CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	021797/021798
Priority or Standard	Priority
Submit Date(s)	September 20, 2013
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Division / Office	Division of Antiviral Products Office of Antimicrobial Products
Reviewer Name(s)	Kimberly Martin, D.O.
Review Completion Date	February 22, 2014
Established Name	Entecavir
Trade Name	Baraclude
Therapeutic Class	Cyclopentyl guanosine nucleoside analog
Applicant	Bristol-Myers Squibb
Formulation(s)	Tablet and solution
Dosing Regimen	(b) (4) 0.5 mg/day
Indication(s)	Chronic Hepatitis B
Intended Population(s)	Pediatric subjects aged 2-<18 years

Template Version: March 6, 2009

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Commonly used terms will be abbreviated in this document, as indicated below:

AE: Adverse Event
ALT: Alanine aminotransferase
ANC: Absolute neutrophil count
AST: Aspartate aminotransferase
AUC: Area under the curve
CHB: Chronic Hepatitis B
ETV: Entecavir
HBeAg: Hepatitis B early antigen
HBsAg: Hepatitis B surface antigen
HBV: Hepatitis B virus
HIV: Human Immunodeficiency virus
LVD-Lamivudine
PT: Preferred Term
SAE: Serious Adverse Event
SOC: System Organ Class
TEAE: Treatment Emergent Adverse Event
ULN: Upper limit of normal

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is the opinion of this clinical reviewer that the data from Study AI463028 and AI463189 support approval of Baraclude® (entecavir, ETV) for treatment of pediatric patients aged 2- <18 with Chronic Hepatitis B (CHB).

Additionally, this study fulfills PMR 279-1 and 279-2 which required a pediatric PK study followed by a pediatric safety and efficacy study in children aged birth to 16 years. As noted in the Written Request for pediatric studies dated November 28, 2006, the Agency asked that studies be conducted in subjects greater than 2 years of age. Because of the high rate of spontaneous HBV clearance in pediatric subjects under 2 years of age, studies in patients younger than 2 years will be waived.

1.2 Risk Benefit Assessment

Few therapeutic options for treatment of CHB are approved for young children. Currently, only interferon and lamivudine are approved for children less than 12 years of age therefore greatly limiting the options available to both providers and pediatric patients. In the Phase 2 and Phase 3 pediatric trials, ETV has been shown to have few Serious Adverse Events and no major safety signals were found. The Adverse Events (AEs) observed in this study are consistent with those observed in prior adult ETV studies. ETV in pediatric subjects will provide another option for treatment of CHB which is both safe and effective.

Subjects in both studies had high virologic success. In trial AI463028, a non-placebo controlled Phase 2 study, 33.3% of treatment naïve subjects had virologic success (HBV DNA < 50 IU/ml plus HBeAg seroconversion) and 58.3% had HBV DNA <50 IU/ml. In Study AI463189, the Phase 3 trial, 24% of ETV treated subjects had virologic success compared to 2% of placebo treated subjects.

Overall, the potential treatment benefits outweigh the potential risks as determined in this review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to this NDA submission.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for Postmarket Requirements and Commitments related to this NDA submission.

2 Introduction and Regulatory Background

Hepatitis B infection is a global health problem, affecting approximately two billion people worldwide and 1.4 million people in the United States.[1, 2] The majority of infections result in acute hepatitis which spontaneously resolves, although a subset of patients will develop chronic infection. An estimated 240 million people worldwide and 1.2 million people in the United States have CHB infection.

Although universal hepatitis B virus vaccination is recommended in the United States and much of the rest of the world, chronic HBV infection remains a significant global health problem resulting in chronic liver disease, cirrhosis, hepatocellular carcinoma and death. There is no national surveillance program for chronic hepatitis B in children in the United States, and the prevalence of this infection in not known but generally thought to be very low.

Most children with chronic hepatitis B in the United States have acquired the infection vertically, were adopted from countries where the infection is endemic, or are adolescents with high risk behaviors. However, among pediatric patients who acquire HBV infection in the perinatal period, up to 95% are expected to develop chronic HBV infection. In the US, of those with chronic HBV, an estimated 5-10% spontaneously clear hepatitis B early antigen (HBeAg) each year. Upon HBeAg clearance, the infection usually becomes inactive, although in some subjects the virus will later reactivate. Because the spontaneous clearance rate is significant but somewhat variable, there is no consensus regarding optimal timing of treatment in pediatric patients. Most experts do not recommend treatment until the age of 2 or 3 years given the possibility of spontaneous clearance.

The decision to treat CHB in children is based upon HBV viral load and degree of hepatic inflammation and/or dysfunction. Current treatment options for pediatric patients are limited with few options for the youngest subjects. To date the only approved oral products for the treatment of chronic HBV in pediatric patients include: lamivudine, approved for use in pediatric patients greater than 2 years of age and adefovir dipovoxil and tenofovir disoproxol, both approved for use in patients greater than 12 years of age. In addition, interferon alfa-2b, an injectable product, is approved for use in pediatric patients greater than 1 year of age.

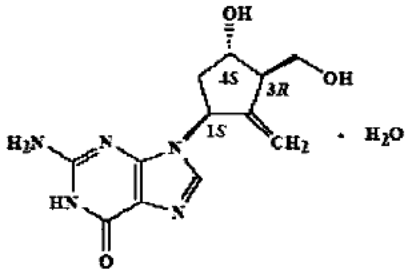
2.1 Product Information

Chemical name: 2-amino-1, 9-dihydro-9-[(*1* S, 3R, 4S)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one, monohydrate.

Molecular Formula: $C_{12}H_{15}N_5O_3 \cdot H_2O$

Molecular weight: 295.3

Chemical structure:



2.2 Tables of Currently Available Treatments for Proposed Indications

Currently approved drugs for treatment of CHB are summarized in Table 1.

Table 1: Drugs Approved for Chronic Hepatitis B

Generic Name	Trade Name	Adult Dose	Approved Ages
Interferon-alfa-2b	Intron A®	30-35 million IU per week	≥ 1 year of age
Pegylated interferon	Pegasys®	180 mcg once weekly	Adults
Lamivudine	Epivir-HBV®	100 mg once daily	≥ 2 years of age
Adefovir	Hepsera®	10 mg once daily	≥ 12 years of age
Entecavir	Baraclude®	0.5 mg once daily	≥ 16 years of age
Telbivudine	Tyzeka®	600 mg once daily	≥ 16 years of age
Tenofovir DF	Viread®	300 mg once daily	≥ 12 years of age

2.3 Availability of Proposed Active Ingredient in the United States

ETV is approved for the treatment of CHB infection in adults and children ≥ 16 years of age. As such, it is widely available in the United States in tablet and oral solution formulations.

2.4 Important Safety Issues With Consideration to Related Drugs

On treatment and post-treatment ALT flares are known to occur in adults receiving CHB therapy. Please see Section 7.3.5 for details of pediatric ALT flares related to this submission.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

ETV was approved on March 29, 2005 for treatment of CHB in nucleoside treatment naïve or lamivudine-refractory or known lamivudine/ telbivudine resistant adults ≥ 16 years of age. Dosing in treatment naïve subjects is 0.5 mg once daily while treatment experienced subjects are dosed 1 mg once daily. For regulatory history prior to this approval, please see the initial NDA review completed by Dr. Linda Lewis.

The pediatric study protocol for AI463028 was submitted on May 24, 2006 and a preliminary proposal for development of Study AI463189 was received on June 19, 2008, both reviewed by Dr. Lewis. The protocol for AI463189 was initially submitted on July 23, 2009 with a revision submitted on August 28, 2009 and both were reviewed by Dr. Peter Miele.

Although the original adult trials included subjects ≥ 16 years of age, few subjects between 16 and 18 were recruited. In discussion with the Sponsor, the Agency agreed that subjects 2- <18 years of age should be enrolled in the pediatric ETV trials in order to gather more information in subjects aged 16 to 18. As detailed above, two years of age was written into the Pediatric Written Request as the minimum age of enrollment. Studies in pediatric subjects under 2 years of age will be waived.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submission were adequate. From a clinical review perspective, the submission was organized and reasonable to navigate.

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in accordance with the ICH Good Clinical Practice guidelines. The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects prior to any trial-related procedures.

3.3 Financial Disclosures

Please see section 9.4 for the Clinical Investigator Financial Disclosure Form.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No major Chemistry or Manufacturing information was submitted apart from a new dosing spoon which updated the measurement increments to 0.5ml to allow for doses from 0.5 mL to 10 mL. Please see the initial CMC review by Dr. Lorenzo Rocca and the supplemental efficacy review by Dr. Stephen Miller for CMC details and the Division of Medication Errors Prevention and Analysis (DMEPA) review by Aleksander Winiarski, PharmD for full details of the dosing spoon and related studies.

4.2 Clinical Microbiology

4.2.1 Mechanism of Action

Entecavir, a cyclopentyl guanosine analog, is a potent and selective inhibitor of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) polymerase. By competing with the natural substrate deoxyguanosine triphosphate, entecavir triphosphate is a potent and selective inhibitor of all three functional activities of the viral polymerase (priming, reverse transcription and DNA-dependent DNA synthesis). In addition to competing directly with deoxyguanosine, the natural substrate for the HBV polymerase, entecavir-triphosphate (entecavir-TP) is a terminator of HBV DNA chain elongation.

4.2.2 Resistance

Clinical resistance analysis was performed from the submitted virologic information. In the pooled population of the two studies, AI463028 and AI463189, paired genotypic data were obtained from 52 subjects. In the treatment-naïve cohorts, no subject

developed any entecavir, lamivudine, and telbivudine resistance-associated amino acid substitutions (rtL80I, rtI169V, rtV173L, rtL180M, rtT184, rtM204I/V, rtS202, or rtM250). In the LVD-experienced cohort, 5 of 8 subjects had the entecavir, lamivudine, and telbivudine resistance-associated amino acid substitutions rtL180M and/or rtM204I/V at baseline. All of these subjects had virologic failure at 48 weeks. In the LVD-experienced cohort, two subjects developed the entecavir, lamivudine, and telbivudine resistance-associated amino acid substitutions rtT184I or rtM204I on ETV-treatment and both had virologic failure. In addition, there were 9 other subjects who developed substitutions of interest and all had virologic failure. These substitutions will be further studied to determine if they are associated with treatment failure. Please see the Clinical Virology review by Dr. Takashi Komatsu for full details.

4.3 Preclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology information was submitted for this pediatric efficacy analysis. Please see the initial Pharm/Tox review by Dr. Pritam Verma for details of the preclinical analysis.

4.4 Clinical Pharmacology

The Phase 2 study, AI463028, was the initial pilot study conducted to obtain PK results which produced exposures in children comparable to adult dosing. In this study, overall exposures (AUC) were comparable between treatment naïve adults (0.5 mg dosing) and treatment naïve pediatric patients (0.015 mg/kg up to 0.5 mg dosing). A slightly lower exposure was observed in adolescent patients in this study as compared to historical data from the adult studies. In the adult trials, an AUC of 18.7 ng.h/mL was calculated while an AUC of 15.4 ng.h/mL was found during intensive PK sampling of adolescents. Similar ETV exposure among treatment experienced adult and pediatric subjects dosed at 1 mg daily was also observed.

Additionally, when analyzing the relationship between ETV AUC value and efficacy (as defined for this analysis as HBV DNA < 50 IU/ml), no trend was found. It should be noted that this analysis did not consider baseline HBV viral load and did not evaluate the primary composite endpoint or other secondary endpoints.

In further analysis, adverse events were evaluated in terms of ETV exposures. A signal of increased vomiting and other Gastrointestinal AEs was noted. Upon further analysis, none of the gastrointestinal AEs, apart from vomiting, were found to be significantly correlated with exposure. Of the vomiting AEs, only 1 reported event was Grade 2 or higher.

For a full description of the Clinical Pharmacology review please see the review by Drs. Su-Young Choi and Jeffry Florian.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Two studies, a Phase 2b and a Phase 3 trial, were included in this submission and are described in Table 2.

Table 2: Summary of Entecavir Studies

Trial Name	Study Design	Study Population	Age Strata Distribution	# Randomized/ #Treated	Study Regimen	Primary Endpoint
AI463028	Phase 2b single arm, open label	Pediatric subjects with CHB infection ≥2 to ≤18 years of age	≥ 2- ≤ 6 :12 >6 - ≤12 :18 >12-<18: 18	64/48 Group A: (LVD-naïve):24 Group B: (LVD-experienced): 19 Group C (nucleoside-experienced): 5	Group A: 0.015 mg/kg ETV, max 0.5mg Group B: 0.030 mg/kg ETV, max 1 mg Group C: 0.030 mg/kg/day ETV, max 1 mg	Determine dose of ETV in children and adolescents that produces drug exposures comparable to adult dosing
AI463189	Phase 3, randomized, double-blind, placebo-control	Pediatric subjects with CHB infection who are HBeAg positive and nucleoside naïve (2 to ≤18 years of age)	≥2-≤ 6: 41 >6-≤ 12: 46 >12-<18: 93	228/180 (2:1 randomization)	ETV 0.015 mg/kg/day, max 0.5 mg/day using oral solution or tablets	Proportion of subjects who achieved both: 1) HBV DNA <50 IU/ml 2) HBeAg seroconversion at Week 48

5.2 Review Strategy

The Sponsor analyzed safety data separately for the two trials (AI463028 and AI463189) and further separated AI463028 subjects into three cohorts (naïve, LVD-experienced and nucleoside experienced) for analysis. Placebo subjects with virologic failure in Study AI463189 were started on open label ETV after 48 weeks and included in the Sponsor's integrated ETV safety population. This strategy was employed as not

all randomized subjects had reached the minimum 48 weeks of therapy prior to data submission. Using this rollover method, placebo subjects were compared to themselves during different phases of the trial when assessing safety events.

The FDA safety analysis for this review was conducted by pooling the entecavir safety data from the Phase 2 trial (regardless of pre-trial treatment history) and the Phase 3 trial through 48 weeks. Safety analysis was limited to 48 weeks to avoid use of placebo subjects in both the placebo and ETV-treated arms. Additionally, the 90 day safety update submitted on December 11, 2013 was reviewed and all data for deaths, SAEs and drug discontinuations was included and not limited to 48 weeks.

All data analysis tables in this section were generated by the clinical reviewer using JReview®, a statistical analysis software package.

5.3 Discussion of Individual Studies/Clinical Trials

AI463028: A Phase 2b, single arm, open label study to assess the PK, safety, tolerability and preliminary efficacy of ETV in pediatrics subjects with HBeAg positive chronic hepatitis B infection aged ≥2 to ≤18 years.

Subjects were enrolled at 21 sites in 8 countries (Argentina, Belgium, Brazil, Canada, Korea, Taiwan, UK and USA).

The primary objective of the study was to determine the doses of ETV in children and adolescents that produce drug exposures comparable to those observed in treatment-naïve and treatment experienced adults given the 0.5mg or 1mg doses, respectively.

Subjects were divided into 3 age strata (≥ 2 - ≤ 6, > 6 - ≤ 12 and > 12 - <18). Subjects were also divided into cohorts based on their history of treatment (LVD-naïve, LVD-experienced and nucleoside experienced).

Major inclusion criteria included HBeAg positive and HBeAb negative at screening and at least once ≥ 4 weeks prior to screening, hepatitis B virus DNA ≥ 10^5 copies/ml at screening and evidence of the presence of hepatitis B DNA at least once ≥ 4 weeks prior to screening and ALT 2 to 10 x ULN at screening and at least twice during the 24 weeks prior to screening and no value falling within the normal reference range in the intervening period.

Notable exclusion criteria included subjects coinfected with HIV, hepatitis C virus, hepatitis D virus or liver transplant recipients.

A total of 48 subjects received at least one dose of open label ETV. Dosing was based on treatment history cohort and ranged from 0.015 mg/kg with a max of 0.5 mg/day in the LVD naïve group to 0.030 mg/kg with a max of 1 mg/day in the LVD-experienced

and nucleoside experienced cohorts. Subjects were treated for a minimum of 48 weeks and a maximum of 120 weeks.

AI463189: A Phase 3, randomized, double-blind, placebo controlled study to assess the efficacy and safety of ETV in pediatric subjects with CHB infection who are HBeAg positive and nucleoside naïve aged 2 to ≤18 years of age.

Subjects were enrolled at 43 sites in 14 countries (Argentina, Belgium, Canada, Germany, Greece, India, Israel, Korea, Poland, Romania, Russia, Taiwan, UK, and USA).

The primary objective of the study was to compare the proportion of subjects in each treatment group who achieved a combination of HBV DNA suppression and HBeAg seroconversion at Week 48.

Subjects were divided into 3 age strata (≥ 2 - ≤ 6, > 6 - ≤ 12 and > 12 - <18).

Major inclusion criteria included HBeAg positive and HBeAb negative at screening and at least once ≥ 4 weeks prior to screening, hepatitis B virus DNA ≥ 10^5 copies/ml at screening and evidence of the presence of hepatitis B DNA at least once ≥ 4 weeks prior to screening and ALT 1.5 to10 x ULN at screening and at least once within 8 to 24 weeks prior to screening.

Notable exclusion criteria included subjects treated with ≥ 12 weeks of prior therapy with any nucleoside or nucleotide antiviral agent with activity against HBV, subjects coinfected with HIV, hepatitis C virus, hepatitis D virus or liver transplant recipients.

A total of 180 subjects were randomized and received at least one dose of blinded study drug. All ETV subjects received 0.015 mg/kg with a max of 0.5 mg/day. Subjects will be treated with blinded therapy for a minimum of 48 weeks and a maximum of 96 weeks.

6 Review of Efficacy

Efficacy Summary

Efficacy was based on analysis of the Phase 3 placebo controlled study, AI463189. In this trial a total of 180 subjects were randomized, 120 in the ETV arm and 60 in the placebo arm. The current submission contains efficacy endpoint data from the first 123 subjects (82 ETV and 41 placebo subjects) who had received the minimum 48 weeks of blinded therapy. The Sponsor termed this group the “primary cohort” and based all efficacy calculations on this group.

ETV was found to be superior to placebo with respect to efficacy. In trial AI463189, utilizing the sponsor's submitted data, 24% of ETV treated subjects had virologic success (HBV DNA < 50 IU/ml plus HBeAg seroconversion) compared to 2% of placebo treated subjects.

6.1 Indication

ETV is indicated for the treatment of CHB in pediatric subjects at least 2 years of age.

6.1.1 Methods

Efficacy data for the two trials was analyzed separately. Review of efficacy was conducted in collaboration with Dr. Thomas Hammerstrom, the statistical reviewer from the Division of Biometrics. All data analysis tables in this section were generated by the clinical reviewer using JReview®, a statistical analysis software package.

6.1.2 Demographics

In the combined Phase 2 and Phase 3 trials, the intent-to-treat population (ITT) included 228 subjects; 48 received open label ETV in Study AI463028 while 120 received ETV and 60 received placebo in Study AI463189. Subjects ranged in age from 2 to 17 with a majority of subjects in the > 12 to <18 cohort.

Table 3: Demographics and Baseline Characteristics

	AI463028 (n=48)	AI463189 (n=120)	Pooled ETV (n=168)	Placebo (n=60)
Gender n (%)				
Male	25 (52.1%)	78 (65.0%)	103 (61.3%)	31 (51.7%)
Female	23 (47.9%)	42 (35.0%)	65 (38.7%)	29 (48.3%)
Race n (%)				
Asian	32 (66.7%)	57 (47.5%)	89 (53.0%)	30 (50.0%)
Black or African American	2 (4.2%)	14 (11.7%)	16 (9.5%)	2 (3.3%)
Native Hawaiian/ Other Pacific Islander	1 (2.1%)	1 (0.8%)	2 (1.2%)	0 (0.0%)
White	11 (22.9%)	44 (36.7%)	55 (32.7%)	27 (45.0%)
Other	2 (4.2%)	4 (3.3%)	6 (3.6%)	1 (1.7%)
Ethnicity n (%)				
Hispanic or Latino	1 (2.1%)	2 (1.7%)	3 (1.8%)	0 (0.0%)
Not Hispanic or Latino	17 (35.4%)	48 (40.0%)	65 (38.7%)	21 (35.0%)
Not Reported	30 (62.5%)	70 (58.3%)	100 (59.5%)	39 (65.0%)
Age (years)				
Median (min, max)	10.0 (2,17)	12.0 (2,17)	11 (2,17)	12.0 (2,17)
Age Category				
≥ 2 - ≤ 6	12 (25.0%)	27 (22.5%)	39 (23.2%)	14 (23.2%)

> 6 - ≤ 12	18 (37.5%)	31 (25.8%)	49 (29.2%)	15 (25.0%)
>12 - ≤ 18	18 (37.5%)	62 (51.7%)	80 (47.6%)	31 (51.7%)
HBV Genotype n (%)				
A	4 (8.3%)	22 (18.3%)	26 (15.5%)	11 (18.3%)
B	3 (6.3%)	17 (14.2%)	20 (11.9%)	11 (18.3%)
C	15 (31.3%)	31 (25.8%)	46 (27.4%)	16 (26.7%)
D	7 (14.6%)	42 (35.0%)	49 (29.2%)	20 (33.3%)
E	--	4 (3.3%)	--	1 (1.7%)
F	1 (2.1%)	2 (1.7%)	3 (1.8%)	0 (0.0%)
Indeterminate/Not Reported	18 (37.5%)	2 (1.7%)	20 (11.9%)	1 (1.7%)
HBV DNA (Log_{10} IU/ml)				
Median (min,max)	7.94 (5.2, 9.4)	8.29 (4.9, 10.0)	8.12 (5.1,9.7)	8.00 (4.7, 9.7)
Geographic Region n (%)				
Asia	19 (39.6%)	25 (20.8%)	44 (26.2%)	13 (21.7%)
Europe	5 (10.4%)	53 (44.2%)	58 (34.5%)	33 (55.0%)
North America	17 (35.4%)	41 (34.2%)	58 (34.5%)	14 (23.0%)
South America	7 (14.6%)	1 (0.8%)	8 (4.8%)	0 (0.0%)
Country n (%)				
Argentina	3 (6.3%)	1 (0.8%)	4 (2.4%)	0 (0.0%)
Belgium	2 (4.2%)	1 (0.8%)	3 (1.8%)	3 (5.0%)
Brazil	4 (8.3%)	--	4 (2.4%)	--
Canada	1 (2.1%)	6 (5.0%)	7 (4.2%)	1 (1.7%)
Germany	--	10 (8.3%)	10 (6.0%)	2 (3.3%)
Greece	--	0 (0.0%)	0 (0.0%)	1 (1.7%)
India	--	2 (1.7%)	2 (1.2%)	1 (1.7%)
Israel	--	7 (5.8%)	7 (4.2%)	4 (6.7%)
Korea	16 (33.3%)	17 (14.2%)	33 (19.6%)	6 (10.0%)
Poland	--	4 (3.3%)	4 (2.4%)	6 (10.0%)
Romania	--	9 (7.5%)	9 (5.4%)	10 (6.7%)
Russia	--	13 (10.8%)	13 (7.7%)	6 (10.0%)
Taiwan	3 (6.3%)	6 (5.0%)	9 (5.4%)	6 (10.0%)
UK	3 (6.3%)	9 (7.5%)	12 (7.1%)	1 (1.7%)
USA	16 (33.3%)	35 (29.2%)	51 (30.4%)	13 (21.7%)

6.1.3 Subject Disposition

Although the numbers are small, the percentage of subjects discontinuing study treatment before 48 weeks was lower in the combined ETV group as compared to the placebo group. As can be seen below in Table 4, three subjects withdrew consent in the combined ETV arm as compared to one subject in the placebo arm. No ETV treated subjects discontinued secondary to AEs whereas 2 subjects in the placebo group discontinued for this reason. One placebo treated subject discontinued due to a pregnancy, a pre-specified cause for study termination.

Table 4: Reasons for Prematurely Discontinuing Study Drug in the Combined ETV and Placebo Arms

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number of Subjects Discontinuing Study	3 (1.8%)	4 (6.7%)
Reason for Discontinuation n (%)		
Subject Withdrew Consent	3 (1.8%)	1 (1.7%)
Poor/Non-Compliance	0 (0.0%)	0 (0.0%)
Lost To Follow-Up	0 (0.0%)	0 (0.0%)
Pregnancy	0 (0.0%)	1 (1.7%)
Adverse Event	0 (0.0%)	2 (3.3%)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for the Phase 3 trial, AI463189, was the percentage of subjects with virologic success (HBV DNA < 50 IU/ml) combined with HBeAg seroconversion. At 48 weeks, utilizing efficacy data from the first 123 randomized subjects, 24% (20/82) of ETV treated subjects met this primary endpoint versus 2% (1/41) of placebo treated subjects.

6.1.5 Analysis of Secondary Endpoints(s)

Numerous secondary endpoints were analyzed in both the Phase 2 and Phase 3 studies. See Table 5 below for full details.

In Study AI463028, dose finding was the primary endpoint as detailed above in Section 4.4. The combined efficacy endpoint of HBV DNA < 50 IU/ml with HBeAg seroconversion was a secondary endpoint and achieved in 33% (8/24) of treatment naïve subjects at 48 weeks. Other secondary endpoints achieved in treatment naïve subjects included: HBV DNA < 50 IU/mL reported in 14 (58%) subjects, HBeAg seroconversion in 10 (42%) subjects and ALT Normalization in 20 (83%) subjects. In this study, 16 of the 24 treatment naïve subject (66%) failed to meet the combined virologic endpoint (HBV DNA < 50 IU/mL and HBeAg seroconversion), none secondary to premature discontinuation of the study. In the LVD experienced cohort (n=19), 3 subjects (15.9%) achieved the combined efficacy endpoint and 9 (47.4%) achieved HBV DNA < 50 IU/ml. In the nucleoside experienced cohort, only 3 of the 5 subjects reached 48 weeks at the time of data submission. None of the 3 subjects achieved the combined efficacy endpoint or HBV DNA < 50 IU/ml.

Table 5: Efficacy Endpoint Results at 48 Weeks

	Study AI463189	
	ETV (N=82)	Placebo (N=41)
Primary Endpoint:		
Virologic Success (HBV DNA < 50 IU/mL) and HBeAg seroconversion	20 (24%)	1 (2%)
Secondary Endpoints:		
HBV DNA < 50 IU/mL	38 (46%)	1 (2%)
HBeAg seroconversion	20 (24%)	5 (12%)
ALT Normalization	55 (67%)	9 (22%)
HBV DNA < 29 IU/ml	35 (43%)	1 (2%)
HBV< 50 IU/ml (by baseline HBV DNA)	< 8 log10 IU/mL: 26/34 (77%) ≥ 8 log10 IU/mL: 12/48 (25%)	--

In Study AI463189, only 2 of the 62 subjects labeled as virologic failures were secondary to premature discontinuation of the study. These two subjects both withdrew consent prior to 48 weeks. Therefore, 60 of the 82 ETV subjects (73%) failed to meet the combined virologic endpoint of HBV DNA < 50 IU/mL and HBeAg seroconversion, primarily due to low rates of HBeAg seroconversion. As compared to adult trial information, in treatment naïve subjects, HBeAg seroconversion was achieved in 21% of adults versus 24% in pediatric subjects while HBV DNA <400 copies/ml was achieved in 72% of adults versus 46% of pediatric subjects achieving HBV DNA < 50 IU/ml.

In the placebo group, 4 of the 40 subjects labeled as virologic failures were secondary to premature discontinuation of the study. One subject withdrew consent, one subject had a pregnancy and 2 subjects had AEs. Therefore 36 of the 41 placebo subjects (88%) failed to meet the combined virologic endpoint of HBV DNA < 50 IU/mL and HBeAg seroconversion.

6.1.6 Other Endpoints

No other endpoints were analyzed.

6.1.7 Subpopulations

A number of subgroup analyses were performed on the primary efficacy endpoint (see Table 6 below). In the placebo controlled study AI463189, no substantive difference in efficacy based on gender was appreciated. White race, older age cohorts, subjects from Europe and high baseline HBV DNA level (≥ 8 log10 IU/mL) were associated with

decreased rates of efficacy. Additionally, genotypes B and D were found to have significantly decreased rates of efficacy as compared to the other genotypes reported. Please see the Clinical Virology review by Dr. Takashi Komatsu for further details regarding genotype associated efficacy.

Table 6: Subgroup Analyses on the Primary Endpoint of HBV DNA < 50 IU/mL and HBeAg seroconversion

	Study AI463189	
	ETV (N=82)	Placebo (N=41)
Overall Virologic Success (HBV DNA < 50 IU/mL) and HBeAg seroconversion	20 (24%)	1 (2%)
Gender		
Male	14 (17.9%)	0 (0.0%)
Female	6 (14.3%)	1 (3.4%)
Race		
Asian	12 (21.1%)	0 (0.0%)
White	4 (9.1%)	0 (0.0%)
Black	3 (21.4%)	0 (0.0%)
Other	1 (20.0%)	1 (100%)
Age Cohort		
≥ 2 - ≤ 6	7 (25.9%)	1 (7.1%)
> 6 - ≤ 12	5 (16.1%)	0 (0.0%)
> 12 - ≤ 18	8 (12.9%)	0 (0.0%)
Region		
North/South America	9 (22.0%)	0 (0.0%)
Asia	5 (20.0%)	0 (0.0%)
Europe	6 (11.3%)	1 (3.0%)
HBV DNA Level		
< 8 log10 IU/mL	15 (31.9%)	1 (5.9%)
≥ 8 log10 IU/mL	5 (6.8%)	0 (0.0%)
Genotype		
A	6 (27.3%)	0 (0.0%)
B	1 (5.9%)	0 (0.0%)
C	8 (25.8%)	0 (0.0%)
D	3 (7.1%)	1 (5.0%)
Other	2 (25.0%)	0 (0.0%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The doses for treatment naïve and treatment experienced pediatric ETV subjects was selected and confirmed in Study AI463028. Confirmation was based on comparable pediatric and adult AUC exposures in both treatment cohorts and preliminary evidence of pediatric efficacy. After confirmation of the appropriate dose, Study AI463189 was undertaken in treatment naïve subjects and utilized ETV 0.015 mg/kg with a maximum of 0.5 mg/day. Favorable efficacy analysis in the Phase 3 study confirmed the appropriate pediatric pharmacodynamics of ETV.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Study AI463028, the mean duration of time on study drug for ETV treated subjects in the treatment naïve, LVD-experienced and nucleoside/tide experienced groups was 88, 91 and 43 weeks, respectively. In Study AI463189, the mean duration of time on study drug for ETV and placebo treated subjects was 47 and 44 weeks, respectively. For this NDA submission, safety and efficacy data was analyzed up to 48 weeks.

6.1.10 Additional Efficacy Issues/Analyses

No other analyses were performed.

7 Review of Safety

Safety Summary

The most common treatment emergent adverse events identified in the Phase 2 and 3 trials by System Organ Class (SOC) included Infections and Infestations and Gastrointestinal Disorders although both SOC categories had fewer AEs as compared to placebo. The most common adverse events by preferred term included upper respiratory tract infection, pyrexia, nasopharyngitis, and headache.

When evaluating the most common adverse events, numerous AEs were reported which are considered to be frequent pediatric complaints. These include upper respiratory infection, cough, bronchitis, etc. In order to better delineate possible drug effect, common adverse events with a 3% difference between treatment groups were further analyzed. Utilizing this method and removing the common pediatric complaint of URI, headache was reported in a higher percentage of ETV subjects, as was noted in the adult studies, while vomiting, diarrhea and fatigue were reported in fewer ETV treated subjects as compared to placebo. Although these differences were small and possibly secondary to chance, it is possible that ETV has a beneficial effect on the subtle symptoms of underlying liver disease.

Pooled abdominal pain AEs in the gastrointestinal SOC were slightly higher in the ETV group as compared to placebo. Specifically, pooled abdominal pain terms (including abdominal pain, abdominal pain upper and abdominal discomfort) were reported in 9.5% of ETV subjects and 8.3% of placebo subjects. No abdominal pain adverse events were reported as serious. Abdominal pain was reported as related to study drug in 5 ETV treated subjects (3%) compared to zero in the placebo group. As compared to placebo, vomiting (ETV 8.9%, placebo 13.3%) diarrhea (ETV 6.0%, placebo10.0%) and nausea (ETV 4.2%, placebo 5.0%) were reported in fewer ETV treated subjects. The overall incidence of adverse events was very similar in the Gastrointestinal Disorders

SOC between the ETV group (25.6%) and the placebo group (26.7%). Gastroenteritis adverse events, although located in the Infections and Infestations SOC, was felt to be similar to other GI related AEs and was analyzed as such. Gastroenteritis was similarly reported in 2.4% of ETV subjects and 1.7% of placebo subjects with one ETV gastroenteritis AE subject labeled as serious.

ALT flare, defined in this study as ALT >2x baseline value and >10x ULN, is a known adverse event while on and off CHB therapy. During the on-treatment period, five ETV treated subjects and five placebo treated subjects had ALT flares. Five subjects, all in the ETV treatment group, had ALT flares after completion of study drug (off treatment period). No placebo subjects had off treatment ALT flares reported. No events were reported in the Hepatobiliary SOC for ETV treated subjects but two placebo subjects (3.3%) had AEs of hepatic function abnormal. One subject in the ETV treated group had two SAEs of Alanine Aminotransferase and Aspartate Aminotransferase increased, both were considered by the investigator as related to study drug.

No ETV treated subjects discontinued study drug due to an adverse event while two placebo subjects discontinued study drug due to Hepatobiliary AEs.

No deaths or malignancies were reported in ETV or placebo treated subjects.

No major differences in laboratory abnormalities were noted between the treatment and placebo groups. In the ETV treatment group, 10% of subjects had a graded ANC laboratory AE as compared to 3.3% in the placebo group. Most of these were Grade 1 or 2 with only one ETV treated subject experiencing a Grade 3 decline in ANC.

7.1 Methods

Review of this supplemental pediatric NDA included analysis of safety data through 48 weeks for AI463028 and AI463189. An analysis of the 90 day safety update and longer term safety data was also undertaken but will not be the focus of this review. All data for deaths, SAE and drug discontinuations were assessed as submitted by the sponsor and not limited to 48 weeks.

Although the Sponsor analyzed safety data separately for the two trials (AI463028 and AI463189) and further separated AI463028 subjects into three pre-trial treatment cohorts, the FDA safety analysis was conducted by pooling the entecavir safety data from the two trials, regardless of pre-trial treatment history. This strategy was employed as not all randomized subjects had reached the minimum 48 weeks of therapy prior to data submission. Data was therefore limited to 48 weeks prior to placebo subjects receiving open label ETV.

Because these trials are relatively small, they are not powered to detect statistically significant differences in rates of AEs. Multiple AEs were counted only once per subject for each preferred term and if pooling adverse event terms, subjects were only counted once if they had multiple of the combined preferred terms. Laboratory abnormalities were limited to subjects with at least one post-baseline laboratory value for each test. Subjects were counted only once for their post-baseline maximum severity for each laboratory test. Clinical adverse events and laboratory abnormalities were graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0.

All data analysis tables in this section were generated by the clinical reviewer from the provided datasets using JReview®.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This NDA review focuses on the safety data from the Phase 2 Trial, AI463028 and the Phase 3 trial, AI463189.

7.1.2 Categorization of Adverse Events

The sponsor coded AEs using MedDRA 15.1. An assessment of the Applicant's coding of events was carried out with attention given to assuring proper agreement between the investigators' verbatim terms and the selected MedDRA Preferred terms. Particular attention was given to adverse events that led to study drug discontinuation and serious adverse events judged related to study drug. Additionally, a random check of adverse events without respect to severity or causality of adverse events was performed. No issues of concern were identified.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Subject safety data in the ETV treated groups was pooled for estimating and comparing rates of events from the Phase 2 and Phase 3 trials. This approach was undertaken because in the absence of cirrhosis, no major differences in the safety profiles of treatment naïve and treatment experienced subjects have been identified.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The dose and formulation selected for the Phase 3 trial (ETV 0.015 mg/kg/day, maximum 0.5 mg/day using oral solution or tablets) was investigated during the Phase 2 trial in lamivudine treatment naïve subjects (n=24). This dosage was utilized during the Phase 3 trial in 120 subjects. A total of 144 subjects from the combined Phase 2 and 3 ETV treatment group received at least one dose of the 0.015 mg/kg/day ETV dosage. Additionally, 24 treatment experienced subjects in the Phase 2 trial received a dosage of ETV 0.030 mg/kg, maximum 1 mg using oral solution or tablets.

In Study AI463028, the mean duration of time on study drug for ETV treated subjects was 88, 91 and 43 weeks for the treatment naïve, LVD-experienced and nucleoside/tide experienced subjects, respectively. In Study AI463189, the mean duration of time on study drug for ETV and placebo treated subjects was 47 and 44 weeks, respectively. For this NDA submission, data was analyzed up to 48 weeks.

In the adult ETV trials, dosages of 0.5 mg and 1 mg were investigated. In the current ETV label, 0.5 mg is indicated for nucleoside treatment naïve subjects aged ≥ 16 years and the 1 mg tablet is indicated for subjects aged ≥ 16 years with lamivudine-refractory CHB or known lamivudine or telbivudine resistance mutations.

Please refer to Section 6.1.2 for demographic information.

7.2.2 Explorations for Dose Response

Study AI463028 evaluated preliminary efficacy and matched pediatric and adult drug exposures in treatment naïve and experienced subjects. Using the confirmed pediatric dosage, Study AI463189 evaluated efficacy and found results to be similar to historical efficacy data from the adult trials. For full details of this analysis please see the Pharmacometrics review by Dr. Jeffry Florian.

7.2.3 Special Animal and/or In Vitro Testing

No new data was submitted.

7.2.4 Routine Clinical Testing

Routine clinical evaluations for safety in studies AI463028 and AI463189 included safety laboratory assessments and medical history taking for assessment of adverse events and changes in concomitant medications at all scheduled visits (Weeks 4, 8, 12 and every 6 weeks to end of study drug plus off treatment and long-term follow up for Trial AI463028 and every 12 weeks to end of study drug plus off treatment and observation long-term follow up for Trial AI463189). A complete physical exam was performed at screening and end of study drug and targeted physical examinations were performed at Day 1, at all scheduled visits and in the off treatment and long term follow up period for Study AI463028 and in the observational long- term follow up period for Study AI463189.

7.2.5 Metabolic, Clearance, and Interaction Workup

Pharmacokinetic assessments were performed on all subjects in Study AI463028 for dose finding and sparse PK assessments were performed on all subjects in addition to semi-intense PK assessments on a subset of subjects in Study AI463189. Please see the Clinical Pharmacology review by Drs. Jeffry Florian and Su-Young Choi for full details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known safety profile of ETV was taken into consideration in this pediatric safety evaluation.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in the study population.

7.3.2 Nonfatal Serious Adverse Events

A total of 10 treatment-emergent SAEs were reported among 6 (3.6%) ETV treated subjects while 8 treatment emergent SAEs were reported in 7 (11.7%) placebo treated subjects through 48 weeks. No treatment-emergent SAEs were reported in 2 or more ETV treated subjects. SAEs in ETV treated subjects included Bronchitis, Cleft palate, Ear infection, Hydrocele, Tonsillar hypertrophy, Asthma, Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Lobar Pneumonia and Gastroenteritis with none of these events also observed in the placebo group.

Other SAEs included Cellulitis, Chronic Hepatitis B, Diabetic Ketoacidosis, Gastritis, Hepatic Function abnormal, Inflammatory Bowel Disease, Juvenile Arthritis and Schizophrenia but all took place in the placebo arm and were not observed in the combined ETV Arm.

Three SAEs were considered related by the investigator: one subject in the ETV group had 2 SAEs (Grade 3 elevations in ALT and AST) and one subject in the placebo group had an SAE of Hepatic Function Abnormal. Treatment emergent SAEs led to drug discontinuation in 2 placebo subjects and no ETV subjects.

Data received in the 90 day safety update reported two further treatment-emergent SAEs which occurred in subjects originally randomized to placebo but switched to open-label ETV after Week 48. These SAEs were reported as infectious enterocolitis and arthralgia in 1 subject each. Neither SAE was considered related to the study drug by the investigator.

7.3.3 Dropouts and/or Discontinuations

Two (3.3%) placebo treated subjects discontinued study drug due to AEs of Hepatic Function Abnormal and Chronic Hepatitis B in 1 subject each. No ETV treated subjects discontinued study drug due to an adverse event.

7.3.4 Significant Adverse Events

All of the events summarized in Table 7 below are of grade 2 severity in both the combined ETV and Placebo groups. Through Week 48, 37 ETV subjects (22%) experienced a grade 2 or grade 3 event. The majority of events were grade 2 with only 6 (3.6%) subjects in the combined ETV group experiencing a grade 3 event. In the placebo group, 19 (31.7%) subjects had a grade 2 or grade 3 event. Grade 3 events were also uncommon with only 3 (5%) subjects experiencing grade 3 events. None of the Grade 3 adverse events occurred in more than one subject and no Grade 4 adverse events occurred in either group.

Table 7: Treatment-Emergent Adverse Events of at Least Moderate Severity (Grades 2-3) Reported in at least 1% of Subjects in the Combined ETV Arms

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any Moderate (Grade 2-3) TEAE	37 (22.0%)	19 (31.7%)
Upper Respiratory Tract Infection	5 (3.0%)	0 (0.0%)
Pyrexia	4 (2.4%)	1 (1.7%)
Abdominal Pain	3 (1.8%)	2 (3.3%)
Ear Infection	3 (1.8%)	0 (0.0%)
Nasopharyngitis	3 (1.8%)	2 (3.3%)
Bronchitis	2 (1.2%)	1 (1.7%)
Chest Pain	2 (1.2%)	0 (0.0%)
Gastroenteritis	2 (1.2%)	0 (0.0%)
Oral Herpes	2 (1.2%)	0 (0.0%)
Tonsillitis	2 (1.2%)	0 (0.0%)

7.3.5 Submission Specific Primary Safety Concerns

HEPATIC FLARES

ALT flares, defined as ALT >2x baseline value and >10x ULN in this submission, are known adverse events during the on and off treatment phases of CHB therapy. ALT flares were infrequent during the study period and were reported in five ETV treated subjects and five placebo treated subjects during the first 12 weeks of the study period for both ETV and placebo treated subjects but took a variable period of time to resolution, ranging from 3 to 35 weeks. As is commonly seen in subjects with ALT flares, a majority of subjects had HBeAg loss or seroconversion which accompanied the flare. HBV DNA was not collected at the time of flare based on the protocol specified laboratory testing schedule in AI463028 subjects therefore precluding determination of an association in ETV treated subjects with a decrease in HBV DNA at the time of flare. Only one placebo treated subject required drug discontinuation secondary to ALT flare. See Table 8 for details of the subjects with on-treatment ALT flares.

Table 8: Treatment-Emergent ALT Flares in the Combined ETV Arms

Subject ID	Treatment Group	Time of Flare	Max ALT (Baseline)	Time to resolution	Associated with Decrease in HBV DNA	HBeAg loss or seroconversion	Drug D/C secondary to Flare
028-13-8017	ETV	Wk 8	646(282)	8 weeks	Unavailable	Yes	No
028-7-8009	ETV	Wk 9	427(113)	3 weeks	Unavailable	Yes	No
028-8-8036	ETV	Wk 3	488(126)	6 weeks	Unavailable	Yes	No
189-16-8664	ETV	Wk 5	505 (115)	7 weeks	Yes	No	No
189-8-8605	ETV	Wk 12	648 (79)	12 weeks	Yes	Yes	No
189-18-8511	Placebo	Wk 1	422 (87)	24 weeks	No	No	No
189-18-8629	Placebo	Wk 7	2861 (108)	8 weeks	No	No	Yes
189-42-8592	Placebo	Wk 4	328 (112)	8 weeks	No	No	No
189-52-8573	Placebo	Wk 12	643 (107)	35 weeks	No	No	No
189-52-8576	Placebo	Wk 3	2339 (82)	4 weeks	No	E Ag loss at Wk 6, reversion at Wk 36	No

Five subjects, all in the ETV treatment group had ALT flares after completion of study drug (off treatment period). Time to flare after end of ETV therapy ranged from 22 to 44 weeks and in three of the five subjects, resolution was noted after 2 to 12 weeks. In 2 subjects, ALT flare resolution had not occurred at the time of data submission. No placebo subjects had ALT flares reported. See Table 9 for details of the off treatment ALT flares.

Table 9: Off-Treatment ALT Flares in the Combined ETV Arms

Subject ID	Treatment Group	Time to Flare after end of active therapy	Max ALT (ALT at end of active therapy)	Time to resolution
028-15-8012	ETV	24 weeks	908 (35)	5 weeks
028-6-8039	ETV	31 weeks	550 (38)	2 weeks
028-20-8016	ETV	31 weeks	874 (20)	12 weeks
189-4-8522	ETV	22 weeks	894(108)	Unresolved
189-18-8509	ETV	44 weeks	321 (16)	Unresolved *

* Reported in 90 day Safety Update

GASTROINTESTINAL

Gastrointestinal adverse events occurred in a very similar percentage in the ETV (25.6%) and placebo groups (26.7%). The pooled abdominal pain terms (including abdominal pain, abdominal pain upper and abdominal discomfort) were the most frequently reported AE in the Gastrointestinal Disorders SOC with 9.5% of ETV subjects and 8.3% of placebo subjects reporting these adverse events. When pooling these terms, subjects were only counted once if they had multiple of the combined preferred terms.

No abdominal pain adverse events were reported as serious. Abdominal pain was reported as related to study drug in 5 ETV treated subjects (3%) compared to zero in the placebo group. As compared to placebo, vomiting (ETV 8.9%, placebo 13.3%) diarrhea (ETV 6.0%, placebo10.0%) and nausea (ETV 4.2%, placebo 5.0%) were reported in fewer ETV treated subjects.

Gastroenteritis adverse events, although located in the Infections and Infestations SOC, were felt to be similar to other GI related AEs and were analyzed as such. Gastroenteritis was reported in 2.4% of ETV subjects and 1.7% of placebo subjects with one ETV gastroenteritis AE subject labeled as serious. When combined with enteritis and gastritis, both terms in the Gastrointestinal SOC, the pooled total in ETV treated subjects is similar at 4.2% compared to 3.4% in the placebo group.

Table 10: Gastrointestinal Treatment-Emergent Adverse Events in the Combined ETV Arms

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any Gastrointestinal TEAE by Preferred Term	43 (25.6%)	16 (26.7%)
Vomiting	15 (8.9%)	8 (13.3%)
Abdominal Pain	12 (7.1%)	4 (6.7%)
Diarrhea	10 (6.0%)	6 (10.0%)
Nausea	7 (4.2%)	3 (5.0%)
Abdominal Pain Upper	4 (2.4%)	1 (1.7%)
Abdominal Discomfort	3 (1.8%)	1 (1.7%)
Dental Caries	3 (1.8%)	0 (0.0%)
Constipation	2 (1.2%)	0 (0.0%)
Enteritis	2 (1.2%)	0 (0.0%)
Abdominal Distension	1 (0.6%)	0 (0.0%)
Anorectal Discomfort	1 (0.6%)	0 (0.0%)
Aphthous Stomatitis	1 (0.6%)	0 (0.0%)
Flatulence	1 (0.6%)	0 (0.0%)
Gastritis	1 (0.6%)	1 (1.7%)
Gastroesophageal Reflux Disease	1 (0.6%)	0 (0.0%)
Mouth Ulceration	1 (0.6%)	0 (0.0%)
Dry Mouth	0 (0.0%)	1 (1.7%)
Dyspepsia	0 (0.0%)	1 (1.7%)
Inflammatory Bowel Disease	0 (0.0%)	1 (1.7%)
Toothache	0 (0.0%)	2 (3.3%)

NEUROLOGIC/PSYCHIATRIC

Given the concern for Neurologic adverse events found in the Pre-clinical toxicology studies, select Neurologic and Psychiatric Adverse Events were analyzed and presented in Table 11 below. Apart from a higher rate of headache, as noted in the adult ETV studies, all other rates were similar to placebo.

Table 11: Select Neurologic and Psychiatric Adverse Events in the Combined ETV Arms

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Nervous System Disorders		
Headache	20 (11.9%)	5 (8.3%)
Dizziness	2 (1.2%)	2 (3.3%)
Lethargy	2 (1.2%)	1 (1.7%)
Psychiatric Disorders		
Anxiety	2 (1.2%)	0 (0.0%)
Mood Swings	1 (0.6%)	0 (0.0%)
Depression	0 (0.0%)	1 (1.7%)
Insomnia	0 (0.0%)	1 (1.7%)

DERMATOLOGIC

When evaluating for rash, multiple preferred terms were combined (including rash, rash pruritic, pruritus, urticarial, dermatitis allergic, rash maculo-papular and rash erythematous). When pooling these terms, subjects were only counted once if they reported multiple of the combined preferred terms. The ETV arm and placebo arms had similar pooled totals (8.9% and 8.3%, respectively).

Table 12: Skin and Subcutaneous Tissue Disorders in the Combined ETV Arms

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any Skin or Subcutaneous Tissue Disorder TEAE by Preferred Term	25 (14.9%)	6 (10.0%)
Pooled Rash Terms	15 (8.9%)	5 (8.3%)
Rash	9 (5.4%)	2 (3.3%)
Acne	4 (2.4%)	1 (1.7%)
Eczema	3 (1.8%)	0 (0.0%)
Rash Pruritic	3 (1.8%)	0 (0.0%)
Skin Fissures	3 (1.8%)	0 (0.0%)
Dry Skin	2 (1.2%)	0 (0.0%)
Pruritus	2 (1.2%)	0 (0.0%)
Urticaria	2 (1.2%)	1 (1.7%)
Dermatitis Allergic	1 (0.6%)	1 (1.7%)
Erythema	1 (0.6%)	0 (0.0%)
Night Sweats	1 (0.6%)	0 (0.0%)
Petechiae	1 (0.6%)	0 (0.0%)
Rash Maculo-Papular	1 (0.6%)	0 (0.0%)
Skin Depigmentation	1 (0.6%)	0 (0.0%)
Skin Mass	1 (0.6%)	0 (0.0%)
Rash Erythematous	0 (0.0%)	1 (1.7%)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 13 below details the treatment emergent AEs by SOC. Infections and Infestations and Gastrointestinal disorders contained the highest number of AEs in the ETV arms but both were reported in slightly lower proportions compared to the placebo arm. In the ETV arm, no SOC categories had significantly increased percentages compared to placebo although Skin and Subcutaneous Tissue disorders was slightly higher (ETV 14.9%, placebo 10%). When AEs in this SOC were evaluated and grouped together for rash events, ETV and placebo were similar with 8.9% and 8.3%, respectively. For a full description of Dermatologic AEs please see section 7.3.5.

Table 13: Treatment Emergent Adverse Events by System Organ Class in the Combined ETV Arms

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any TEAE by SOC	112 (66.7%)	42 (70.0%)
Infections and Infestations	69 (41.1%)	27 (45.0%)
Gastrointestinal Disorders	43 (25.6%)	16 (26.7%)
Respiratory, Thoracic and Mediastinal Disorders	34 (20.2%)	12 (20.0%)
General Disorders and Administration Site Conditions	32 (19.0%)	12 (20.0%)
Skin and Subcutaneous Tissue Disorders	25 (14.9%)	6 (10.0%)
Nervous System Disorders	25 (14.9%)	9 (15.0%)
Musculoskeletal and Connective Tissue Disorders	7 (4.2%)	3 (5.0%)
Injury, Poisoning and Procedural Complications	7 (4.2%)	3 (5.0%)
Metabolism and Nutrition Disorders	6 (3.6%)	1 (1.7%)
Immune System Disorders	5 (3.0%)	1 (1.7%)
Investigations	5 (3.0%)	5 (8.3%)
Ear and Labyrinth Disorders	3 (1.8%)	1 (1.7%)
Psychiatric Disorders	3 (1.8%)	3 (5.0%)
Cardiac Disorders	3 (1.8%)	0 (0.0%)
Reproductive System and Breast Disorders	3 (1.8%)	0 (0.0%)
Eye Disorders	3 (1.8%)	1 (1.7%)
Renal and Urinary Disorders	2 (1.2%)	0 (0.0%)
Blood and Lymphatic System Disorders	2 (1.2%)	1 (1.7%)
Vascular Disorders	2 (1.2%)	0 (0.0%)
Hepatobiliary Disorders	0 (0.0%)	2 (3.3%)

Treatment-emergent adverse events (TEAEs) were commonly reported in both study groups, the majority of which were Grade 1 or Grade 2 events. Below, Table 14 provides a summary of TEAEs that were reported in at least 2% of the study population in either arm.

Table 14: Treatment-Emergent Adverse Events Reported in 2% of the Combined ETV Arms

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any TEAE by Preferred Term	112 (66.7%)	43 (71.7%)
Upper Respiratory Tract Infection	25 (14.9%)	6 (10.0%)
Pyrexia	23 (13.7%)	7 (11.7%)
Nasopharyngitis	21 (12.5%)	7 (11.7%)
Headache	20 (11.9%)	5 (8.3%)
Vomiting	15 (8.9%)	8 (13.3%)
Cough	14 (8.3%)	6 (10.0%)
Abdominal Pain	12 (7.1%)	4 (6.7%)
Diarrhea	10 (6.0%)	6 (10.0%)
Rash	9 (5.4%)	2 (3.3%)
Nausea	7 (4.2%)	3 (5.0%)
Bronchitis	7 (4.2%)	2 (3.3%)
Ear Infection	7 (4.2%)	1 (1.7%)
Oropharyngeal Pain	6 (3.6%)	3 (5.0%)
Epistaxis	6 (3.6%)	2 (3.3%)
Rhinorrhea	5 (3.0%)	1 (1.7%)
Sinusitis	5 (3.0%)	1 (1.7%)
Abdominal Pain Upper	4 (2.4%)	1 (1.7%)
Acne	4 (2.4%)	1 (1.7%)
Fatigue	4 (2.4%)	5 (8.3%)
Gastroenteritis	4 (2.4%)	1 (1.7%)
Influenza	4 (2.4%)	2 (3.3%)
Decreased Appetite	4 (2.4%)	1 (1.7%)

Below, Table 15 details the Treatment-Related Adverse Events that occurred. Events labeled Treatment Related were reported by the Investigator as Possible, Probable or Certainly Related. In the combined ETV group, 10.7% of subjects experienced these events compared to 10% of subjects in the placebo group. Of the adverse events that occurred in greater than 1% of subjects, only abdominal pain, rash (combined events) and product taste abnormal were reported in a greater percentage of ETV subjects.

Table 15: Treatment- Related Adverse Events in the Combined ETV Arms

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any Related TEAE by Preferred Term	18 (10.7%)	6 (10.0%)
Abdominal Pain	5 (3.0%)	0 (0.0%)
Rash*	4 (2.4%)	0 (0.0%)
Product Taste Abnormal	3 (1.8%)	1 (1.7%)
Nausea	2 (1.2%)	1 (1.7%)
Diarrhea	2 (1.2%)	1 (1.7%)
Vomiting	2 (1.2%)	2 (3.3%)
Decreased Appetite	1 (0.6%)	1 (1.7%)
Dental Caries	1 (0.6%)	0 (0.0%)
Aspartate Aminotransferase Increased	1 (0.6%)	1 (1.7%)
Alanine Aminotransferase Increased	1 (0.6%)	1 (1.7%)
Eczema	1 (0.6%)	0 (0.0%)
Headache	1 (0.6%)	0 (0.0%)
Lethargy	1 (0.6%)	1 (1.7%)
Mood Swings	1 (0.6%)	0 (0.0%)
Myalgia	1 (0.6%)	0 (0.0%)
Dizziness	1 (0.6%)	0 (0.0%)
Product Odor Abnormal	1 (0.6%)	0 (0.0%)
Skin Fissures	1 (0.6%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (1.7%)
Hepatic Function Abnormal	0 (0.0%)	1 (1.7%)

* Rash terms Rash, Rash pruritic and Pruritus combined

Full details of the 90 day safety update were reviewed and adverse events reported were felt to be similar to data presented in the first 48 week analysis and in the period beyond 48 weeks. Additional subjects with SAEs and ALT flares are included in the relevant sections above.

7.4.2 Laboratory Findings

Table 16 summarizes the mean Baseline, Week 48 and Change from Baseline for select laboratory parameters in the combined ETV arms. The only clinically significant change was seen in mean ALT which decreased by 78.4 U/L at Week 48.

Table 16: Change from Baseline in Select Laboratory Parameters

Mean Laboratory Parameters		Combined ETV Cohort
WBC ($x10^3$ c/uL)	Baseline Week 48 Change	6.7 (N=167) 6.9 (N=129) +0.2
Hemoglobin (g/dL)	Baseline Week 48 Change	13.3 (N=167) 13.4 (N=129) +0.1
Platelet Count ($x10^9$ c/L)	Baseline Week 48 Change	259.7 (N=167) 268.6 (N=128) +8.9
ALT (U/L)	Baseline Week 48 Change	105.8 (N=165) 27.4 (N=130) -78.4
Creatinine (mg/dL)	Baseline Week 48 Change	0.53 (N=168) 0.55 (N=129) +0.02
INR	Baseline Week 48 Change	1.16 (N=168) 1.1 (N=127) -0.06
Total Bilirubin (mg/dL)	Baseline Week 48 Change	0.4 (N=165) 0.38 (N=127) -0.02

Table 17 summarizes the pancreatic laboratory abnormalities by maximum post-baseline severity grade. There is no evidence of a concerning trend with respect to pancreatic laboratory findings in the combined ETV group compared to the placebo group.

Table 17: Lipase Laboratory Abnormalities

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any TE Graded Lipase Adverse Event	37 (22.0%)	16 (26.7%)
Grade 1	27 (16.1%)	10 (16.7%)
Grade 2	8 (4.8%)	5 (8.3%)
Grade 3	2 (1.1%)	0 (0.0%)
Grade 4	0 (0.0%)	1 (1.7%)

Table 18 summarizes the ALT laboratory abnormalities by maximum post-baseline severity grade. Given the inclusion criteria requiring subjects to have elevated ALT at baseline, the post baseline graded abnormalities in the combined ETV group are significantly reduced as compared to the placebo group.

Table 18: ALT Laboratory Abnormalities

Treatment Arm (Number of Subjects)	ETV (N= 168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any TE Graded ALT Adverse Event	45 (26.7%)	44 (73.3%)
Grade 1	3 (1.8%)	12 (20.0%)
Grade 2	17 (10.1%)	19 (31.7%)
Grade 3	18 (10.7%)	9 (15.0%)
Grade 4	7 (4.2%)	4 (6.7%)

Table 19 summarizes the absolute neutrophil count laboratory abnormalities by maximum post-baseline severity grade. More graded abnormalities occurred in the ETV group as compared to the placebo group although most adverse events were in the lower and less clinically significant grades.

Table 19: Absolute Neutrophil Count Laboratory Abnormalities

Treatment Arm (Number of Subjects)	ETV (N=168)	PLACEBO (N=60)
Number (%) of Subjects Experiencing Any TE Graded ANC Adverse Event	12 (10.0%)	2 (3.3%)
Grade 1	7 (5.8%)	1 (1.7%)
Grade 2	4 (3.3%)	0 (0.0%)
Grade 3	1 (0.8%)	0 (0.0%)
Grade 4	0 (0.0%)	1 (1.7%)

There was no clinically meaningful difference between ETV and the placebo group with respect to the incidence of hyperglycemia, hypoglycemia, hyperkalemia, hypokalemia, hypernatremia or hyponatremia.

7.4.3 Vital Signs

No clinically relevant difference in blood pressure, heart rate or respiratory rate was noted between the combined ETV or placebo groups.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in the studies.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted with this pediatric supplement.

7.4.6 Immunogenicity

No immunogenicity studies were submitted with this pediatric supplement.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No major differences in adverse events were noted among Study AI463028 which utilized two dose levels depending on cohort (0.015 mg/kg, max 0.5mg/day and 0.030 mg/kg, max 1mg/day) and Study AI463189 which utilized only 0.015 mg/kg with a maximum dose of 0.5mg per day.

7.5.2 Time Dependency for Adverse Events

Exacerbations of hepatitis or ALT flares are a well-known complication of chronic HBV and its treatment and have been documented in both the on and off treatment periods. On treatment ALT flares were infrequent and occurred in five ETV and five placebo treated subjects. In analyzing the time to ALT flare event, all flares occurred during the first 12 weeks of the study period for both ETV and placebo treated subjects. During the off treatment follow up period, five ETV and zero placebo treated subjects had ALT flares. Time to flare event after end of ETV therapy ranged from 22 to 44 weeks. This time pattern is similar to the adult ETV trials for on treatment flares. Comparing the on and off treatment periods, a similar percentage of pediatric subjects had ALT flares while more adult subjects had off treatment flares reported.

7.5.3 Drug-Demographic Interactions

The overall incidence of treatment-emergent AEs in the combined ETV group was similar in male and female subjects (67% in males, 66.2% in females). The incidence of

SAEs was somewhat higher in females, (4.6% in females, 1% in males) while related SAEs were reported in only 1 (1.5%) female subject and no male subjects. No discontinuations due to adverse events were identified in either male or female ETV treated subjects.

In the combined ETV group, 53% of subjects were Asian, 33% were White, 9.5% were Black or African American, and other racial groups accounted for very small numbers. The overall incidence of treatment-emergent AEs in the combined ETV group was similar in Asians, Whites and Blacks (68.5%, 63.6% and 62.5%, respectively). Proportions of subjects reporting SAEs were similar between White and Asian subjects.

With respect to ethnicity, only 3 subjects in the combined ETV group were Hispanic or Latino therefore no conclusions can be drawn in regards to trends related to ethnicity.

7.5.4 Drug-Disease Interactions

Subjects co-infected with HIV, hepatitis C or hepatitis D infection were excluded from the studies therefore no information is available in pediatric subjects co-infected with these diseases.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were submitted with this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No neoplasms were reported during the study period. For a full description of post-marketing neoplasms seen in an adult cohort please see Section 8.

7.6.2 Human Reproduction and Pregnancy Data

Please see the initial Pharmacology/Toxicology review by Dr. Pritam Verma for the non-clinical reproductive toxicology information.

Pregnancy and breastfeeding were exclusion criteria for all adult and pediatric clinical trials. In addition, pregnancy was a predefined condition triggering discontinuation of study drug therefore no controlled study data is available in pregnant women. ETV is currently listed as a Category C medication.

No pregnancies were reported in the ETV treated group in these pediatric trials.

7.6.3 Pediatrics and Assessment of Effects on Growth

No clinically relevant difference in mean height or weight among the ETV or placebo groups was found.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No medication overdoses were reported in Study AI463028 or AI463189. Additionally, ETV is a cyclopentyl guanosine (nucleoside) analog and therefore not expected to have any abuse potential.

Hepatic flares are well known to occur after discontinuation of entecavir. Please see Section 7.3.5 for a listing of subjects with post-treatment ALT flares.

7.7 Additional Submissions / Safety Issues

No further information was submitted.

8 Postmarket Experience

Entecavir was approved for usage in adults in 2005. At the time of approval, a Post Marketing Commitment required a large, long term, simple safety trial, comparing ETV to standard care, on the outcomes of death, progression of liver disease, and cancer to occur over 5-10 years. Carcinogenicity findings in premarketing rodent studies motivated the request for this study to be a postmarketing commitment. Positive findings included, among others, lung carcinomas and splenic hemangiosarcomas in mice, hepatocellular carcinomas (HCC) in mice, and gliomas in rats; all were with supra-therapeutic exposures, and the clinical relevance of these findings is uncertain.

Study AI463080 is a multinational, open label trial involving 12,500 adults with chronic HBV infection randomized to either another approved HBV nucleoside/nucleotide analog drug or ETV. Randomization is stratified according to nucleoside/tide naïve or experienced status at enrollment. Subjects are to receive medical evaluations twice per year and will be followed for 10 years. Serious adverse events attributed to the HBV drugs are to be reported in real time. Outcomes to be adjudicated and analyzed are HCC, non-HCC malignancies, deaths, and HBV disease progression. As of 8/3/2009, all subjects had been randomized. There are 311 study sites in 24 countries. Reports are submitted yearly with the 6th update received March 13, 2013. Information regarding this study is taken from Dr. Andrew Mosholder's OSE/DEPI review. Please see his review from June 12, 2013 for full details.

Of 12,483 patients randomized, 533 of 6346 ETV patients (8%) and 733 of 6237 non-ETV patients (12%) had discontinued, which includes those designated as "Lost to

follow-up." In this category, 177 (3%) ETV subjects and 281 (5%) non-ETV subjects were reported. Sixty five subjects switched from ETV to non- ETV therapy, while 385 subjects switched from non-ETV therapy to ETV. A total of 1102 study outcomes had been reported, of which 803 had been adjudicated; 110 (14%) of these could not have a diagnosis assigned, and 23 were deemed to represent a pre-existing condition, yielding 670 adjudicated study events so far. The following table summarizes these adjudicated events.

Table 20: Epidemiology Study AI463080 Events by Category

	Total ETV N=6216	Total Non-ETV N=6163
Deaths--adjudicated	95	117
Deaths—all reported	135	155
Non-HCC malignancy	27	32
HCC	113	126
Non-HCC events of disease progression	81	79

(adjudicated events only unless noted)

Per Dr. Mosholder's review, the incidence of non-HCC malignancies has been less than expected, while the HCC incidence has been greater than expected, with HCC representing a majority of all malignancies. Despite the positive carcinogenicity findings from preclinical studies, the outcome data on malignancies and death numerically favor ETV, and the lower overall risk of mortality in the ETV arm is close to statistically significant (upper bound of relative risk is 1.02). This lower mortality risk does not seem to be accounted for by less disease progression with ETV, however, since disease progression outcomes were similar between the ETV and non-ETV arms.

In addition to the above OSE review of Study AI463080, FAERS reports submitted through December 2013 were analyzed for neoplasms in ETV treated subjects. Hepatic cancer and Hepatocellular carcinoma were the most frequently reported neoplasm. Of note, FAERS is a passive surveillance system therefore the incidence of disease cannot be estimated nor can causality be truly determined.

9 Appendices

9.1 Literature Review/References

1. World Health Organization. Hepatitis B Fact Sheet, updated July 2013. Available at: http://www.who.int/mediacentre/factsheets/fs204/en/. Last accessed December 6, 2013.
2. Centers for Disease Control and Prevention. Hepatitis B Information for Healthcare Professionals, updated May 2012. Available at: http://www.cdc.gov/hepatitis/HBV/index.htm. Last accessed December 6, 2013

9.2 Labeling Recommendations

The label was reviewed by the review team, the Division of Medication Errors Prevention and Analysis (DMEPA) team and the Study Endpoints and Labeling Development (SEALD) team who made recommendations. These were forwarded to the Sponsor and the final language for some sections is still being negotiated at the time of review completion. Major clinical changes to the label consist of adding in relevant pediatric trial information and PK data for both treatment naïve and lamivudine experienced subjects. Although a small number of lamivudine experienced subjects were studied (n=19), similar ETV exposure among treatment experienced adult and pediatric subjects dosed at 1 mg daily was observed. The Indications and Usage section now updated with pediatric information states:

> BARACLUDE® (entecavir) is indicated for the treatment of chronic hepatitis B virus infection in adults and pediatric patients 2 years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.
>
> In pediatric patients 2 years of age and older, this indication is based on clinical trial data in nucleoside-inhibitor-treatment-naïve (b) (4) and (b) (4) a limited number of lamivudine-experienced subjects with HBeAg-positive chronic HBV infection and compensated liver disease

Other sections updated with pediatric information include: Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology and Clinical Studies.

The following information will be included in the Clinical Studies section of the label:

> The pharmacokinetics, safety, and antiviral activity of BARACLUDE in pediatric (b) (4) were initially assessed in Study AI463028. Twenty-four treatment-naïve and 19 lamivudine-experienced HBeAg-positive pediatric (b) (4) 2 to less than 18 years of age with compensated CHB and elevated ALT were treated with BARACLUDE 0.015 mg/kg (up to 0.5 mg) or 0.03 mg/kg (up to 1 mg) once daily. Fifty-eight percent (14/24) of treatment-naïve subjects and 47% (9/19) of lamivudine-experienced subjects achieved HBV DNA <50 IU/mL at Week 48 and ALT normalized in 83% (20/24) of treatment-naïve and 95% (18/19) of lamivudine-experienced patients.
>
> Safety and antiviral efficacy were confirmed in Study AI463189, an ongoing study of BARACLUDE among 180 nucleoside-inhibitor-treatment-naïve pediatric subjects 2 to less than 18 years of age with HBeAg-positive chronic hepatitis B infection,

compensated liver disease, and elevated ALT. Subjects were randomized 2:1 to receive blinded treatment with BARACLUDE 0.015 mg/kg up to 0.5 mg/day (N=120) or placebo (N=60). The randomization was stratified by age group (2 to 6 years; >6 to 12 years; and >12 to <18 years). Baseline demographics and HBV disease characteristics were comparable between the 2 treatment arms and across age cohorts. At study entry, the mean HBV DNA was 8.1 $\log_{10}$ IU/mL and mean ALT was 103 U/L. The primary efficacy endpoint was a composite of HBeAg seroconversion and serum HBV DNA <50 IU/mL at Week 48 assessed in the first 123 subjects reaching 48 weeks of blinded treatment. Twenty-four percent (20/82) of subjects in the BARACLUDE-treated group and 2% (1/41) of subjects in the placebo-treated group met the primary endpoint. Forty-six percent (38/82) of BARACLUDE-treated subjects and 2% (1/41) of placebo-treated subjects achieved HBV DNA <50 IU/mL at Week 48. (b) (4)

ALT normalization occurred in 67% (55/82) of BARACLUDE-treated subjects and 22% (9/41) of placebo-treated subjects; 24% (20/82) of BARACLUDE-treated subjects and 12% (5/41) of placebo-treated subjects had HBeAg seroconversion.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was conducted for this supplement. Please see the initial review for details from the Advisory Committee which took place on March 11, 2005.

9.4 Financial Disclosure Form

Clinical Investigator Financial Disclosure
Review Template

Application Number: 021797/021798

Submission Date(s): September 20, 2013

Applicant: Bristol-Myers Squibb

Product: Entecavir

Reviewer: Kimberly C. Martin

Date of Review: February 22, 2014

Covered Clinical Study (Name and/or Number): AI463028 and AI463189

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 93 in Study AI463028 and 180 in AI463189 (Some investigators participated in both studies)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): zero		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): zero		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: zero Significant payments of other sorts: zero Proprietary interest in the product tested held by investigator: zero Significant equity interest held by investigator in sponsor of covered study: zero		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒ N/A	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒ N/A	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) zero		
Is an attachment provided with the reason:	Yes ☒ N/A	No ☐ (Request explanation from applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY C MARTIN
02/22/2014

LINDA L LEWIS
02/24/2014
I concur with Dr. Martin's assessment.