-8502 | 4.89 | 1.00 | 0.326 |

A: 2 to ≤ 6 years of age  B: > 6 to ≤ 12 years of age  C: > 12 to < 18 years of age

**Efficacy and safety results**

Key efficacy endpoints at Week 48 are summarized in Table 4. The proportion of subjects who achieved the primary endpoint (combined HBV DNA < 50 IU/mL and HBeAg seroconversion at Week 48) was significantly higher in the entecavir group than in the placebo group (24% vs. 2%, *P*=0.0049). In addition, the proportion of patients who achieved key secondary endpoints [HBV DNA < 50 IU/mL, ALT normalization, HBV DNA <limit of quantitation (29 IU/mL)] was significantly higher in the entecavir group than the placebo group. The proportion of subjects who had HBeAg seroconversion was higher in the entecavir group (24%) than in the placebo group (12%), but the difference was not statistically significant.

Entecavir was safe and well tolerated in pediatric patients. No death, malignancies or events of HBV disease progression were reported during the treatment or follow up phases. The safety experience was mostly consistent with the established safety profile in adults. The most common drug related adverse reactions were gastrointestinal events including nausea and vomiting. Please refer to Dr. Kimberly Martin's review for detailed efficacy and safety analysis.

**Table 4. Primary and key secondary endpoints at Week 48 – Primary cohort**

| Endpoint | Number with Response/Number Evaluable (%) ETV N = 82 | PBO N = 41 | Difference in Prop. (ETV - PBO) (95% CI) [P-value] |
|---|---|---|---|
| PRIMARY: HBV DNA < 50 IU/ML AND HBEAG SEROCONVERSION AT WEEK 48 | 20/82 (24.4) | 1/41 ( 2.4) | 20.2 (9.1, 31.4) [0.0049] |
| KEY SECONDARY: | | | |
| HBV DNA < 50 IU/ML AT WEEK 48 | 38/82 (46.3) | 1/41 ( 2.4) | 41.8 (29.4, 54.2) [<0.0001] |
| ALT NORMALIZATION AT WEEK 48 | 55/82 (67.1) | 9/41 (22.0) | 45.2 (29.2, 61.2) [<0.0001] |
| HBV DNA < LOQ AT WEEK 48 | 35/82 (42.7) | 1/41 ( 2.4) | 38.2 (25.9, 50.5) [<0.0001] |
| HBEAG SEROCONVERSION AT WEEK 48 | 20/82 (24.4) | 5/41 (12.2) | 12.1 (-1.5, 25.7) [0.11] |

**Conclusions**

Entecavir 0.015 mg/kg up to 0.5 mg once daily was superior to placebo for the primary efficacy endpoint and key secondary endpoints (except HBeAg seroconversion) in pediatric CHB patients [2 to < 18 years old who are nucleoside naïve]. A greater proportion of subjects in the entecavir group achieved HBeAg seroconversion than subjects in placebo group, but the difference did not reach statistical significance. Entecavir was safe and well tolerated in the pediatric population. The safety experience was mostly consistent with the established safety profile in adults. The semi-intensive pharmacokinetic results in subset (n=10) of study subjects were comparable to the intensive pharmacokinetic results in AI463028.

# OFFICE OF CLINICAL PHARMACOLOGY:

# PHARMACOMETRIC REVIEW

| | |
|---|---|
| **Application Number** | NDA 21797 S-18 and 21798 S-19 |
| **Submission Number (Date)** | September 20, 2013 |
| **Drug Name** | Entecavir (Baraclude®) |
| **Proposed Indication** | Treatment of chronic hepatitis B infection in pediatrics at least 2 years of age to 18 years of age |
| **Formulation** | Tablet: 0.5 mg and 1.0 mg<br><br>Oral solution: 0.05 mg/mL |
| **OND Division** | Division of Antiviral Products |
| **OCP Division** | Division of Clinical Pharmacology IV |
| **Primary CP Reviewer** | Su-Young Choi, Pharm.D., Ph.D |
| **Primary PM Reviewer** | Jeffry Florian, Ph.D |
| **Secondary CP Reviewer** | Shirley Seo, Ph.D |
| **Secondary PM Reviewer** | Yaning Wang, Ph.D |
| **Applicant** | Bristol-Myers Squibb |

## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The main purpose of this review is to determine whether the proposed dosing regimen for entecavir in pediatric subjects at least 2 years of age (Table 1) is acceptable. Approval of this submission is based on the efficacy data in treatment-naïve HBV-infected pediatric patients 2 to <18 years of age from AI463189. Supportive entecavir pharmacokinetic data in this population is available from AI463189 and AI463028.

**Table 1. Proposed Dosing Regimen of Entecavir Tablets and Oral Solution for Chronic Hepatitis B Virus Infection with Compensated Liver Disease in Nucleoside-Treatment Naïve Pediatric Subjects at Least 2 Years of Age**

| Body Weight | Once Daily Dose of Entecavir (Volume of Oral Solution [0.05 mg/mL]) |
|---|---|
| [redacted] (b) (4) | |


### 1.1.1 Does the proposed entecavir dosing regimen in pediatric subjects at least 2 years of age (>10 kg) achieve similar exposures to that of other pediatric and adults receiving the approved dosing regimens?

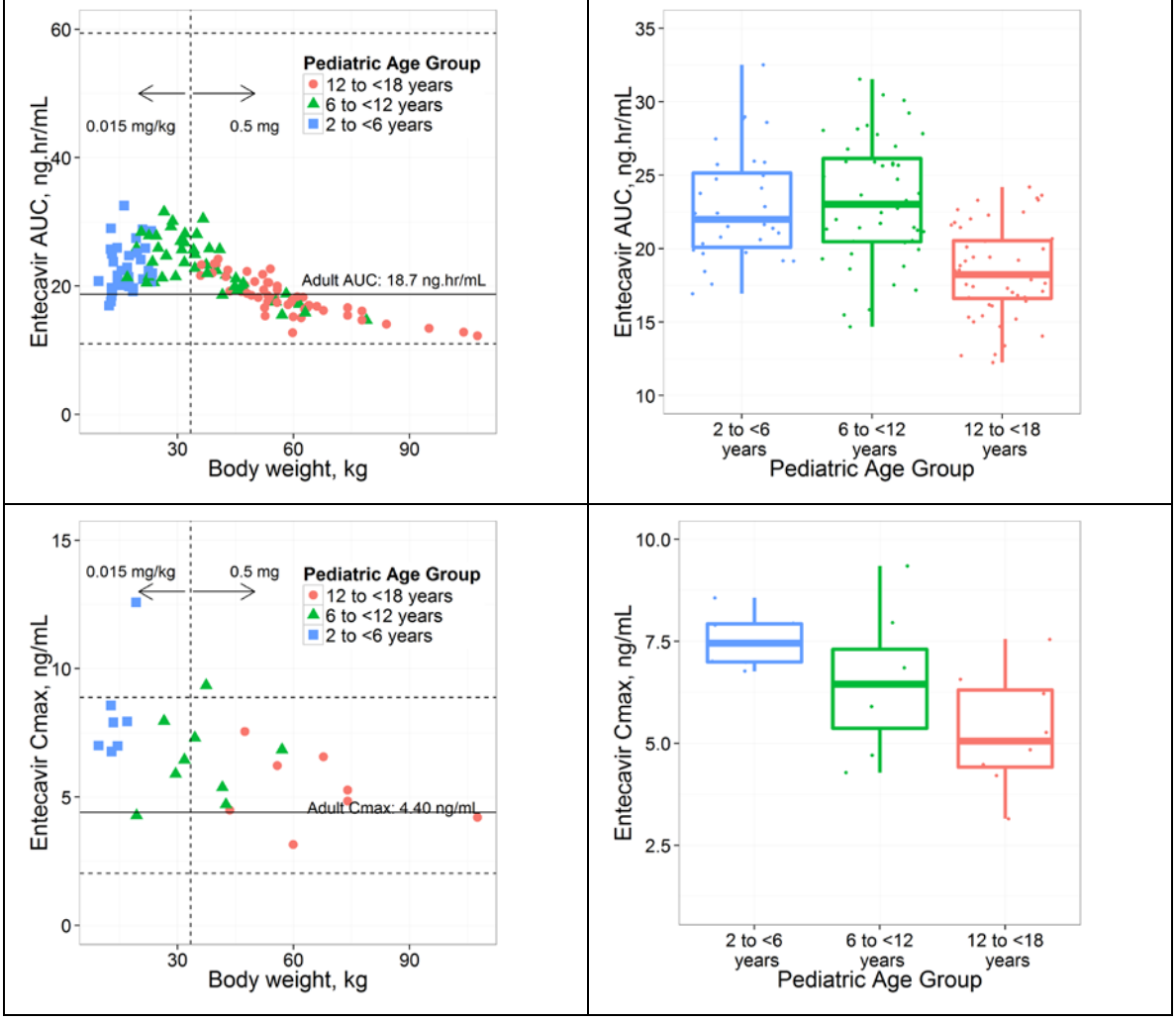
The proposed entecavir dosing regimen (Table 1) in pediatric subjects at least two years of age achieves higher exposures compared to entecavir exposures in adults receiving the approved dosing regimen. The pharmacokinetic data were derived from subjects ages 2- <6 years (N=33), 6 to <12 years (N=44), and 12 to <18 years (N=53) after oral administration of entecavir in AI463189 and AI463028 using population pharmacokinetic modeling. Due to sparse sampling in AI463189, $C_{max}$ observations were only available from pediatric subjects from AI463028 (ages 2- <6 years [N=7], 6 to <12 years [N=9], and 12 to <18 years [N=8]). The comparison of $C_{max}$ values is based on the observed measurements in pediatrics from AI463028.

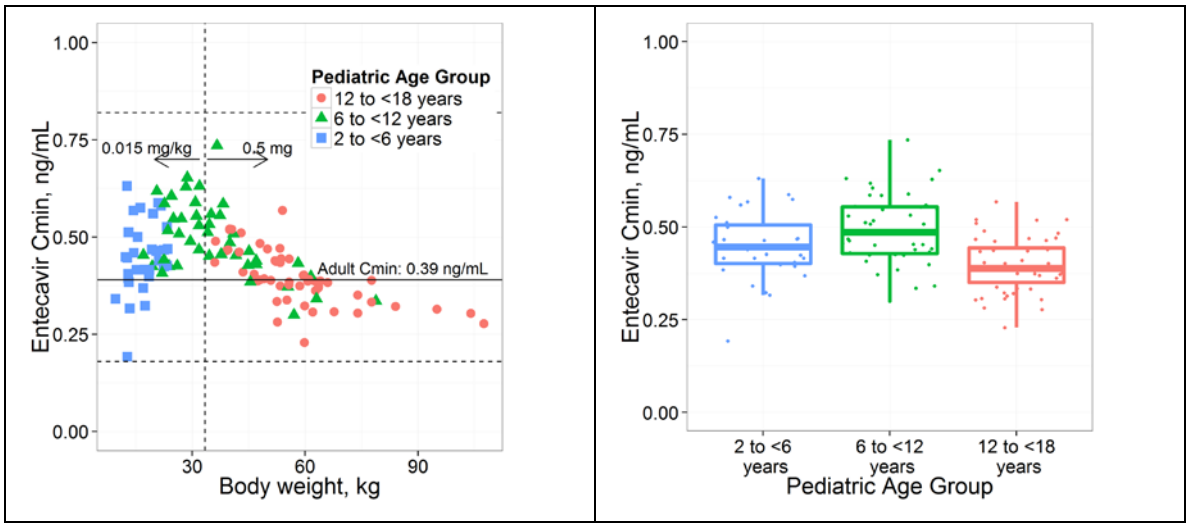
The results showed that the geometric mean entecavir exposure (AUC) was 20-22% higher (Figure 1) in pediatrics 2 to <6 years and 6 to <12 years administered entecavir according to the dosing regimen in Table 1 compared to adults administered 0.5 mg q.d. In addition, the entecavir AUC was similar (3% lower) in pediatrics 12 to <18 years of age compared to adults. An observed trend of increasing exposure with decreasing body weight was observed over the range of pediatric body weights were the fixed tablet dose (0.5 mg q.d.) was administered, though no further increase in observed exposures with respect to body weight were observed following the transition to weight-based dosing using the oral solution.

Evaluations for $C_{max}$ and $C_{min}$ versus body weight for the three age categories were also conducted based on the data from AI463189 and AI463028. Similar to the observations for entecavir AUC, entecavir $C_{0h}$ was also higher in pediatrics 2 to <6 years of age (22% higher) and 6 to <12 years of age (28% higher) compared to adults while no difference in

$C_{min}$ was observed between pediatrics 12 to <18 years of age and adults. Entecavir $C_{max}$ comparisons were less conclusive given the limited number of subjects with data available, however the entecavir $C_{max}$ was higher in all pediatric groups (pediatrics 2 to <6 years of age: 92% increase; pediatrics 6 to 12 years of age: 50% increase; pediatrics 12 to 18 years of age: 22% increase) compared to the multiple dose steady state for adults reported in the entecavir label (4.2 ng/mL). The elevated $C_{max}$ was not considered acceptable given the similar AUC observed between adults and pediatrics and as the $C_{max}$ concentrations were within the range of adults administered 1.0 mg q.d., which is an approved regimen for the treatment-experienced HBV patients.

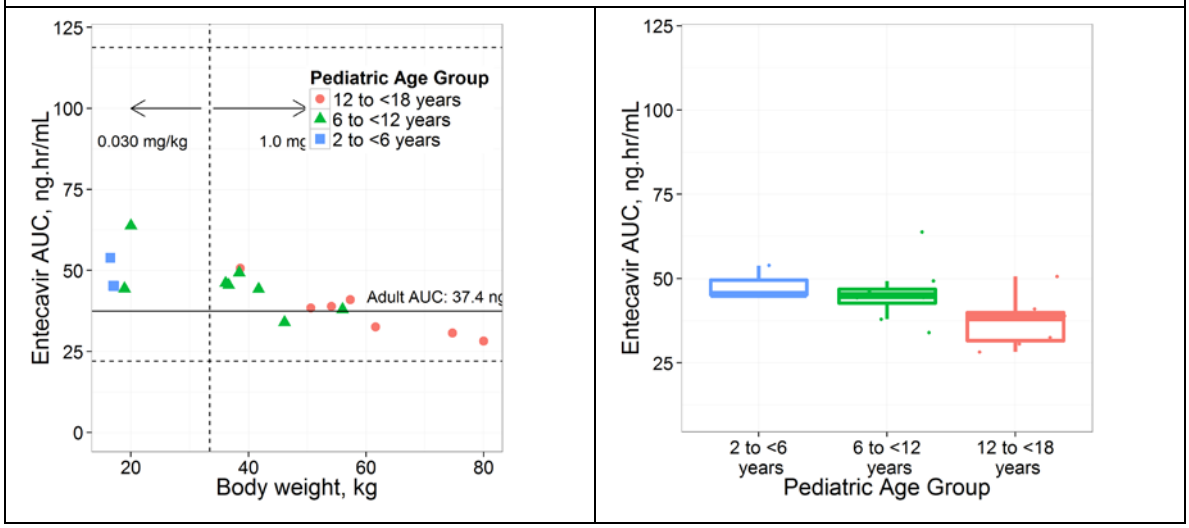
**Figure 1: Entecavir AUC (top), $C_{max}$ (middle), and $C_{min}$ (bottom) versus Body Weight (left) and Grouped by Age Category (Right) for Treatment-Naïve Pediatric Patients >2 Years of Age. The transition from solid capsules (0.5 mg) to solution dosing (0.015 mg/kg) is denoted as a vertical line on at a body weight of 32.6 kg. Median adult exposures are denoted as a horizontal solid black line. Due to sparse sampling in Study AI463189, $C_{max}$ values are only plotted for subjects from Study AI463028**






The sponsor also submitted data from AI463028 where they compared entecavir dosing in treatment-experienced pediatric patients administered 1.0 mg q.d (tablet) or 0.030 mg/kg q.d. (oral solution) to exposures in adults administered 1.0 mg q.d. The pharmacokinetic data were derived from subjects ages 2- <6 years (N=3), 6 to <12 years (N=8), and 12 to <18 years (N=7) after oral administration of entecavir (Figure 1). The reference adult exposures were obtained by 'doubling' the AUC of entecavir that was observed for 0.5 mg q.d. Only a comparison of entecavir AUC is shown below. Similar to the observations for treatment-naïve pediatric patients, entecavir AUC was 20% and 28% higher in pediatrics 6 to <12 years of age and 2 to <6 years of age compared to adults, while there was no difference in pediatric patients 12 to <18 years of age (3% lower).

**Figure 2: Entecavir AUC versus Body Weight (left) and Grouped by Age Category (Right) for Treatment-Experienced Pediatric Patients >2 Years of Age. The transition from solid capsules (1.0 mg) to solution dosing (0.030 mg/kg) is denoted as a vertical line on at a body weight of 32.6 kg. Median adult exposures are denoted as a horizontal solid black line.**



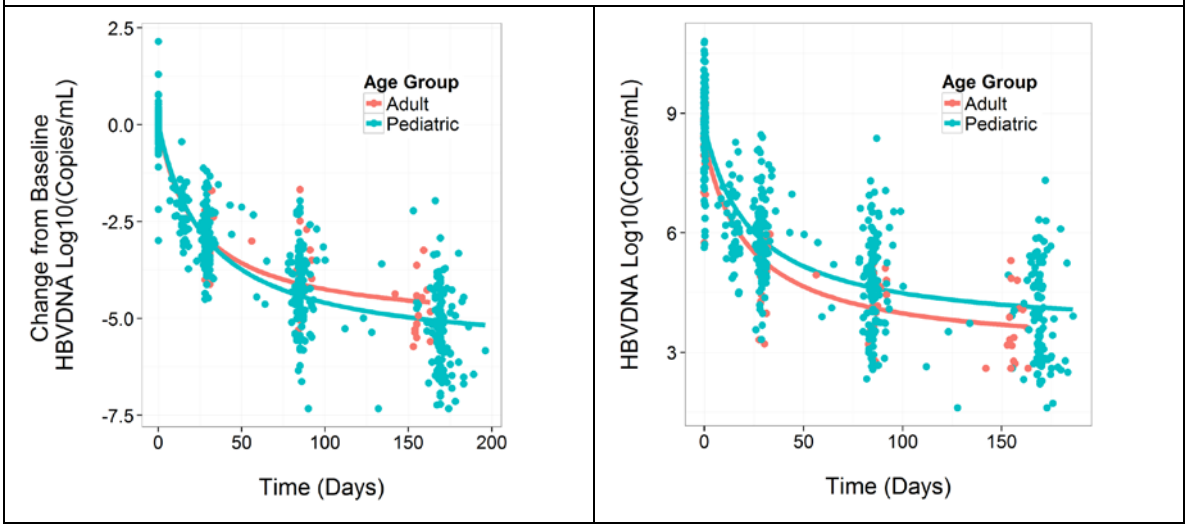
### 1.1.2 Is the exposure-response relationship for efficacy in pediatric subjects at least 2 years of age consistent with that of adults?

Yes, a comparison of the overall hepatitis B viral time course and the exposure response relationship between entecavir AUC and HBV change from baseline at day 84/168 was similar between pediatric and adult subjects. In addition, there was an insignificant exposure response relationship between entecavir AUC and the endpoint of HBV < 50 IU/mL at week 48, supporting that higher entecavir exposures may not further improve the observed treatment response.

To assist in identifying whether the disease-response relationship was similar between pediatrics and adults subjects infected with HBV, the sponsor provided data from three adult HBV trials (AI463004, AI463005, and AI463014). Details on these studies can be found below in Section 2. Briefly, these studies included a range of entecavir doses (0.05, 0.1, 0.5, and 1.0 mg q.d.) with consistent pharmacodynamic sampling through day 168. As such, comparisons between the adult and pediatric response were limited to assessments over the first 168 days of treatment.

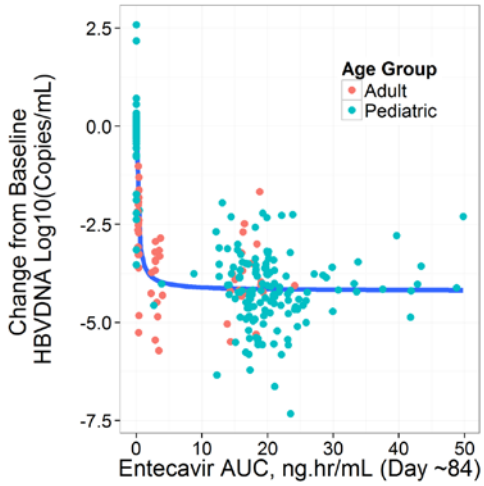
For a comparison of the viral load time course, the analysis was restricted to treatment naïve adults administered 0.5 mg q.d. (n=25) and treatment naïve pediatrics administered the dosing regimen in Table 1 (n=155) (Figure 1). An $E_{max}$ relationship was evaluated with $EC_{50}$ based on elapsed time. Both age and entecavir AUC were evaluated as covariates in this model. The entecavir exposure interquartile range was similar, though slightly higher, in pediatric subjects included in this analysis (median [$25^{th}$; 75th] entecavir AUC: 19.2 [16.7; 22.4]) compared to adult subjects (median [$25^{th}$; 75th] entecavir AUC: 16.4 [15.3; 18.8], but this exposure difference was not significant in predicting viral load decreases over this narrow exposure range. Similarly, a slightly higher but non-significant impact of age on $E_{max}$ (pediatric patients had a higher $E_{max}$) was identified in the change from baseline analysis but not in the absolute HBV viral load analysis. No significant effects of either exposure or age on the time to 50% of response were identified during this analysis. A separation in the adult and pediatric absolute HBV time course profiles was identified, though this was driven by a difference in baseline HBV (i.e., $E_0$ in the model) and was already known from the observed data (baseline HBV 8.1 $\log_{10}$ copies/mL for adults compared to 8.7 $\log_{10}$ copies/mL for pediatrics). Overall, no difference in the HBV viral time course was identified between treatment-naïve pediatric and adults patients with similar entecavir exposure supporting that the exposure-response relationship for this disease may be similar between pediatrics and adults.

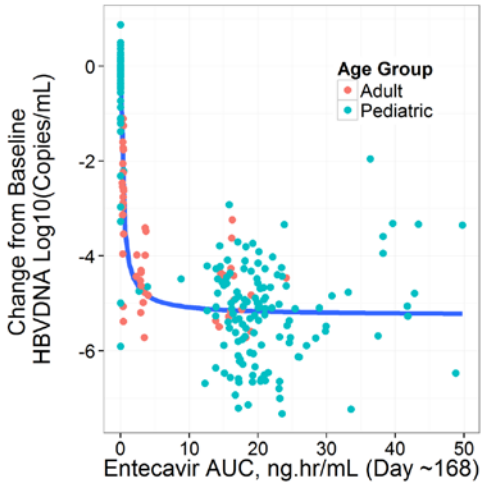
**Figure 3: Change in HBV Time-Course Based on Change from Baseline (Left) and Absolute HBV Viral Load (Right) For Treatment-Naive Pediatrics (blue) and Adults (pink) administered Entecavir According to the Dosing Regimen Listed in Table 1 (Only Adults Administered 0.5 mg Q.D. Were Included).**




A second analysis used all available data from the adult dose-ranging studies, including adult and pediatric patients treated with placebo, to identify whether there was a relationship between change from baseline in HBV viral load at day 84 or day 168 and entecavir exposure in pediatric (n=131; n=46 on placebo) and adult (0.01 mg: n=20; 0.1 mg: n=15; and 0.5 mg: n=16) patients. An $E_{max}$ relationship was evaluated with age as a covariate on $E_{max}$ and $EC_{50}$. A significant $E_{max}$ relationship was identified with an $EC_{50}$ of 3.1 ng·hr/mL for the day 84 and 168 analysis. This exposure is similar to the mean AUC predicted for adults administered 0.1 mg q.d. and suggests that the selected entecavir dose may have saturated HBV response. No age effect on either $E_{max}$ or $EC_{50}$ was identified during this analysis and the both maximum change in viral load for adults administered 0.5 mg and pediatrics administered the dosing regimen in Table 1 were overlapping in terms of entecavir exposure and change from baseline in HBV viral load at day 84 and 168. This analysis also suggests the HBV treatment response for entecavir is similar between pediatrics and adults.

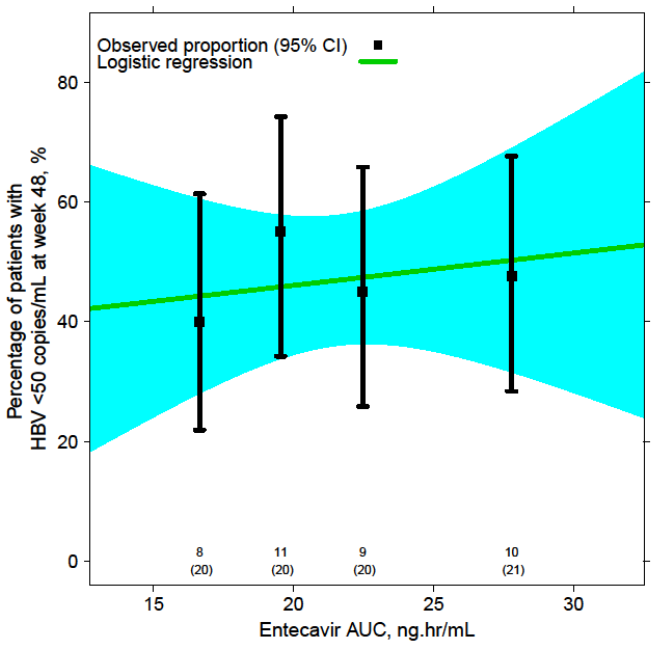
**Figure 4: Entecavir Exposure-Response Relationship Between Change in HBV Viral Load From Baseline at Day 84 and Day 164 for Pediatrics (blue) and Adults (pink)**




Finally, an exposure-response relationship between entecavir AUC and the endpoint of HBV <50 IU/mL at week 48 from the pediatric studies (AI463189) for was assessed to determine if the penultimate response between pediatrics and adults was also similar. There was not sufficient accompanying data from adults to perform an exposure-response comparison, but the label does report that 67% of treatment-naïve adult subjects administered 0.5 mg q.d. entecavir achieved <300 copies/mL (approximately 50 IU/mL based on a conversion of 5.6-5.8). In this assessment, 46% (38/82) of the pediatric patients achieved HBV <50 IU/mL at week 48. In addition, there was no significant relationship with respect to entecavir exposure supporting that the response may have been saturated in the pediatric population for the selected dose for this endpoint. The overall response in pediatrics was lower than that observed in adults, but this may be due to the higher HBV baseline or other patient factors not accounted for in this analysis. For example, if the pediatric response rate is divided into two groups based on a baseline HBV viral load of 8 $\log_{10}$ IU/mL, 77% (26/34) of subjects with baseline HBV viral load <8 $\log_{10}$ IU/mL achieved <50 IU/mL at week 48 compared to 25% (12/48) with baseline HBV viral load ≥8 $\log_{10}$

**Figure 5: Exposure-Response Relationship Between HBV <50 copies/mL at week 48 and Entecavir AUC in Pediatrics from AI463189**




### 1.1.3 What are the characteristics of the exposure-safety relationship in pediatric subjects at least 2 years of age?

The exposure-response safety relationship in pediatric subjects indicates that vomiting and nausea were more likely in pediatric subjects with higher exposures. However, the entecavir exposure range is within the range of exposures observed in adults. The overall percentage of grade 2 or higher events for vomiting (n/N = 1/148; <1%) is similar to the vomiting adverse event rate reported in the label for adults (<1%). Similarly, the grade 2 or higher event rate for gastrointestinal adverse events was 2% (n/N: 3/148; 2%) in pediatric patients. Finally, no subjects in the entecavir treatment group discontinued drug due to adverse events. Due to the lack of any major safety signal, the 20% higher entecavir exposures in pediatric subjects 2 to <12 years of age are acceptable.

## 1.2 Recommendations

The proposed dosing entecavir regimen in pediatric subjects at least 2 years of age results in entecavir exposures similar to adults. However, as the proposed table contains (b) (4) weight bands, all of which encompass less than 2 kg intervals, the sponsor was requested to provide a less granulated table for assessment. Discussions on the final dosing recommendations are ongoing at the time this review was completed. Currently proposed dosing recommendations from clinical pharmacology are shown above in the Executive Summary of the QBR.

## 2 PERTINENT REGULATORY BACKGROUND

Entecavir (ETV) is a guanosine nucleoside analogue with activity against hepatitis B virus (HBV) polymerase. Entecavir is phosphorylated intracellulaly to its active triphosphate form where it competes with the natural substrate, deoxyguanosine triphosphate, and inhibits viral polymerase activities. The recommended adult dose for ETV is 0.5 mg once daily in nucleoside-naive patients and 1.0 mg once daily in lamivudine-refractory patients.

The ETV pediatric development program is comprised of 2 ongoing studies. The first, Study AI463028 is a Phase 2b, single-arm, open-label study to assess the pharmacokinetics, safety, tolerability, and preliminary efficacy of ETV in pediatric subjects with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B. The second, Study AI463189, is a Phase 3 comparative, randomized, double-blind, placebo-controlled, multicenter study that compares the efficacy and safety of ETV with placebo in nucleoside-naive subjects with HBeAg-positive chronic hepatitis B. The primary endpoint of the study was the proportion of subjects achieving a composite of HBV DNA < 50 IU/mL and HBeAg seroconversion at Week 48. At Week 48, treatment the sponsor concluded that treatment with ETV was superior to placebo in achieving this composite endpoint with 24% responders on ETV compared to 2% on placebo.

## 3 RESULTS OF SPONSOR'S ANALYSIS

### 3.1 Entecavir Population Pharmacokinetic and Pharmacodynamic Analysis

The purpose of the sponsor's analysis was to develop a population pharmacokinetic model to describe the pharmacokinetics of entecavir, to use the developed model to evaluate demographic and laboratory factors that may influence entecavir pharmacokinetics, and to compare the pharmacokinetics of entecavir in pediatric and adults. Entecavir exposure estimates were then used to graphically examine exposure-response relationships between entecavir exposures and response (percent change in baseline HBV; HBV DNA <50 IU/mL at week 48) and adverse event measures.

#### 3.1.1 Datasets Used for Model Development

The analyses utilized PK and PD data collected in pediatric HBV subjects between 2 and 18 years of age from Studies AI463028 and AI463189. In addition, PK and PD data collected from adults who received ETV in Studies AI463004, AI463005, and AI463014 were included to enhance the model stability. For all studies, both lamivudine-naive and lamivudine-experienced subjects were included in the population PK dataset, but lamivudine-experienced subjects were excluded from the PD dataset. Brief summaries of each study that was included in this analysis (AI463028, AI463189,
AI463004, AI463005, and AI463014) are provided below in Table 3.

**Table 2 Summary of Clinical Studies Used in the Population Pharmacokinetic Analysis**

| Study | Study Population | Study Design | Study Drug Dosage Regimens | # of Planned Subjects | Nominal PK Assessments |
|---|---|---|---|---|---|
| AI463028 | Pediatric HBV | A Phase 1/2 open-label, multicenter, AUC-controlled study to determine the PK, safety, tolerability, and efficacy in children enrolled into 1 of 3 age cohorts as follows: Cohort 1 (≥ 2 to ≤ 6 years); Cohort 2 (> 6 to ≤ 12 years); and Cohort 3 (> 12 to ≤ 18 years) | Group A: 24 LVD-naïve subjects at a starting dose of 0.015 mg/kg up to a maximum dose of 0.5 mg as oral solution or tablets<br><br>Group B: 20 LVD-experienced subjects at a starting dose of 0.030 mg/kg up to a maximum of 1.0 mg as oral solution or tablets | 48 | PK samples were collected on Day 14 (±4 days) at the following nominal times: 0 (pre-dose), 0.5, 1, 2, 4, 8, and 24 hours. If ETV dosing was modified, then subjects whose doses were modified, should have had repeat PK assessments 14 days (± 4 days) after dose modification |
| AI463189 | Pediatric HBV | a comparative, randomized, double-blinded, placebo-control, multicenter study designed to assess the efficacy and safety of ETV in pediatric subjects with chronic HBV infection who are HBeAg-positive and nucleoside naïve 2 to < 18 years of age. Subjects were randomized 2:1 to ETV or placebo for a maximum of 96 weeks, with the primary endpoint at Week 48. The randomization was stratified by age group (2 to ≤ 6 years; > 6 to ≤ 12 years; > 12 to < 18 years) | ETV was dosed at 0.015 mg/kg/day up to a maximum dose of 0.5 mg/day using oral solution or tablets | 123 | For a subset of subjects participating in the semi-intense PK substudy, 1 pre-dose and 3 post-dose samples drawn during a single visit scheduled between Day 14 and Week 4 at the following nominal times: 0 (pre-dose) 1, 2, and 4 hours post-dose. In addition, for subjects participating in the PK substudy, a single sparse sample was collected during Weeks 12, 24, and 48 any time between 1 to 24 hours after dosing. For all other subjects, a single sparse sample was collected during Weeks 4, 12, 24, and 48 any time between 1 to 24 hours after dosing |
| AI463004 | Adult HBV | A pilot study in adults with chronic HBV infection (both treatment naïve and LVD/interferon pretreated) who had well-compensated liver disease. It was a randomized, double-blind, placebo-controlled; dose-escalating trial in which the treatment period was 28 days and the post-dosing follow-up period was 6 months | Doses of 0.05, 0.1, 0.5, and 1.0 mg ETV QD as an oral capsule | 40 | PK sampling was conducted at the following nominal times: pre-dose (Days 1, 7, 14, 21, and 28) |
| AI463005 | Adult HBV | Phase 2, randomized, double-blind study of 3 doses of ETV given for 24 weeks compared to LVD in adults with chronic HBV infection who were nucleoside-naïve. Randomization was stratified by HBeAg status | Doses of 0.01, 0.1, and 0.5 mg ETV QD as a capsule<br><br>LVD 100 mg QD as active control | 185 | PK sampling was conducted at the following nominal times: Day 1: 1.5, 3, 6, 10 hours after dosing, Weeks 4, 12, 22: > 1 hour post-dose sample was taken |
| AI463014 | Adult HBV | Phase 2, randomized, double-blind study of 3 doses of ETV compared to LVD in subjects with chronic HBV with viremia while treated with LVD. Study dosing was continued for up to 48 weeks | Doses of 0.01, 0.1, and 0.5 mg ETV QD as a capsule<br><br>LVD 100 mg QD as active control | 181 | PK sampling was conducted at the following nominal times: Day 1: 1.5, 3, 6 hours post-dose, Weeks 4, 12, 24, 36, 48: > 1 hour post-dose |

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For the PKPD model building dataset, all observed concentration and HBV DNA data from Studies AI463028 and AI463189 were pooled with the existing nonlinear mixed effects model (NONMEM) model building database from a previous evaluation of ETV involving the three adult studies (AI463004, AI463005, and AI463014).

In all, there were a total of 540 concentration records from 121 pediatric subjects and 989 concentration records from 177 adult subjects included in the population PK analysis. A total of 916 HBV DNA records from 139 pediatric subjects and 376 HBV DNA records from 110 adult subjects were included in the pharmacodynamics analysis. Details on the

number of subjects and number of samples included by study are summarized below in Table 3.

**Table 3 Pharmacokinetic (top) and Pharmacodynamic Analysis Datasets Used for Analysis**

Pharmacokinetic Subset

| Study | Formulation | No. Subjects Included[a] | No. Samples Included | Total No. of Samples by Study |
|---|---|---|---|---|
| AI463028 | Tablet[b] | 24 | 166 | 291 |
| | Solution | 18 | 125 | |
| AI463189 | Tablet | 41 | 129 | 249 |
| | Solution | 38 | 120 | |
| AI463004 | Capsule | 30 | 242 | 242 |
| AI463005 | Capsule | 93 | 471 | 471 |
| AI463014 | Capsule | 54 | 276 | 276 |
| Total | | 298 | 1529 | 1529 |

Pharmacodynamic Subset

| Study | Formulation | No. Subjects Included[a] | No. Samples Included | Total No. of Samples by Study |
|---|---|---|---|---|
| AI463028 | Tablet | 11 | 85 | 232 |
| | Solution | 16 | 147 | |
| AI463189 | Tablet | 63 | 384 | 684 |
| | Solution | 49 | 300 | |
| AI463004 | Capsule | 21 | 43 | 43 |
| AI463005 | Capsule | 89 | 333 | 333 |
| AI463014[b] | Capsule | 0 | 0 | 0 |
| Total | | 249 | 1292 | 1292 |

*Sponsor's pediatric-modeling-simulation-report.pdf, page 23-24*

Entecavir concentration time course profiles for pediatric and adults as well as HBV DNA time course plots for pediatrics and adults based on the observed data are shown in Figure 2 and Figure 2, respectively.

**Figure 6: Concentration versus Time After Last Dose Pediatrics and Adults Administered Entecavir**

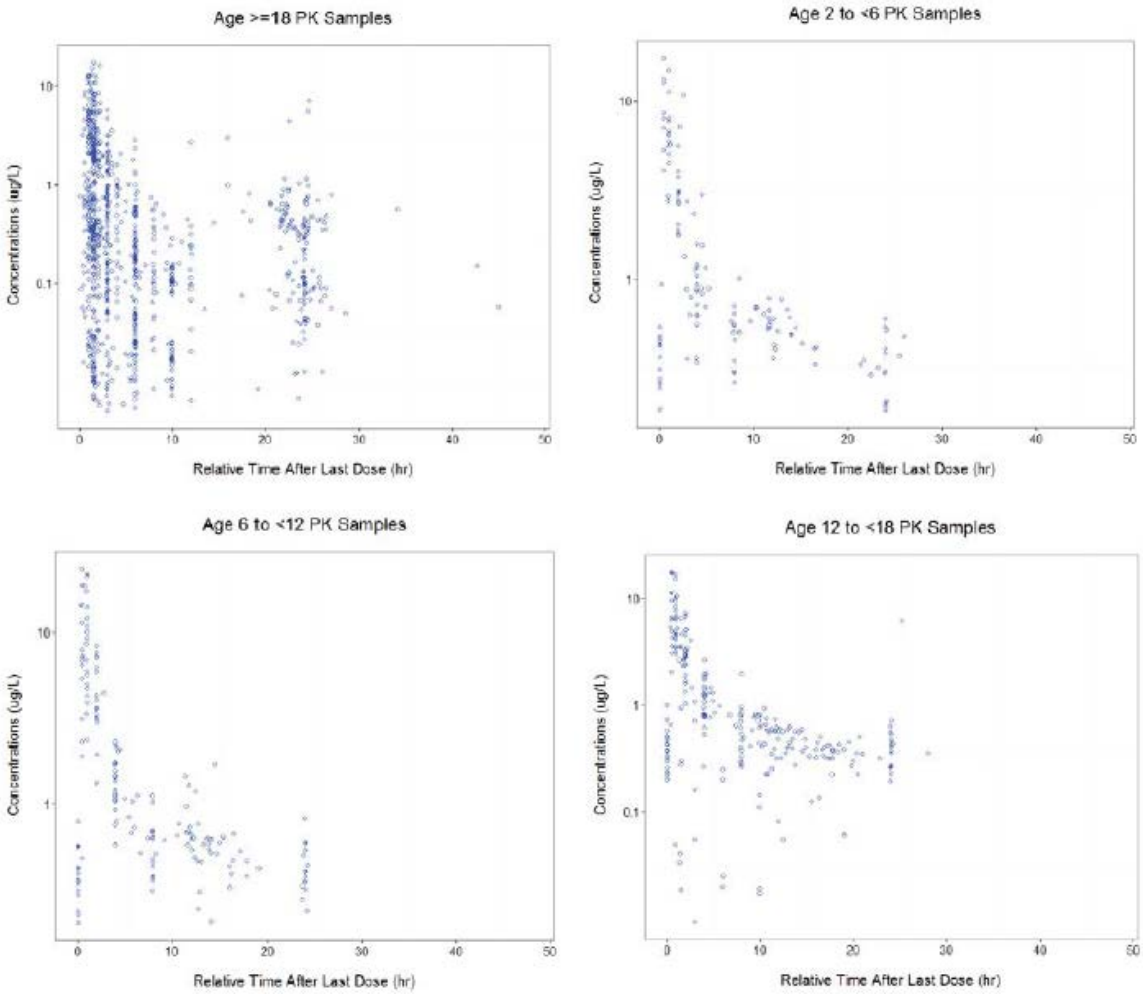


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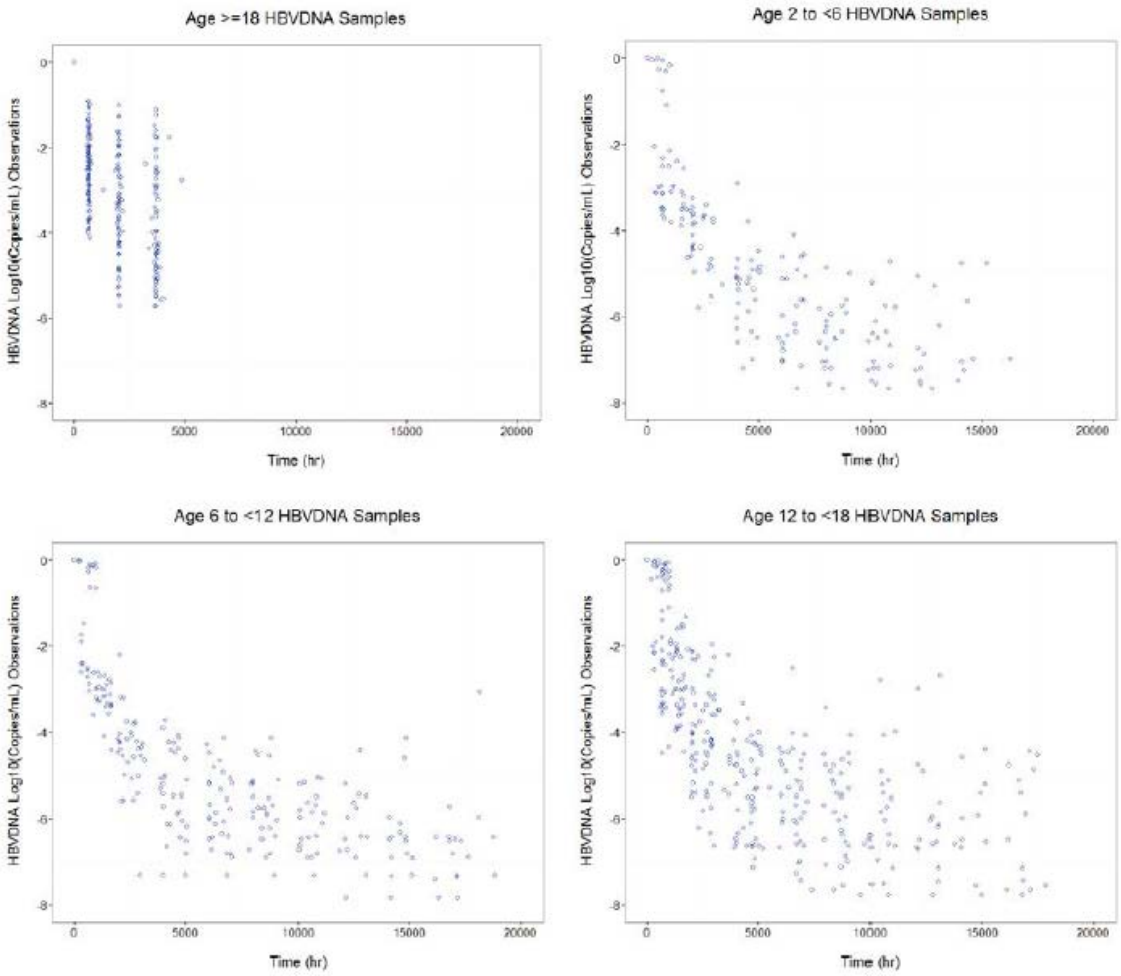
**Figure 7: HBV DNA versus Time (bottom) for Pediatrics and Adults Administered Entecavir**

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### 3.1.2 Model Development

The PK and PKPD of ETV were characterized by nonlinear mixed-effects ("population") compartmental models. In order to characterize the PK and PD of ETV in children, pediatric and adult data were used for the model development but the number of adult subjects was limited to preclude a major influence of the adult data on ETV PK parameters.

The base model consisted of the following components: a structural model that described plasma concentrations of ETV as a function of time for the PK model, or the change from baseline HBV DNA as a function of time for the PD model, an interindividual variability (IIV) model that described random variability among individuals in the study population, and a residual error model that characterized the random variability in observed data within an individual.

The criteria used for model selection was based on successful achievement of NONMEM minimization and covariance steps, assessment of goodness-of-fit plots, reduction in the NONMEM objective function values, and reduction in IIV and residual variability.

Pharmacokinetic Structural Model

A 2-compartment model with first-order absorption and first-order elimination was used as a base model. The 2-compartment model for the base structural model was defined in terms of the following parameters: absorption rate constant (Ka), apparent clearance (CL/F), apparent central volume of distribution (Vc/F), apparent peripheral volume of distribution (Vp/F), and apparent inter-compartmental clearance (Q/F) between the central and peripheral compartments.

Pharmacodynamic Structural Model

An inhibitory maximum effect (Emax) model was used as a base PD model. The model for the base PD structural model was defined in terms of the following parameters: time to half-maximal reduction in viral load (TDay50), and maximal change from baseline viral load (RespMax). The value at time 0 (E0) was fixed to 0.

Interindividual Variability Model (IIV Model)

Individual values of structural model parameters that were constrained to positive values followed were assumed to follow a lognormal distribution. During the population PK model development, the eta distribution for the central volume of distribution was observed to be skewed and was addressed using a Manly transformation. In addition, high correlation was observed between IIV on Q/R and $V_p$/F and was addressed using a shared scaling parameter on eta. No transformations were necessary based for the PD analysis.

Covariate Model

Covariates evaluated for the population PK analysis included age, formulation, sex, race, body weight, ideal body weight, body surface area, and body mass index. Covariates evaluated for the PD analysis included sex, age, body weight, and baseline viral load.

Once all important covariates were identified, a full model including all relevant covariates was tested. A stepwise backward elimination from the full model was implemented. Covariate-parameter relationships in the full-covariate model were retained in the final model provided they were statically significant ($p < 0.001$). A continuous covariate was considered clinically relevant if its inclusion resulted in more than a 20% change in point estimates for low (5%) and high (95%) values of the covariate and the 95% confidence interval (CI) was outside the range of 80%-120% of the typical value of the PK parameter without this covariate (but including all other significant covariates in the model). For a categorical covariate, the clinical relevance was defined as 20% change in point estimates compared to the typical parameter values of the reference population and the 95% CI was outside the range of 80%-120% of the typical value without this covariate. For both continuous and categorical covariates, covariates that resulted in less than 20% change in point estimates and the 95% CI fell within 20% of the reference value were determined to be not clinically important. If the point estimates of a covariate

effect were within 80%-120% of the reference value, but the 95% CIs exceeded the range of 80%-120%, it was concluded that there was insufficient information in the present dataset.

Simulations from the Population PK Model

The final population PK model was used to simulated steady-state entecavir concentrations at the proposed dosing regimens for both the oral and tablet formulations. Comparisons between ETV AUC values for the adult and pediatric subjects were made to support dose regimens recommended for pediatric subjects. Other evaluated exposure metrics included $C_{max}$ and $C_{min}$.

Simulated datasets (N=1,000) were created with each dataset containing 100 pediatric subjects per covariate category. Subject demographics were sampled with replacement from the observed dataset for simulation. Mean individual drug exposure values for each age group were calculated and the distribution of the mean values was examined graphically.

### 3.1.3 Population Pharmacokinetic Model Results

The base model characterized entecavir PK in pediatric subjects with a first-order absorption and 2-compartment disposition model. As described above, transformation of the $V_c/F$ IIV structure and use of a scaled eta IIV term for $V_p/F$ and $V_c/F$ improved model performance. The covariate analysis identified body size (body weight, body surface area, body mass index) as important predictive factors of entecavir PK. Covariate effects of body size were included on all model parameters using allometric scaling (0.75 for clearance terms; 1.0 for volume terms) and normalizing the relationship to a reference body weight of 70 kg. In addition, renal function was identified as significant on CL/F and age on $k_a$. Dose was included as a covariate on Q/F as entecavir PK was observed to be less than dose-proportional for single doses but dose proportional at steady state. Parameter estimates and relationships for the final model are shown below in Table 3. Goodness-of-fit plot for the final population pharmacokinetic model by age group are shown below in Figure 4. There remained bias in the estimation of the highest concentration values from the younger pediatric age groups, but the bias was diminished compared to the base model.

**Table 4 Final Population Pharmacokinetic Model Parameters and Relationships**

| Parameter (units) | Model Parameter | Estimate | Standard Error | Lower 95% CI | Median | Upper 95% CI |
|---|---|---|---|---|---|---|
| Ka (1/hr) | θ1 | 3.25 | 40.3 | 1.635 | 3.6 | 9.219 |
| CL/F (L/hr) | θ2 | 29.6 | 3.1 | 27.8 | 29.5 | 31.4 |
| Vc/F (L) | θ3 | 120 | 6.4 | 99.53 | 118 | 139 |
| Vp/F (L) | θ4 | 1800 | 8 | 1530 | 1830 | 2300 |
| Q/F (L/hr) | θ5 | 81.5 | 9.9 | 64.53 | 78.6 | 95 |
| Residual error (%CV) | θ6 | 42.6 | 4.5 | 38.43 | 42.5 | 45.8 |
| LAMV2S[a] | θ7 | 0.75 | 45.3 | 0.1548 | 0.792 | 2.237 |
| SHARE[b] | θ8 | 1.21 | 11.2 | 0.6166 | 1.18 | 1.54 |
| Effect of dose on Q/F | θ9 | -0.39 | 9.3 | -0.452 | -0.376 | -0.292 |
| Effect of CrCL on CL/F | θ10 | 0.294 | 13.7 | 0.2083 | 0.295 | 0.3707 |
| Effect of age on Ka | θ11 | 0.26 | 59.6 | 0.00681 | 0.297 | 0.6464 |
| IIV CL (%CV) | η1 | 18.57 | 25.10 | 13.61 | 18.60 | 23.17 |
| IIV Vc (%CV) | η2 | 54.95 | 24.00 | 36.10 | 53.29 | 67.96 |
| IIV Q (%CV) | η3 | 39.12 | 23.90 | 26.76 | 39.24 | 49.06 |
| Corr (CL, Vc) | -- | 0.461 | Not Estimated | 0.2349 | 0.477 | 0.6727 |
| Corr (CL, Q) | -- | 0.5 | Not Estimated | 0.186 | 0.515 | 0.7831 |
| Corr (Vc, Q) | -- | 0.828 | Not Estimated | 0.534 | 0.836 | 0.9957 |

$$Ka = \theta 1 * \left(\frac{Age\ (yr)}{45}\right)^{\theta 11}$$

$$\frac{CL}{F} = \theta 2 * \left(\frac{Weight(kg)}{70}\right)^{0.75} * \left(\left(\frac{Creatinine\ Clearance\ \left(\frac{mL}{min}\right)}{100}\right) * \left(\frac{70}{Weight(kg)}\right)\right)^{\theta 10} * exp(\eta 1)$$

$$TVVc = \theta 3 * \left(\frac{Weight\ (kg)}{70}\right)$$

$$LAMV2 = \theta 7$$

$$ET2 = \frac{(\exp(\eta 2 * LAMV2) - 1)}{LAMV2}$$

$$\frac{Vc}{F} = TVVc * exp(ET2)$$

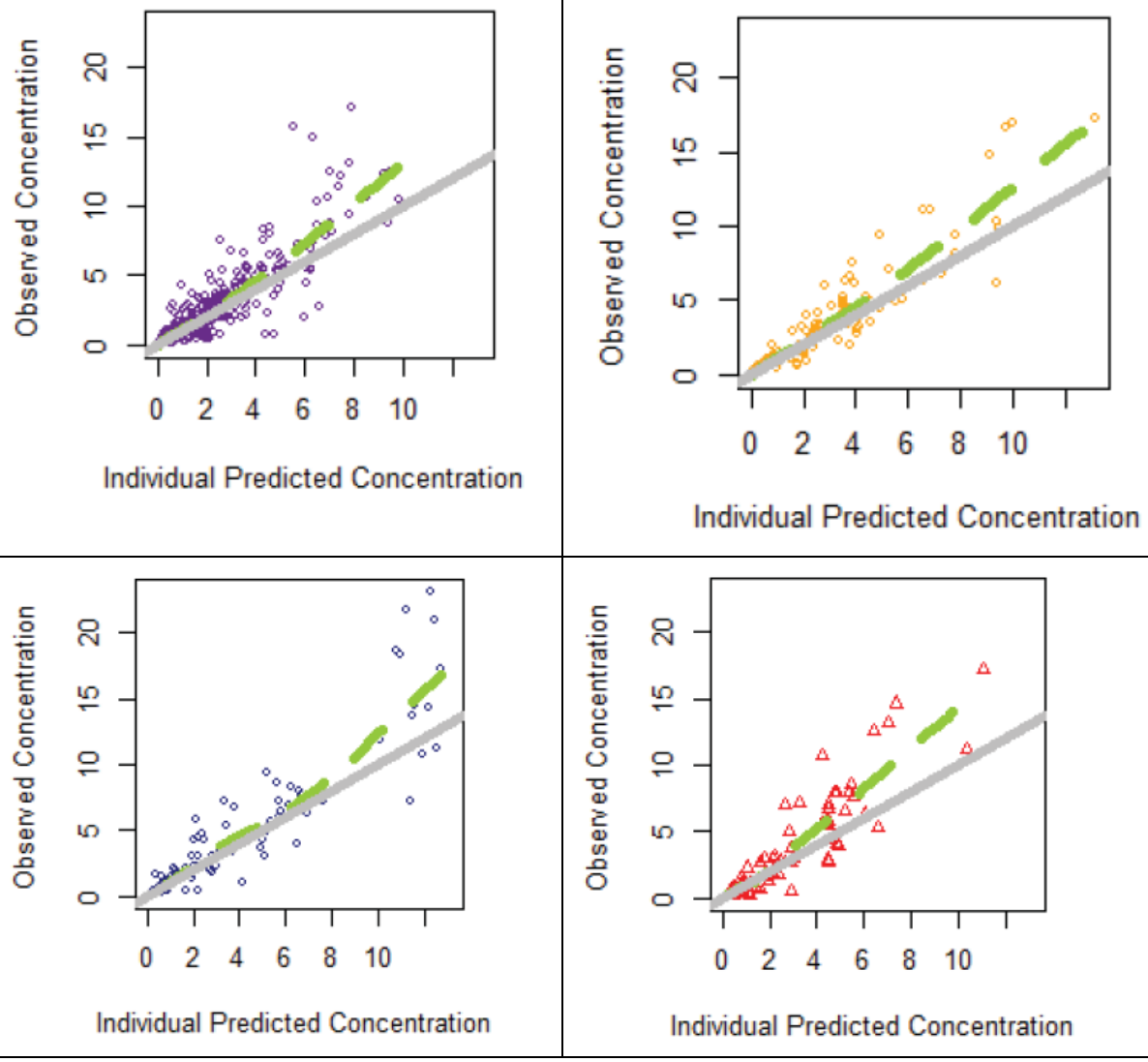
$$\frac{Q}{F} = \theta 5 * \left(\frac{Dose\ (ug)}{100}\right)^{\theta 9} * \left(\frac{\text{Weight (kg)}}{70}\right)^{0.75} * \exp\ (\eta 3)$$

$$Share = \theta 8$$

$$\frac{Vp}{F} = \theta 4 * \left(\frac{Weight(kg)}{70}\right) * exp(\eta 2 * Share)$$

*Sponsor's pediatric-modeling-simulation-report.pdf, page 83-84*

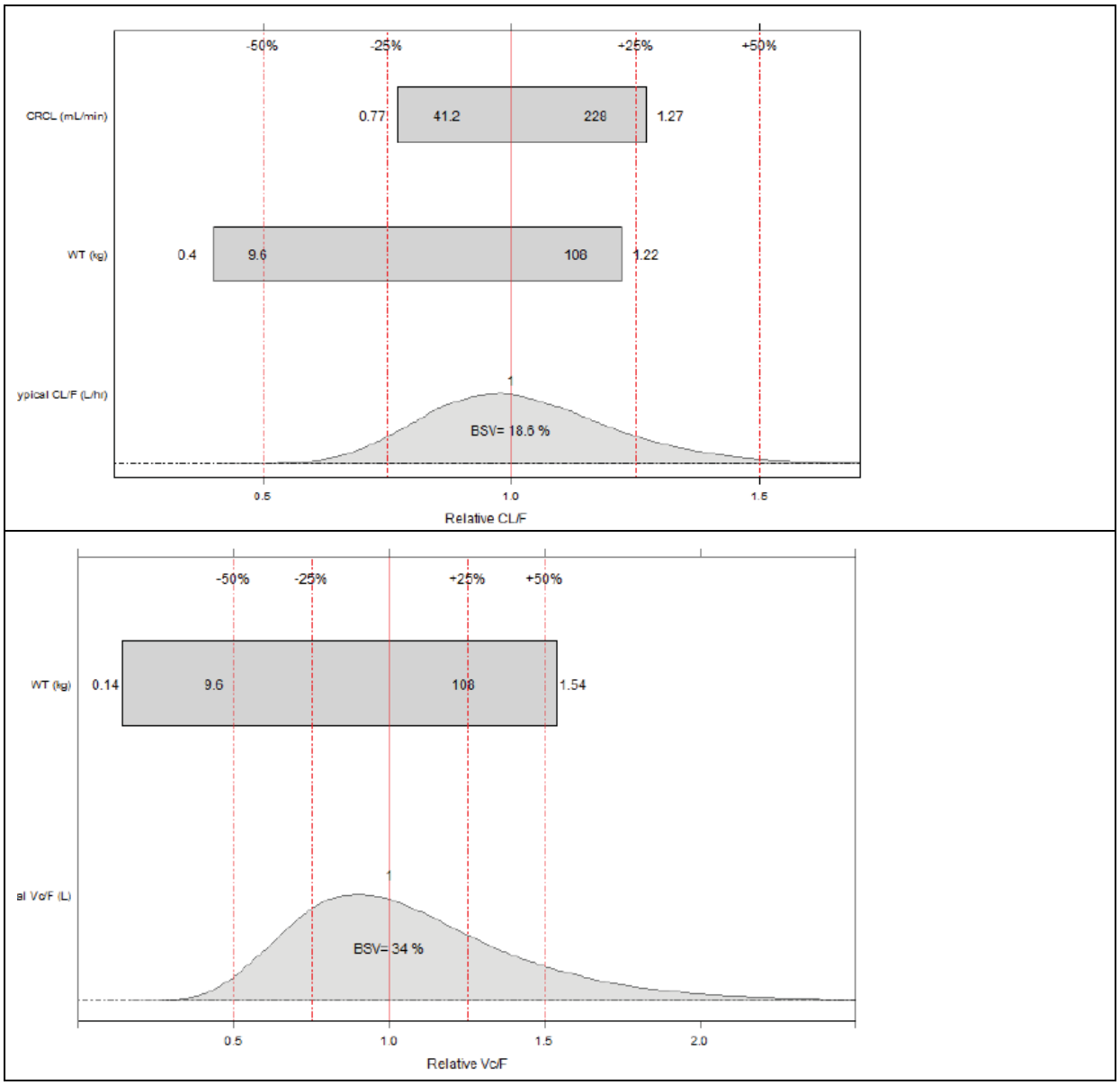
Figure 8: Goodness-of-fit plots (observed versus individual predicted concentrations) for adults (top, left), pediatrics 12-18 years of age (top right), pediatrics 6-12 years of age (bottom left) and pediatrics 2-6 years of age (bottom right).

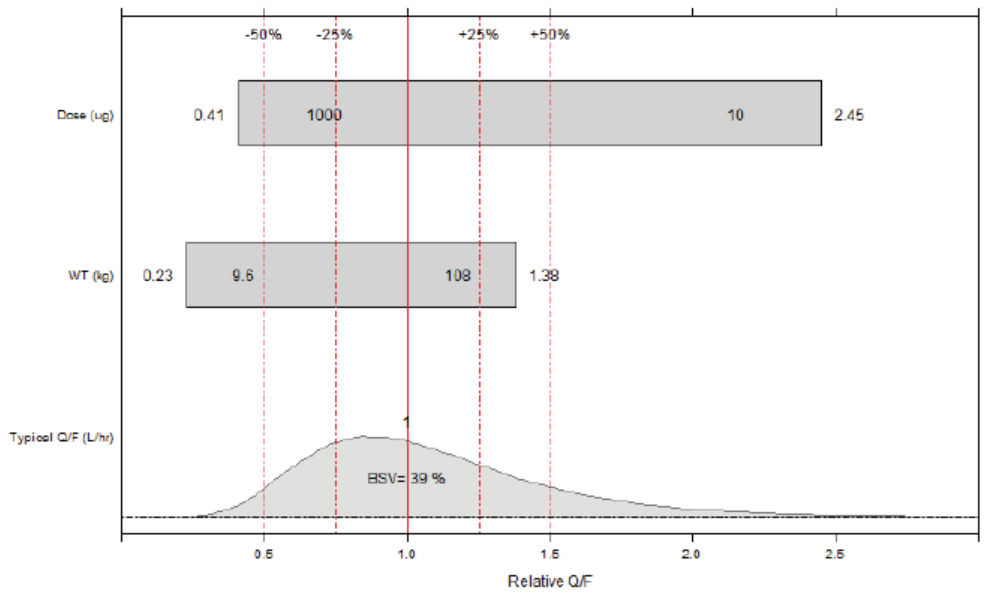



*Sponsor's pediatric-modeling-simulation-report.pdf, page 85-88*

The effects of covariates on the final PPK parameters are shown graphically in Figure 5. It should be noted that the effect of dose on Q/F was necessary for reproducing the apparent lack of dose proportional behavior for single dose data, but this covariate does not have substantial impact for multiple dose PK.

Figure 9: Graphical illustration of the impact of covariates on CL/F, $V_C$/F, and Q/F based on the final population pharmacokinetic model.


-50%
-25%
+25%
+50%
CRCL (mL/min)
0.77
41.2
228
1.27
WT (kg)
0.4
9.6
108
1.22
ypical CL/F (L/hr)
1
BSV= 18.6 %
0.5
1.0
1.5
Relative CL/F
-50%
-25%
+25%
+50%
WT (kg)
0.14
9.6
108
1.54
al Vc/F (L)
1
BSV= 34 %
0.5
1.0
1.5
2.0
Relative Vc/F




*Sponsor's pediatric-modeling-simulation-report.pdf, page 93, 95, 98*

Finally, the sponsor conducted simulations to assess the appropriateness of the proposed pediatric doses to the approved adult entecavir doses. While AUC was the main criterion for dose recommendations, $C_{max}$ and $C_{min}$ were considered as well. Simulated datasets (N=1,000) were created, with each dataset containing 100 pediatric subjects per age group. Subject demographics were sampled with replacement from the observed dataset for simulation. For each subject, sampling times of 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post a steady-state dose were created and the concentration time profiles were simulated using the final PPK model. For each simulated dataset, mean individual AUC per dose age group was calculated, and the distribution of the mean AUC was used to evaluate the recommended dose regimen for the corresponding age group.

The following tables present the simulation results using the final model and the three entecavir exposure parameters (Table 3). These simulated AUC values show that the recommended dose regimens produce comparable exposure between adults and children for all age groups. The simulation results for $C_{max}$ and $C_{min}$ are also in reasonable agreement across all age groups, supporting the recommended dose for pediatric subjects.

**Table 5 Simulation Results of Entecavir Mean AUC, $C_{min}$ (µg/L), and $C_{max}$ (µg/L) at Recommended Doses by Age Group**

| Age | $10^{th}$ | $25^{th}$ | $50^{th}$ | $75^{th}$ | $90^{th}$ |
|---|---|---|---|---|---|
| Adult | 12.36 | 14.47 | 16.96 | 19.80 | 23.00 |
| 2 to < 6 yrs | 13.25 | 15.55 | 18.18 | 20.93 | 24.15 |
| 6 to < 12 yrs | 14.24 | 17.54 | 20.72 | 22.32 | 25.83 |
| 12 to < 18 yrs | 11.32 | 14.14 | 16.91 | 19.96 | 23.11 |

| Age | 10th | 25th | 50th | 75th | 90th |
|---|---|---|---|---|---|
| Adult | 0.18 | 0.27 | 0.39 | 0.57 | 0.82 |
| 2 to < 6 yrs | 0.16 | 0.24 | 0.36 | 0.56 | 0.77 |
| 6 to < 12 yrs | 0.18 | 0.27 | 0.42 | 0.63 | 0.94 |
| 12 to < 18 yrs | 0.15 | 0.24 | 0.36 | 0.53 | 0.77 |

| Age | 10th | 25th | 50th | 75th | 90th |
|---|---|---|---|---|---|
| Adult | 2.02 | 3.02 | 4.40 | 6.32 | 8.88 |
| 2 to < 6 yrs | 2.38 | 3.44 | 5.15 | 7.56 | 10.33 |
| 6 to < 12 yrs | 2.45 | 3.87 | 5.89 | 8.64 | 10.13 |
| 12 to < 18 yrs | 1.82 | 2.94 | 4.45 | 6.59 | 9.45 |

*Sponsor's pediatric-modeling-simulation-report.pdf, page 4*

*Reviewer's comments: The reviewer was able to recreate the sponsor's analysis and identified a similar model structure and covariates based upon the methodology outlined by the sponsor. The developed model was able to adequately describe the available entecavir pediatric data, though the model was not able to accurately describe $C_{max}$ observations. Simulations from this developed model as well as observed entecavir concentration data from AI463028 support the selected entecavir pediatric dosage regimen; however, the sponsor was requested to propose alternative dosing tables which may have fewer dosing increments in order to reduce the likelihood of dosing errors.*

*The sponsor provided a response to this query on February 14, 2014 agreeing with the Agency's concern about the proposed dosing table. Based on updated simulations performed by the sponsor, they proposed the pediatric dosing table shown in Table 6. Note, this updated table included fewer dosing increments and body weight intervals rounded to the nearest kilogram.*

**Table 6 Updated Pediatric Entecavir Dosing Table from the Sponsor (2/14/2014)**

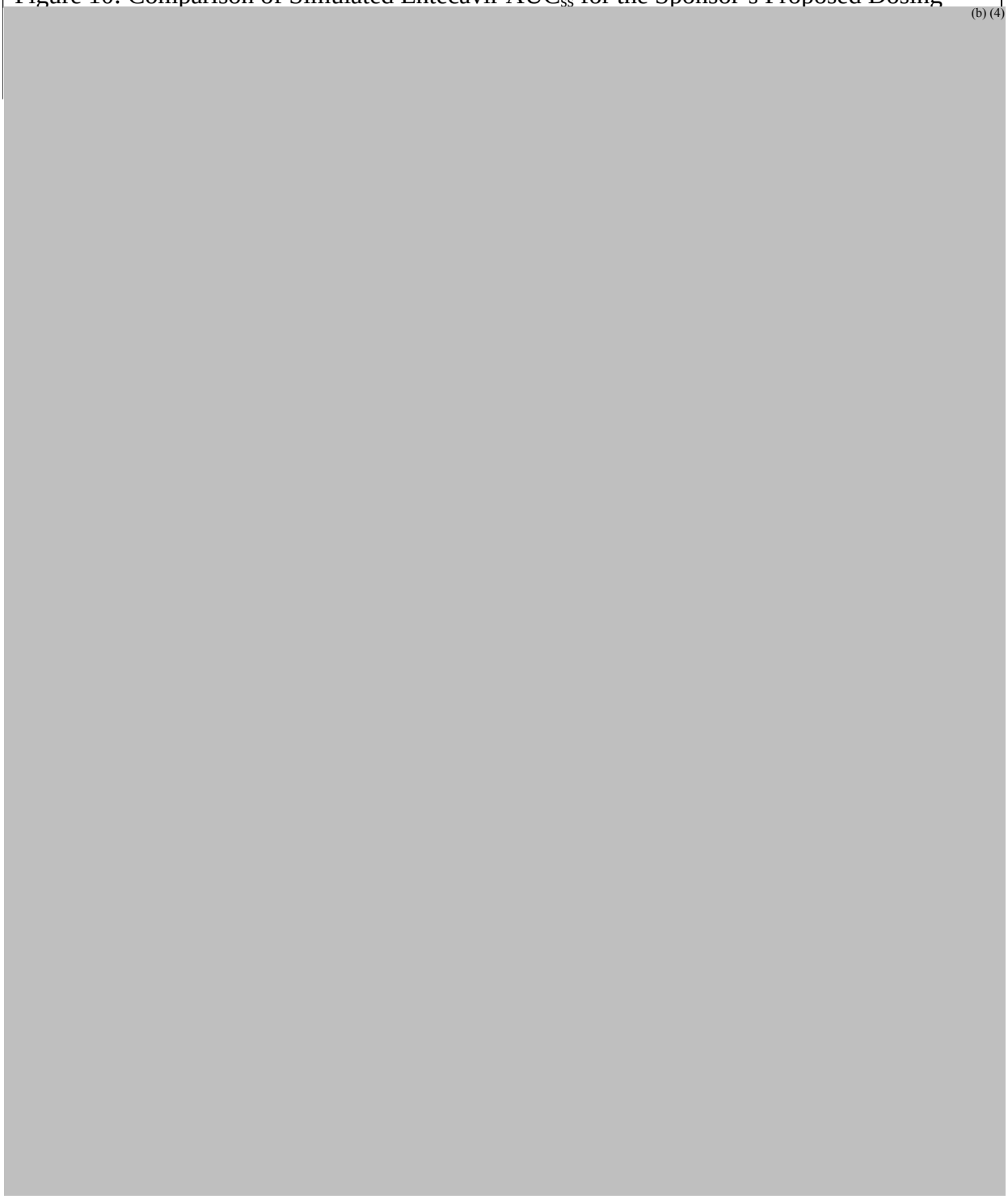
| Recommended Once-Daily Dose of Oral Solution (mL) | | |
|---|---|---|
| **Body Weight (kg)** | **Treatment Naive Subjects[a]** | **Lamivudine Experienced[b]** |
| (b) (4) | | |

[a] Children with body weight greater than (b) (4) kg should receive 10.0 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily.
[b] Children with body weight greater than (b) (4) kg should receive 20.0 mL (1 mg) of oral solution or one 1.0 mg tablet once daily.

*To support this proposed dosing, the sponsor provided additional simulations comparing simulated entecavir $AUC_{ss}$ from the original dosing recommendations to those in Table 6. The results of these simulations are shown graphically*

Figure 10: Comparison of Simulated Entecavir $AUC_{ss}$ for the Sponsor's Proposed Dosing

(b) (4)



*Overall, the proposed changes in the dosing table are expected to have minimal changes in the overall AUC for these pediatric groups. However, it was noted that the new dosing recommendations in pediatrics* (b) (4) *would result in entecavir mg/kg dosing ranging between* (b) (4) *respectively. Of note, in the original dosing recommendations, none of the treatment-naïve pediatrics groups would receive more than* (b) (4)*. As these upper ranges exceeded the targeted dose of* (b) (4) *and as the dosing recommendations would also be extended to lamivudine experienced patients (potential for* (b) (4) *rather than a target of* (b) (4)*), the Division provided alternative dosing recommendations to the sponsor as part of labeling negotiations. These alternative dosing recommendations targeted a maximum dose* (b) (4) *in treatment naïve patients and are shown in the main body of the clinical pharmacology review.*

### 3.1.4 Population Pharmacodynamic Model Results

Base PPD model development was conducted with the model building dataset described above. Once the PPK model was developed, the PK parameters were fixed to their final estimates and the PD parameters were estimated. The PD of entecavir in the pediatric population were characterized by a direct effect inhibitory $E_{max}$ model

Following identification of the basic structural model, the effect of drug exposure was tested. Diagnostic plots with the initial base model indicated no substantial differences between adult and pediatric response to ETV. Drug exposure was evaluated using dose and AUC, with power functions, and natural log and exponential functions that were tested to replicate a nonlinear effect of exposure and response. Entecavir AUC was found to be predictive of both RespMax and TDay50, with RespMax increasing with increasing AUC and TDay50 decreasing with increasing AUC. Final model parameters for the HBV viral time course model are described in Table 7. Key conclusions and observations from this analysis included that ALT normalized baseline viral load was a factor for the maximum response and that entecavir AUC was associated with both a higher maximum response and faster onset of response (lower TDay50). In addition, age was not identified as a factor on any of the model parameters suggesting that the time course of HBV response to entecavir was similar in pediatrics and adults.

**Table 7 Final Population Pharmacodynamic Model Parameters and Relationships**

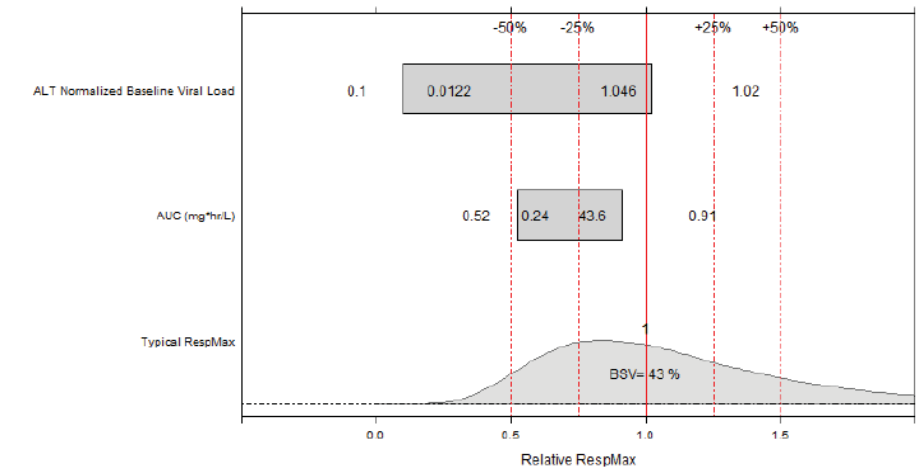
| Parameter (units) | Model Parameter | Estimate | Standard Error | Lower 95% CI | Median | Upper 95% CI |
|---|---|---|---|---|---|---|
| TDay50 (days) | θ12 | 111 | 13.5 | 84.26 | 110 | 148.4 |
| RespMax (change from baseline viral load ($log_{10}$(copies/mL)) | θ13 | 9.26 | 3.7 | 8.65 | 9.25 | 9.96 |
| Residual error ($log_{10}$(copies/mL) | θ14 | 0.652 | 3.9 | 0.599 | 0.65 | 0.702 |
| Effect of AUC on TDay50 | θ15 | 0.477 | 11.3 | 0.3716 | 0.475 | 0.59 |
| Effect of AUC on RespMax | θ16 | 0.222 | 6.4 | 0.193 | 0.222 | 0.25 |
| Effect of ALT normalized baseline viral load on Respmax | θ17 | -0.0511 | 36.2 | -0.08712 | -0.051 | -0.01356 |
| Effect of ALT on TDay50 | θ18 | 0.386 | 15.7 | 0.2636 | 0.388 | 0.508 |
| IIV TDay50 (%CV) | η4 | 61.73 | 17.8 | 50.12 | 61.16 | 72.14 |
| IIV RespMax (additive) | η5 | 0.928 | 18.6 | 0.736 | 0.915 | 1.090 |
| Corr (TDay50,RespMax) | -- | 0.487 | Not estimated | 0.19 | 0.486 | 0.677 |

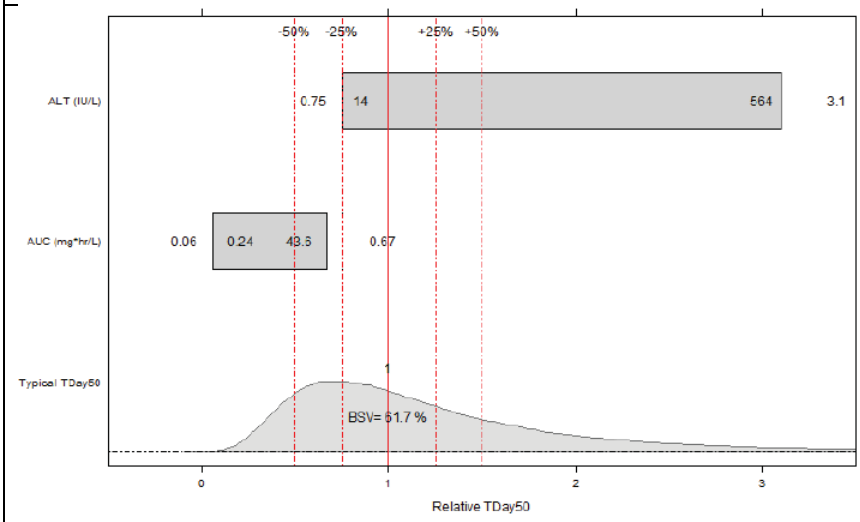
$$TDay50 = \theta12 * \left(\frac{AUC\ \left(\frac{ug}{L}\right)}{100}\right)^{\theta15} * \left(\frac{ALT\ \left(\frac{IU}{L}\right)}{30}\right)^{\theta18} * exp(\eta4)$$

$$RespMax = \theta13 * \left(\frac{AUC\ \left(\frac{ug}{L}\right)}{100}\right)^{\theta16} * \left(\frac{Baseline\ Viral\ Load\ (Log10\ \left(\frac{Copies}{mL}\right)}{ALT(\frac{IU}{L})}\right)^{\theta17} * exp(\eta5)$$

*Sponsor's pediatric-modeling-simulation-report.pdf, page 122-123*

Figure 11: Graphical illustration of the impact of covariates on maximum HBV response (RespMax) and time to 50% of maximum response (TDay50) based on the final population pharmacodynamic model.



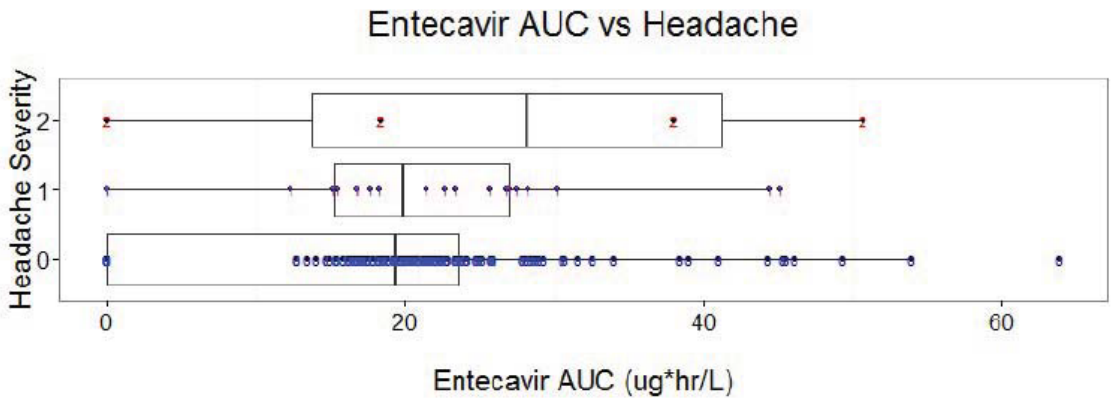



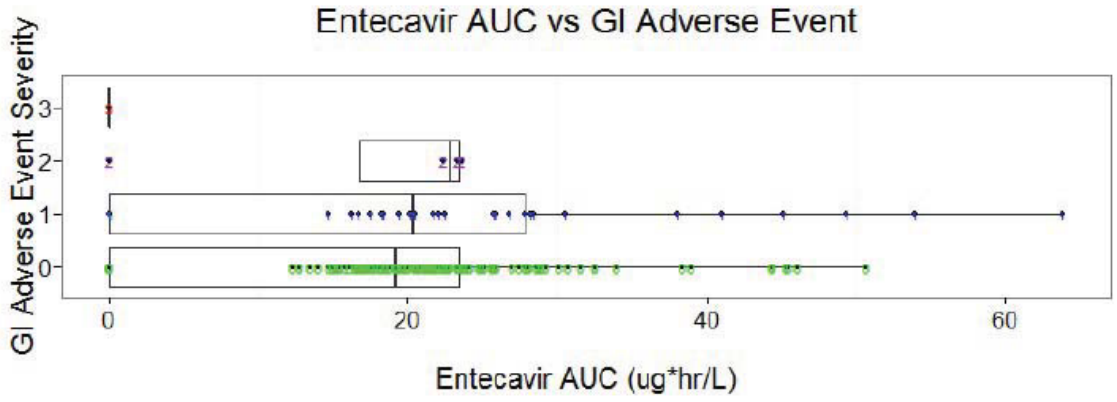

*Sponsor's pediatric-modeling-simulation-report.pdf, page 93, 95, 98*

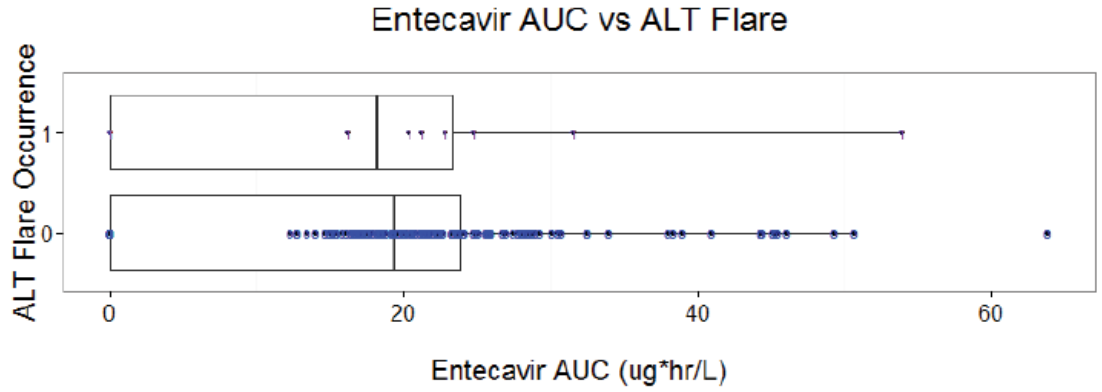
### 3.1.5 Exposure-Response Safety Analyses

Based on the completed population PK analysis, the sponsor conducted graphical comparison of key adverse event rates (headache, GI events, and ALT flares) with entecavir exposure (AUC and $C_{max}$). Plots for headache (top), GI events (middle) and ALT flares (bottom) based on entecavir exposure are shown below in Figure 12. There were 175 subjects with no reported headache, 22 subjects with Grade 1 headache, and 4 subjects with Grade 2 headache. There is a slight visual trend to increasing incidence with increasing measures of ETV exposure. However, this trend was not sufficient to develop an exposure-response model. There were 159 subjects with no GI events, 37 subjects with Grade 1 GI events, 4 subjects with Grade 2 GI events, and 1 subject with a Grade 3 GI event. In these figures, there is no visible trend between ETV exposures and the frequency or severity of the GI events. There were 189 subjects with no ALT flares, and 12 subjects with ALT flares. There is no visible trend between exposure and the ALT flare event.

**Figure 12: Entecavir AUC Versus Frequency and Severity of Headaches (top), GI events (middle), and ALT flares (bottom).**




*Sponsor's pediatric-modeling-simulation-report.pdf, page 140, 143, 146*

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/s/

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