Official Title of Study:

A COMPARATIVE STUDY OF THE ANTIVIRAL EFFICACY AND SAFETY OF ENTECAVIR (ETV) VERSUS PLACEBO IN PEDIATRIC SUBJECTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION WHO ARE HBEAG-POSITIVE

NCT Number: NCT01079806

Document Date (Date in which document was last revised): December 5, 2016

STATISTICAL ANALYSIS PLAN FOR CSR

A COMPARATIVE STUDY OF THE ANTIVIRAL EFFICACY AND SAFETY OF ENTECAVIR (ETV) VERSUS PLACEBO IN PEDIATRIC SUBJECTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION WHO ARE HBEAG-POSITIVE

PROTOCOL AI463-189

VERSION 7.0

REVSION HISTORY

Version Number	Author(s)	Description
1.0	A. Thiry	Original version
2.0	A. Thiry	See SAP Amendment 1.
3.0	A. Thiry	See SAP Amendment 2.
4.0	A. Thiry	See SAP Amendment 3.
5.0	A. Thiry	See SAP Amendment 4.
6.0	A. Thiry	See SAP Amendment 5.
7.0	A. Thiry	See SAP Amendment 6.

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2 STUDY DESCRIPTION

2.1 Study Design

This is a comparative, randomized, double-blinded, placebo-control, multicenter study, assessing the efficacy and safety of ETV in pediatric subjects with chronic HBV infection who are HBeAg-positive and nucleos[t]ide naive (< 12 weeks of prior therapy with any nucleos[t]ide antiviral agent with activity against hepatitis B virus). Chronic HBV-infected children and adolescents from 2 to < 18 years of age will be enrolled. Approximately 180 subjects will be randomized 2:1 to ETV or placebo (PBO) for a maximum of 96 weeks of blinded therapy, with the primary endpoint at Week 48 for the first 123 randomized subjects (the Primary Cohort). The randomization will be stratified by age group (≥ 2 to ≤ 6, > 6 to ≤ 12, > 12 to < 18 years). To ensure adequate representation, the target enrollment will be 30 subjects for each age group, with a minimum requirement of 18 subjects. At Week 52, an assessment of HBeAg seroconversion shall be performed based on Week 48 serology results. At the Week 52 assessment, all subjects who achieve HBeAg seroconversion will remain on blinded therapy through Week 96; subjects without HBeAg seroconversion will be switched to open-label ETV. Thereafter, assessment of HBeAg seroconversion shall be conducted at study Weeks 100 and 148 during the open label treatment. Study subjects who achieve HBeAg seroconversion during open label ETV at the respective assessment time points shall receive up to an additional 48 weeks of study treatment for consolidation (extended treatment to strengthen study drug effects). Open-label ETV may therefore be continued up to Week 144 in ETV randomized subjects and Week 192 for placebo randomized subjects. All randomized study subjects who do not achieve HBeAg seroconversion will receive a maximum of 96 weeks of study ETV therapy.

After completing the blinded treatment or the open-label phase, all subjects will be followed in an observational long-term follow up phase until they complete a total of 5 years of study participation from the start of blinded treatment.

The total duration of the study will be 264 weeks (5 years); the end of the study is defined as the date of the last follow-up visit. Study visits will occur at screening, Baseline, Weeks 4, 8, 12, and

then every 12 weeks during study treatment. Additional 'On Treatment' visits to modify or discontinue study drug based on HBeAg assessments will occur at Weeks 52, 100, and 148, if needed. At selected sites, a subset of up to 9 treated subjects in each age cohort will have 4 plasma specimens collected for semi-intense pharmacokinetic assessments during a single visit between study Day 14 and Week 4. Once in the observational long-term follow-up phase, study visits will occur at Weeks 6, 12, and then every 12 weeks until completion of a total of 264 weeks of "on-study follow-up".

2.2 Treatment Assignment

Eligible subjects will be randomized (2:1) to either ETV or PBO.

At the start of the screening period, the investigative staff will call the Randomization Center designated by the sponsor to register the subject and to obtain a subject number or patient identification number (PID). For subjects who meet the protocol defined eligibility criteria during screening, the investigative staff will again call the Randomization Center for the subject to be randomized into a blinded treatment assignment based on the subject's age at the time of randomization. The subject will be assigned bottle numbers according to the randomization scheme. For each study visit, the site will need to call the Randomization Center for container assignments.

A randomized block design stratified by age group will be used. The target enrollment will be 30 subjects for each age group with a minimum requirement of 18 subjects to support the primary analysis for Primary Cohort.

2.3 Blinding and Unblinding

The subject, investigator and Bristol-Myers Squibb personnel involved in the conduct of the study will be blinded to treatment assignment. Designated staff of Bristol-Myers Squibb pharmacokinetics and modeling departments, as well as personnel from the central and analytical laboratories, will be unblinded to treatment assignments in order to minimize unnecessary analysis of samples from subjects receiving placebo.

A pharmacist at Bristol-Myers Squibb not involved in the study design, assessment, or analyses will be given access to the treatment codes to permit efficient drug distribution. The treatment codes will be maintained in a password-protected file which cannot be accessed by the study personnel or subjects.

HBV DNA results from Day 1 through Week 96 will be blinded to the investigator. Any subject who has achieved HBeAg seroconversion by Week 96 shall remain blinded to their randomized treatment assignment except in the event of a change in clinical status for which knowledge of the randomized arm is critical to subject management. Subjects who have not yet achieved HBeAg seroconversion by Week 96 will be unblinded on an individual basis, as needed in order to determine their further management. Refer to Protocol Section 5.4 for more details on blinding and unblinding.

2.4 Protocol Amendments

2.4.1 Amendment 1 (Country Specific - Brazil Only)

The purpose of this amendment is to incorporate changes requested by the Brazilian Research Ethics Commission (CONEP) regarding post study access to therapy. This country-specific amendment applies to all subjects enrolled in Brazil.

2.4.2 Amendment 2

- The purpose of this amendment is to make the following changes to the protocol:
- Augment the number of randomized subjects from 123 to 180 and increase the estimated number of participating study centers.
- Change the entry ALT entry criteria from ≥ 1.3 to ≥ 1.5 x upper limit of normal (ULN), increase the minimum time span between the 2 pre-randomization ALT measurements from 4 to 8 weeks, and exclude other reasons for elevated ALT.
- Specify the early unblinding and mechanism for doing so if subjects demonstrate significant worsening of HBV clinical symptoms or increases in ALT. The role of the DMC in safeguarding subjects is clarified.
- Specify additional analyses that will be conducted as key secondary and exploratory endpoints.
- Modify the blood volume collected at some visits due to minimum fill volume requirements of available specimen collection tubes.
- Summarize the plan for PK/PD analyses that will integrate Studies AI463-028 and AI463-189.
- Add Tanner Stage assessment and analysis.

2.4.3 Amendment 3 (Site Specific - Site -038)

This amendment has been required by the Ethics Committee (EC) at Rambam Medical Center and it documents the standard of care practices that will take place for all patients prior to possible study enrollment at this site. Per the site's usual standard of care, a liver biopsy will be performed for any patient with a pre-screening ALT > 3 x ULN. Based on the histological findings, those patients for whom possible randomization to PBO is judged not to be in their best interest, will not be consented and enrolled in study AI463-189. This site-specific amendment applies to the pre-enrollment practices at site -038 as requested by their EC.

2.4.4 Amendment 4 (Country Specific - India only)

The purpose of this amendment is to restrict the age of study participants enrolled in this study at sites in India, as required by the Directorate General of Health Services in the Office of Drugs Controller General (India). This amendment will document the modified inclusion criteria for India sites; restricting enrollment to male and female adolescents aged > 12 to < 18 years (oldest age group).

Sites in other participating countries will enroll subjects 2 to < 18 years of age. Therefore, the description of the age groups written in other sections of the protocol will not be modified in this amendment.

2.4.5 Amendment 5

The purpose of this amendment is to address the potential safety issues associated with extreme elevations of ALT due to acute exacerbation of CHB by providing emergency access to rescue open-label ETV for subjects who cannot access acceptable alternative anti-HBV therapy.

2.5 Data Monitoring Committee

There will be a data monitoring committee (DMC) for this study. The DMC shall have access to unblinded data on at least an annual basis, including but not limited to following: the frequency and spectrum of serious adverse events; Grades 3 to 4 laboratory abnormalities; occurrence of malignancies; and other select adverse events of interest. The DMC shall act as an advisor to the sponsor and have responsibility for safeguarding the subjects' interests. The DMC shall bring any safety concerns to the attention of the sponsor so that the sponsor can review the data and prepare appropriate communications to the Regulatory Authorities. A separate charter describes the membership and activities of the DMC.

3 OBJECTIVES

3.1 Primary

To compare the proportion of subjects in each treatment group who achieve a combination of HBV DNA suppression and HBeAg seroconversion (undetectable HBeAg AND detectable anti-HBe antibodies) at Week 48.

3.2 Secondary

- Assess the serologic response rates (defined as HBsAg loss and/or seroconversion; and HBeAg loss and/or seroconversion) including durability of response off treatment;
- Assess the virological response rates;
- Assess the biochemical response rates;
- Assess ETV resistance rates;
- Evaluate the long-term safety of ETV use in pediatric patients.

4 ENDPOINTS

4.1 Primary Endpoint

- The proportion of subjects who achieve: 1) HBV DNA < 50 IU/mL (approximately 300 copies/mL) using the Roche COBAS® TaqMan HBV Test for use with the High Pure System (HPS) assay; **and** 2) HBeAg seroconversion (undetectable HBeAg AND detectable anti-HBe antibodies) at Week 48 of study treatment.

4.2 Key Secondary Endpoints

- Proportion of subjects with HBV DNA < 50 IU/mL using the Roche COBAS® TaqMan HBV Test for use with the High Pure System (HPS) assay at Week 48;
- Proportion of subjects with serum ALT ≤ 1 × ULN at Week 48;
- Proportion of subjects with HBV DNA < limit of quantification (LOQ; 29 IU/mL) using the Roche COBAS® TaqMan HBV Test for use with the High Pure System (HPS) assay at Week 48;
- Proportion of subjects with HBeAg seroconversion (undetectable HBeAg and presence of anti-HBe antibodies) at Week 48;
- Proportion of subjects who achieved sustained HBeAg seroconversion during off-treatment follow-up among subjects who achieved HBe seroconversion (undetectable HBeAg and presence of anti-HBe antibodies) at end of treatment.

4.3 Other Secondary Endpoints

- The number and percent of subjects with adverse events (including palatability issues), serious adverse events (SAEs), discontinuations due to adverse events, and HBV disease progression through Week 48;
- Proportions of subjects with HBeAg loss at Weeks 48 and 96;
- Proportion of subjects with HBeAg seroconversion at Week 96;
- Proportion of subjects who maintained HBeAg seroconversion at Week 96 (end of blinded therapy) among subjects who achieved HBeAg seroconversion at Week 48;
- Histological analysis among subjects with available liver biopsy.

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- [redacted]

4.5 PK Endpoints

PK parameters include Cmin, Cmax and Tmax.

5 SAMPLE SIZE AND POWER

One hundred and twenty-three (123) subjects (randomized 2:1 to ETV vs placebo) in this study provide 90% power to show superiority of ETV versus PBO assuming a response rate for the primary endpoint HBV DNA by PCR < 50 IU/mL (approximately 300 copies/mL) and HBeAg seroconversion of 20% for ETV and 1% for PBO. A two-sided significance level of 0.05 is used. Subjects who either discontinue from study treatment prior to Week 48 or have having missing Week 48 HBV DNA or HBeAg serology measurement are considered as failures at Week 48 (Non-Completer = Failure). The efficacy estimate for ETV is derived from an analysis of the identical endpoint (HBV DNA by PCR < 300 copies/mL and HBeAg seroconversion) in the pivotal Phase 3 study of HBeAg-positive subjects, (AI463022). The efficacy estimate for PBO is derived from evidence in the literature which shows that whereas spontaneous seroconversion occurs at a relatively high rate in children, viral replication remains detectable using sensitive PCR assays. The results of the Gilead Sciences' pediatric CHB study (GS 518) support this estimate; 3 of 57 placebo treated subjects (5.3%) achieved HBeAg seroconversion, but only 1 of 58 subjects (1.7%) achieved HBV DNA < 2.23 $\log_{10}$ copies/mL at Week 48.

This sample size also fulfills the requirement that the ETV integrated pediatric safety database has at least 100 pediatric subjects who have received ETV for at least 48 weeks; this database will be comprised of subjects currently enrolled in study AI463-028 and from this study (AI463-189).

Currently 24 nucleoside naive subjects are enrolled in AI463-028; all 24 would have had 48 weeks of safety data collection by the time study AI463-189 reaches Week 48.

Based on the original planning for study AI463-189, it is estimated that 175 subjects will be enrolled to have approximately 123 subjects randomized (approximately 30% screen failure rate). Randomization is 2:1 (ETV 82: PBO 41); assuming a 10% drop out rate per year and even enrollment for 2 calendar years, approximately 72 ETV randomized subjects will have 48 weeks of safety data by study Week 144. This brings the number of subjects that will be included in the integrated safety database at the end of study Week 144 to approximately 96 subjects.

Additional safety data will be contributed by PBO randomized subjects switching to open label ETV at study Week 52. Because it is expected to take 2 calendar years to randomize 123 subjects

and assuming steady enrollment over that time frame, the last PBO randomized subject will be completing Week 48 by study week 144. Assuming a 10% drop out per year, 18 of the 20 subjects randomized to PBO during the first calendar year will reach Week 48 by study Week 96; 16 of these 18 will be switched to open label ETV (assuming a 10% HBeAg seroconversion rate on PBO). With a 10% drop out rate per year, 14 of these 16 will be completing 48 weeks of open label ETV by study Week 144 and will be added to the integrated safety database. This will bring the number of subjects in the integrated safety database with at least 48 weeks of ETV exposure after two years of enrollment to approximately 110 subjects.

While the analysis of the primary endpoint is based on a randomized sample size of 123, the size of the overall study population has been augmented to 180 randomized subjects in order to meet the requirement of a health authority. Therefore the final safety dataset as described in the previous 2 paragraphs will also be augmented. The accrual of the first 123 randomized subjects is expected to take 2 years. Thereafter, the enrollment will remain open until 180 subjects are randomized. Additional re-analyses will be performed on the augmented population.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Study periods for efficacy and safety analyses are defined as follows:

- **Pre-treatment period** begins at the first visit until initiation of study therapy.
- **On-treatment period** begins after the first day of study therapy and ends at the last dose of study therapy plus 5 days.
- **ETV treatment period** begins after the first day of active ETV and ends at the last dose of active ETV plus 5 days.
- **Off-treatment follow-up period** begins on the last dose of study therapy plus 6 days and ends at the start of alternative anti-HBV therapy minus 1 day.
- **Long-term follow-up period** begins on the last dose of study therapy plus 6 days until the end of the study.
- **Alternative ETV follow-up period** begins on the later of the last dose of study therapy plus 6 days and the start of alternative ETV therapy, until the end of the study.

Note that rescue open-label ETV is considered alternative anti-HBV therapy. See Section 8.9 for additional conventions.

6.2 Treatment Regimens

Treatment regimens are described in Protocol Section 5.1 as ETV treated subjects (ETV) given a starting dose of 0.015 mg/kg up to a maximum dose of 0.5 mg and PBO subjects.

Treatment regimens are defined as follows:

- As-randomized refers to the treatment regimen assigned at randomization. Accrual and efficacy results are presented as-randomized.
- As-treated refers to the actual treatment regimen received. Subjects who receive the incorrect study therapy for the entire period of treatment are grouped according to the treatment regimen associated with the incorrect study therapy. Otherwise, subjects are grouped according to their randomized treatment regimen. Subjects who never receive study therapy have missing as-treated treatment regimen. Results for subject disposition, demographics, baseline characteristics, safety, and PK parameters are presented as-treated. Furthermore, important safety events that occur while a subject is on an incorrect treatment regimen are specifically discussed in the text of the Clinical Study Report.

If a subject receives at least 1 dose of drug in the randomized regimen, then the as-randomized treatment regimen is equal to the as-treated treatment regimen. If ≥ 5% of treated subjects have as-randomized regimen different than as-treated regimen, summaries are presented by both treatment regimens for select endpoints (see Section 7).

6.3 Populations for Analyses

- **Enrolled subjects** are those who sign an informed consent form and are assigned a Patient Identification number (PID). This cohort is used to assess subject disposition, deaths and serious adverse events during the **pre-treatment period**.
- **Randomized subjects** are enrolled subjects who receive a treatment assignment from the central randomization center. This cohort is used to assess subject status and accrual.
- **Treated subjects** are randomized subjects who receive at least 1 dose of study therapy. This cohort is used to assess all data domains.
  - **Primary cohort** is defined as at least the first 123 subjects randomized and treated. The Primary Cohort is used for the primary analyses.
- **Off-treatment follow-up subjects** are treated subjects who discontinue study therapy and have at least 1 of the following assessments during the **off-treatment follow-up period** (see Section 6.1): death date if it exists; adverse event onset date; HBV related diagnosis date; vital signs date; physical measurement date; physical exam date; neurologic exam date; laboratory test date (safety, pregnancy, serology and virology); liver biopsy date; Tanner staging date. This cohort is used to assess safety during the off-treatment follow-up period.
- **Long-term follow-up subjects** are treated subjects who discontinue study therapy and have at least 1 of the following assessments during the **long-term follow-up period** (see Section 6.1): death date if it exists; adverse event onset date; HBV related diagnosis date; vital signs date; physical measurement date; physical exam date; neurologic exam date; laboratory test date (safety, pregnancy, serology and virology); liver biopsy date; Tanner staging date. This cohort is used to assess safety during the long-term follow-up period.
- **Alternative ETV follow-up subjects** are treated subjects who discontinue study therapy, receive at least 1 dose of alternative ETV therapy, and have at least 1 of the following assessments during the **alternative ETV follow-up period** (see Section 6.1): death date if it exists; adverse event onset date; HBV related diagnosis date; vital signs date; physical measurement date; physical exam date; neurologic exam date; laboratory test date (safety, pregnancy, serology and virology); liver biopsy date; Tanner staging date. This cohort is used to assess safety during the alternative ETV follow-up period.

- **Year 2 Efficacy Cohort** is treated subjects grouped as-randomized and according to observed Week 48 seroconversion status: ETV, PBO, ETV S48, PBO S48, ETV NS48 and PBO NS48 (S = seroconverter; NS = non-seroconverter). All treated subjects are included in ETV and PBO.
  - **Year 2 Primary Efficacy Cohort** is treated subjects in both Primary and Year 2 Efficacy Cohorts.
- **Year 3 Efficacy Cohort** is observed Week 48 non-seroconverters grouped as-randomized according to observed Week 96 seroconversion status: ETV S96, ETV NS96, PBO S96 and PBO NS96.
- **Year 4 Efficacy Cohort** is PBO-randomized observed non-seroconverters at both Weeks 48 and 96 who seroconverted at Week 144.
- **All ETV Efficacy Cohort** is treated as-randomized ETV subjects and PBO-randomized subjects who received open-label ETV.
- **Post-Year 1 Efficacy Cohort** is treated subjects grouped as-randomized: ETV, PBO, PBO subjects who only received blinded PBO (PBO BL), PBO subjects who received open-label ETV (PBO OL), and All ETV (ETV and PBO OL combined; see previous bullet).
- **Year 2 Safety Cohort** is treated subjects grouped as-treated: ETV, PBO subjects who only received blinded PBO (PBO BL), and PBO subjects who received open-label ETV (PBO OL). In addition, subjects must have received open-label ETV or > 54 weeks of study therapy (the upper bound of the Week 48 visit window; see Sections 7.4.1 and 8.4).
- **All ETV Safety Cohort** is as-treated ETV subjects and as-treated PBO subjects who received open-label ETV.
- **Post-Year 1 Safety Cohort** is treated subjects grouped as-treated: ETV, PBO, PBO subjects who only received blinded PBO (PBO BL), PBO subjects who received open-label ETV (PBO OL), and All ETV (ETV and PBO OL combined; see previous bullet).

7 STATISTICAL ANALYSES

7.1 General Methods

All analyses (efficacy, safety and PK) are presented by treatment regimen, ie, ETV vs PBO, based on the appropriate cohort and dataset defined in the earlier section. For Week 48 analysis, all the endpoints are to be cut off through Week 48, unless specified otherwise.

The PK analyses are described in Section 7.7. The methods described below are used to analyze safety and efficacy data.

Categorical variables are summarized either with counts and percents or with proportions (number with event divided by number evaluable) and percents, depending on the endpoint.

Continuous variables are summarized with univariate statistics (eg, n, mean, median, standard deviation, standard error, quartiles, minimum, and maximum).

Longitudinal analyses of efficacy and safety parameters use pre-defined visit week windows (see Section 8.4). Windows around planned measurement times are constructed based on the

midpoint between planned measurement visits unless specified otherwise. Data are summarized at each scheduled visit through the analysis week.

Analyses of HBV DNA use values only from the central laboratory from the Roche COBAS® TaqMan HBV Test with limit of quantitation (LOQ) of 29 IU/mL and limit of detection (LLD) of 10 IU/mL.

Analyses of laboratory tests and serology use values from the central or local laboratory. Laboratory parameters are summarized using US standard values and units. Refer to Section 8.11 for conversion of select laboratory test values from the Abbott Architect system to the Roche Diagnostics Hitachi Modular system.

Formats of tables, listings and graphs are described in the Data Presentation Plan (DPP).

7.2 Study Conduct

Relevant protocol deviations are summarized by treatment regimen for treated subjects. Relevant protocol deviations are those that could potentially affect the interpretability of the study results. A list of programmable relevant protocol deviations is provided in Appendix 1, including:

- Eligibility deviations (based on deviations of subject inclusion and exclusion criteria from Protocol Sections 4.2.1 and 4.2.2 which can be programmed from the database) during the pre-treatment period. If multiple measurements are available, a subject is considered to have a deviation only if all measurements fail the inclusion or exclusion criterion, except for pregnancy.
- Deviations during the on-treatment period (eg, incorrect dosing received).
- Deviations related to PK data.

7.3 Study Population

7.3.1 Pre-Randomization Subject Status and Accrual Pattern

Pre-randomization subject status is summarized for enrolled subjects. This presents the number of subjects enrolled, randomized and not randomized. Reasons for not randomized are also included (eg, AE, death, lost to follow-up).

The numbers of subjects enrolled and randomized are summarized by site for each country.

Enrollment by age group is summarized analogously. Age groups are: in utero; preterm newborn (gestational age < 37 weeks); newborns (0 to 27 days); infants and toddlers (28 days to 23 months); children (2 to 11 years); adolescents (12 to 17 years); adults (18 to 64 years); adults (65 to 84 years); adults (≥ 85 years).

7.3.2 Accounting for Patient Identification Number (PID) Assignments

PIDs assigned by the RIVRS randomization system at enrollment are listed in an Appendix to the study report.

7.3.3 Subject Disposition

Summaries are presented by as-treated treatment regimen unless specified otherwise.

Subject disposition from the start to end of treatment is based on the end of treatment subject status CRF, and varies according to the analysis (see Section 9): the number of subjects treated, discontinued before Week 48, discontinued at Week 48 or before Week 96, discontinued at or after Week 96, continuing treatment and completed treatment. Reasons for discontinuation are also included (eg, AE, lost to follow-up). The lower bounds of the on-treatment Week 48 and 96 visit windows are used to define the cuts on discontinuation (see Section 8.4).

Subject disposition from start to end of treatment is also summarized analogously by age randomization strata for each treatment regimen.

If ≥ 5% of treated subjects have as-randomized regimen different than as-treated regimen, then subject disposition from the start to end of treatment is summarized analogously by as-randomized treatment regimen for treated subjects.

Subject disposition from the start to end of long-term follow-up is based on the end of study subject status CRF, and is summarized for the Post-Year 1 Safety Cohort. The summary presents the number of subjects who entered long-term follow-up, did not complete long-term follow-up, completed long-term follow-up, continuing in long-term follow-up, and did not enter long-term follow-up. Reasons for not completing are also included. For subjects who entered long-term follow-up but indicated they were not continuing in the study on the end of treatment subject status CRF, the reason for not completing is set to the reason for not continuing.

7.3.4 Demographic and Other Baseline Characteristics

Summaries are presented by as-treated treatment regimen for treated subjects unless specified otherwise. Summaries identify the number and percent of subjects with not reported (i.e., missing) measurements, unless specified otherwise.

If ≥ 5% of treated subjects have as-randomized regimen different than as-treated regimen, then demographics and baseline disease HBV characteristics are summarized analogously by as-randomized treatment regimen for treated subjects.

Demographic and other baseline characteristics are summarized by treatment regimen and overall for treated subjects:

- Demographics: age (years), age randomization strata (≥ 2 to ≤ 6, > 6 to ≤ 12, > 12 to < 18 years), gender, race, ethnicity, geographic region (Asia, Europe, North America, South America), country
- HBV disease characteristics: HBV DNA (log_{10} IU/mL), Hepatitis B Surface Antigen (positive, negative, indeterminate), Hepatitis B E Antigen (positive, negative, indeterminate), Hepatitis B E Antibody (positive, negative, indeterminate), HBV genotype (e.g., A, B, C, D, E, indeterminate), INR, albumin (g/dL), ALT (U/L), ALT categories (≤ 2 x ULN, > 2 x ULN), total bilirubin (mg/dL), creatinine (mg/dL), glomerular filtration rate (< 50, 50 - 75, > 75 mL/min/1.73 m^2) estimated with Schwartz's formula, route of transmission (mother-to-

child transmission; household/close contact exposure; transfusion; sexual contact; IV drug use; other)

- Physical measurements: height (cm), height for age Z score (HAZ), height for age percentile (HAP), weight (kg), weight for age Z score (WAZ), weight for age percentile (WAP), body mass index (BMI; kg/m^2), BMI for age Z score (BMIAZ), BMI for age percentile (BMIAP) (see Section 7.6.7)
- Laboratory tests (see Section 7.6.6.1)
    - Hematology by toxicity grade (ie, normal, Grade 1, 2, 3, 4)
    - Liver function tests by toxicity grade
    - Pancreatic enzymes by toxicity grade
    - Renal function tests by toxicity grade
    - Electrolytes (low and high) by toxicity grade
    - Glucose categories regardless of fasting status
- Medical history by body system
- Prior medications, defined as non-study medications taken before the first dose of study therapy.

Demographics and baseline disease HBV characteristics are also summarized analogously for the following: Primary Cohort; All ETV Safety Cohort; by age randomization strata for each treatment regimen.

For the All ETV Safety Cohort, age and HBV disease characteristics are summarized at ETV baseline. Age at ETV baseline is defined as (first dose date of active ETV - birth date + 1)/365.25.

See Sections 8.5 and 8.9 for additional conventions.

7.4 Extent of Exposure

Extent of exposure is presented by as-treated treatment regimen for treated subjects to support safety.

7.4.1 Study Therapy

Extent of exposure to study therapy is summarized for blinded therapy (ETV active or PBO), open-label ETV, active ETV (blinded active ETV or open-label ETV), and all therapy (blinded therapy or open-label ETV) by treatment regimen as follows:

- Time on therapy (weeks): (last dose date of drug - first dose date of drug + 1)/7.
- Cumulative dose: total amount (mg) of drug summed across dosing records.
- Average daily dose: cumulative dose divided by time on therapy.

Extent of exposure to study therapy is also summarized analogously for the following: Primary Cohort; All ETV Safety Cohort; by age randomization strata for each treatment regimen.

Time on study therapy is also described by a Kaplan-Meier plot and life table. Discontinuations from study therapy are considered events in this analysis, and are identified by subjects with non-missing last dose date of study therapy. For subjects who have not discontinued, time on study therapy is censored at the maximum of the last dose date of study drug (ETV blinded active or PBO, ETV open-label).

Time in long-term follow up is summarized by treatment regimen for long-term follow-up subjects in the Post-Year 1 Safety Cohort. Time in long-term follow-up (weeks) is defined as (last contact date - last dose date of study therapy)/7.

Time in off-treatment follow up is summarized by treatment regimen for off-treatment follow-up subjects in the Post-Year 1 Safety Cohort. Time in off-treatment follow-up (weeks) is defined as (minimum(last contact date, start date of alternative anti-HBV therapy - 1) - last dose date of study therapy)/7.

Dose interruptions of study therapy more than 3 days are summarized by treatment regimen. Reasons for interruption are also identified.

See Section 8.9 for additional conventions.

7.4.2 Concomitant Medications

Concomitant medications are summarized by treatment regimen for the on-treatment and long-term follow-up periods. Medications are presented alphabetically by anatomic class, therapeutic class and generic name using the WHO dictionary.

Concomitant medications on treatment are those taken any time on or after the first dose of study therapy through the day preceding the earlier of the last dose of study therapy or open-label therapy. These also include prior medications with ‘continuing’ stop dates.

Concomitant medications during long-term follow-up are those taken on or after the day of last dose of study therapy. These also include on-treatment concomitant medications with ‘continuing’ stop dates.

Alternative anti-HBV medications are summarized separately for the long-term follow-up period.

7.5 Efficacy

Efficacy endpoints are presented by as-randomized treatment regimen for treated subjects.

Binary efficacy endpoints are analyzed using 2 algorithms:

- Non-Completer = Failure (NC = F): The numerator is based on subjects meeting the response criteria. The denominator is based on treated subjects. Subjects who have missing data at the analysis week are considered as failures.
- Non-Completer = Missing (NC = M): The numerator is based on subjects meeting the response criteria. The denominator is based on subjects with data at the analysis week. Subjects who have missing data at the analysis week are excluded.

Treatment regimens are compared using a difference in proportions (ETV - PBO), 95% confidence interval (CI) and p-value based on NC = F for the primary endpoint and key secondary endpoints. Analyses are stratified by age randomization strata (see Section 7.3.4). The proportions are computed within each stratum, and combined using a weighted average with weights proportional to stratum size (Cochran-Mantel-Haenszel [CMH] weighting). ETV will be considered superior to PBO if the p-value is < 0.05. CIs for differences in proportions are based on the stratified normal approximation to the binomial distribution with unpooled proportions used in the computation of the standard error of the difference.

A two-stage testing procedure will be employed for testing the primary and key secondary endpoints using NC = F. In the first stage, the test for primary endpoint will be performed. Provided the test result of the primary endpoint is significant (p-value < 0.05), the second stage tests of the key secondary endpoints will be conducted. Because the tests for the key secondary endpoints will be conducted sequentially only if the test for the primary endpoint is successful, significance levels will not be adjusted for the first stage testing. All tests for treatment comparison will be two-sided at a significance level of 0.05.

For binary composite endpoints involving several components (eg, primary efficacy endpoint), only subjects who meet the response criteria for all components are considered to be responders for the composite endpoint. In addition, subjects who meet the response criteria for some components but are missing other components are considered to be missing the composite endpoint.

See also Sections 8.4 to 8.8 for additional conventions.

7.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is a composite endpoint defined as the proportion of treated subjects with HBV DNA < 50 IU/mL (approximately 300 copies/mL) and HBeAg seroconversion (HBeAg negative and HBeAb positive) at Week 48 on treatment. Response rates are presented by treatment regimen with a difference in proportions (ETV - PBO), 95% CI and p-value using NC = F. The difference in proportions and p-value are presented only at Week 48 for the Primary Cohort at the primary analysis (see Sections 6.3 and 9).

A sensitivity analysis using NC = M presents response rates.

Another sensitivity analysis using NC = F presents response rates by imputing successes for subjects randomized to PBO who are missing the primary efficacy endpoint and started rescue open-label ETV before or at Week 48, i.e., (start date of rescue open-label ETV - first dose date of study therapy + 1)/7 ≤ 54 (see Sections 8.4 and 8.9).

The proportions of subjects with HBV DNA < 50 IU/mL and HBeAg seroconversion are also summarized at baseline and each scheduled on-treatment visit through Week 48 by treatment regimen. Response rates are presented using NC = F and NC = M.

The primary efficacy endpoint is also summarized using NC = F and NC = M by treatment regimen and subgroups to examine consistency of effect. Subgroups may include, but are not limited to, the following:

- Age randomization strata (see Section 7.3.4)
- Gender (male, female)
- Baseline HBV DNA (< 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL)
- Baseline ALT (≤ 2 x ULN, > 2 x ULN)
- Geographic region (Asia, Europe, North America, South America)
- HBV genotype (e.g., A, B, C, D, E, etc.)
- Route of transmission (mother-to-child transmission; household/close contact exposure; transfusion; sexual contact; IV drug use; other)

Subgroup categories may be combined based on the availability of data.

7.5.2 Key Secondary Endpoints

The tests of the key secondary endpoints are conducted sequentially in the order specified below, provided the test result of the primary endpoint is significant. The nth key secondary endpoint is tested provided the test result of the (n-1)st key secondary endpoint is significant (n = 1, 2, ..., 5).

Treatment regimens are compared (ETV - PBO) with a difference in proportions and p-value at Week 48 on treatment for the Primary Cohort at the primary analysis (see Sections 6.3 and 9) using NC = F, unless specified otherwise.

7.5.2.1 HBV DNA Below 50 IU/mL

Analyses described in Section 7.5.1 are performed for the proportions of subjects with HBV DNA < 50 IU/mL on treatment.

7.5.2.2 ALT Normalization

Analyses described in Section 7.5.1 are performed for the proportions of subjects with ALT normalization (ALT ≤ 1 x ULN) on treatment.

7.5.2.3 HBV DNA Below LOQ

Analyses described in Section 7.5.1 are performed for the proportions of subjects with HBV DNA < LOQ on treatment.

7.5.2.4 HBeAg Seroconversion

Analyses described in Section 7.5.1 are performed for the proportions of subjects with HBe seroconversion on treatment.

7.5.2.5 Sustained HBeAg Seroconversion During Off-Treatment Follow-up

Response rates of HBeAg seroconversion are presented by treatment regimen at EOD (end of dosing) and each scheduled visit during off-treatment follow-up through Week 192 using NC = F

and NC = M for the Year 2 Efficacy Cohort with HBeAg seroconversion at EOD. Rates using NC = F are shown only through off-treatment follow-up Week 48.

Treatment regimens are compared between treated subjects with HBeAg seroconversion at both on-treatment Week 48 and EOD (ETV S48 - PBO S48; NC = F) with a difference in proportions and p-value at off-treatment follow-up Week 24 at the final analysis, provided the test result of HBeAg seroconversion was significant at the primary analysis (see Section 9).

Sustained HBeAg seroconversion is summarized analogously with response rates using NC = M for the Post-Year 1 Efficacy Cohort with HBeAg seroconversion at EOD.

Sustained HBeAg seroconversion at off-treatment follow-up Week 24 is also summarized by subgroups for treated subjects with HBeAg seroconversion at EOD (see Section 7.5.1).

7.5.3 Other Year 1 Efficacy

7.5.3.1 Response Rates

The following binary endpoints are summarized by treatment regimen with response rates using NC = F and NC = M at baseline and each scheduled visit on treatment through Week 48:

- HBV DNA < 50 IU/mL and ALT normalization
- HBV DNA < LLD
- HBV DNA < LOQ, LOQ - < 50, 50 - < 172, 172 - < 1,720, 1,720 - < 17,200 and ≥ 17,200 IU/mL
- HBeAg loss (HBeAg negative)
- HBsAg loss (HBsAg negative)
- HBsAg seroconversion (HBsAg negative and HBsAb positive).

7.5.3.2 HBV DNA Reduction from Baseline

HBV DNA values and changes from baseline (log_{10} IU/mL) are summarized by treatment regimen at baseline and each scheduled visit on treatment through Week 48.

The difference (ETV - PBO) and 95% CI at Week 48 are also presented. The difference and CI are estimated from a linear regression model of Week 48 HBV DNA change from baseline on covariates baseline HBV DNA, treatment regimen and age randomization strata.

7.5.4 Year 2 Efficacy

The following binary endpoints are summarized by treatment regimen with response rates using NC = F and NC = M at baseline and each scheduled visit on treatment through Week 96 for the Year 2 Efficacy Cohort (see Section 6.3):

- HBV DNA < 50 IU/mL
- HBV DNA < 50 IU/mL and HBeAg seroconversion
- HBV DNA < 50 IU/mL and ALT normalization

- HBV DNA < LOQ
- HBV DNA < LLD
- HBV DNA < LOQ, LOQ - < 50, 50 - < 172, 172 - < 1,720, 1,720 - < 17,200 and ≥ 17,200 IU/mL
- ALT normalization
- HBeAg loss
- HBeAg seroconversion
- HBsAg loss
- HBsAg seroconversion

The Year 2 Efficacy Cohort is defined by as-randomized treatment regimen for all treated subjects and observed (NC = M) Week 48 HBeAg seroconversion status. Therefore, the analysis of HBeAg seroconversion addresses maintenance of HBeAg seroconversion at Week 96 for those who seroconverted at Week 48. Endpoints are summarized for PBO only through Week 48.

Key binary endpoints (e.g., HBV DNA < 50 IU/mL, ALT normalization, HBeAg seroconversion) at Week 96 are summarized by subgroups defined in Section 7.5.1 using NC = F and NC = M for ETV subjects.

HBV DNA values and changes from baseline (log_{10} IU/mL) are summarized by treatment regimen at baseline and each scheduled visit on treatment through Week 96 for the Year 2 Efficacy Cohort.

7.5.5 Year 3 Efficacy

The following binary endpoints are summarized by treatment regimen with response rates using NC = M at baseline and each scheduled visit on treatment through Week 144 for the Year 3 Efficacy Cohort (see Section 6.3):

- HBeAg loss
- HBeAg seroconversion
- HBsAg loss
- HBsAg seroconversion

The Year 3 Efficacy Cohort is defined for observed (NC = M) Week 48 HBeAg non-seroconverters by observed (NC = M) Week 96 HBeAg seroconversion status. Endpoints are summarized for ETV Week 96 non-seroconverters only through Week 96.

7.5.6 Year 4 Efficacy

The binary endpoints described in Section 7.5.5 are summarized with response rates using NC = M at baseline and each scheduled visit on treatment through Week 192 for the Year 4 Efficacy Cohort (see Section 6.3), defined as PBO-randomized observed HBeAg non-seroconverters at both Weeks 48 and 96 who HBeAg seroconverted at Week 144 (NC = M).

7.5.7 All ETV On-Treatment Efficacy

The following binary endpoints are summarized with response rates using NC = M at baseline and each scheduled visit on ETV treatment through Week 144 for the All ETV Efficacy Cohort (see Sections 6.3 and 8.4):

- HBV DNA < 50 IU/mL
- HBV DNA < 50 IU/mL and HBeAg seroconversion
- HBV DNA < 50 IU/mL and ALT normalization
- HBV DNA < LOQ
- HBV DNA < LLD
- HBV DNA < LOQ, LOQ - < 50, 50 - < 172, 172 - < 1,720, 1,720 - < 17,200 and ≥ 17,200 IU/mL
- ALT normalization
- HBeAg loss
- HBeAg seroconversion
- HBsAg loss
- HBsAg seroconversion

7.5.8 Efficacy During Off-Treatment Follow-up

The following binary endpoints are summarized by treatment regimen with response rates using NC = M at EOD (see Section 8.5) and each scheduled visit during off-treatment follow-up through Week 192 for off-treatment follow-up subjects in the Post-Year 1 Efficacy Cohort (see Section 6.3):

- HBV DNA < LOQ, LOQ - < 50, 50 - < 172, 172 - < 1,720, 1,720 - < 17,200 and ≥ 17,200 IU/mL
- HBeAg loss
- HBeAg seroconversion
- HBsAg loss
- HBsAg seroconversion
- ALT ≤ 1 x ULN, > 1 - 2 x ULN, > 2 - 5 x ULN, and > 5 x ULN

In addition, the efficacy response shifts from EOD using an HBV DNA cut-off of 50 IU/mL are summarized at Weeks 24, 48, 72, 96 and 120 during off-treatment follow-up for off-treatment follow-up subjects in the Post-Year 1 Efficacy Cohort (limited to ETV, PBO OL, and All ETV). Efficacy response shift categories are defined as follows:

- Complete response: HBV DNA < 50 IU/mL, ALT normalization, and HBeAg seroconversion.

- Partial response: HBV DNA < 50 IU/mL and ALT normalization without HBeAg seroconversion (including missing HBeAg).
- Virologic response: HBV DNA < 50 IU/mL without ALT normalization and HBeAg seroconversion (including missing ALT or HBeAg).
- Non-response: HBV DNA ≥ 50 IU/mL.

Results are presented by total ETV duration: overall, < 2 years, and ≥ 2 years, using 102 weeks as 2 years.

Efficacy response shifts from EOD using an HBV DNA cut-off of 2000 IU/mL are also summarized analogously.

7.5.9 Histology

Histological parameters are listed, including most recent liver biopsy date, scoring system (Knodell, Ishak, Metavir, other), hepatitis activity index, fibrosis score and findings.

7.5.10 Genotypic Resistance

Analyses of genotypic resistance will be addressed in a separate integrated resistance SAP for studies AI463-028 and AI463-189.

7.6 Safety

The investigators determine the intensity of AEs and the relationship of AEs to study therapy. The investigators' terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in production at BMS.

In order to account for AEs with multiple occurrences in the same subject, AE records are collapsed for each subject and preferred term when records have the same onset date, or when records are contiguous or overlapping (see Section 8.10). All AE presentations are based on collapsed records.

AEs are presented by system organ class and preferred term, both in descending order of incidence on ETV, unless specified otherwise.

AE presentations include both non-serious and SAEs as defined in the protocol, unless specified otherwise. If a subject had an AE with different intensities during the study period, then only the greatest intensity is reported.

On-treatment safety is assessed for the following 3 cohorts (see Sections 6.1 and 6.3):

- Through Week 48 on blinded therapy for treated subjects
  - ETV and PBO are assessed on treatment up to the Week 48 cut, ie, the earlier of (a) 54 weeks, the upper bound of the Week 48 visit window (see Section 8.4), and (b) the first dose of open-label ETV.
- After Week 48 on blinded therapy or on open-label ETV through Week 96 for the Year 2 Safety Cohort

  - ETV, PBO BL and PBO OL are assessed on treatment after the Week 48 cut and up to 102 weeks, the upper bound of the Week 96 visit window (see Section 8.4).
- On ETV treatment for All ETV Safety Cohort

Note that AEs with onset on the first day of study therapy are considered on treatment, AEs with onset on the first day of ETV are considered on ETV treatment and AEs with onset on the first day of open-label ETV are considered on open-label ETV.

Follow-up safety is assessed for the following 3 cohorts (see Sections 6.1 and 6.3):

- During off-treatment follow-up for off-treatment follow-up subjects in the Post-Year 1 Safety Cohort
- During long-term follow-up for long-term follow-up subjects in the Post-Year 1 Safety Cohort.
- During alternative ETV follow-up for alternative ETV follow-up subjects in the Post-Year 1 Safety Cohort (select endpoints only).

7.6.1 Deaths

Deaths are listed for enrolled subjects without regard to study period. The listing includes treatment regimen, death date, start and end date of dosing, source of information, and cause of death. Deaths from multiple sources of information are identified:

- Subject status: study discontinuation reason of death;
- AE/SAE: MedDRA higher level, lower level or preferred term contains 'death'; SAE outcome of death; SAE category of death; death date.

Deaths are also summarized without regard to study period for treated subjects for the following categories: total; due to AE.

7.6.2 Other Serious Adverse Events

Pre-treatment SAEs are summarized by treatment regimen for enrolled subjects (ETV, PBO, not treated). Pre-treatment SAEs are those that occurred prior to the first dose of study therapy.

SAEs are also summarized by treatment regimen for the following cohorts and study periods:

- Through Week 48 on blinded therapy for treated subjects
- After Week 48 on blinded therapy or on open-label ETV through Week 96 for the Year 2 Safety Cohort
- On ETV treatment for the All ETV Safety Cohort
- Off-treatment follow-up for off-treatment follow-up subjects in the Post-Year 1 Safety Cohort
- Long-term follow-up for long-term follow-up subjects in the Post-Year 1 Safety Cohort
- Alternative ETV follow-up for alternative ETV follow-up subjects in the Post-Year 1 Safety Cohort.

SAEs leading to death and SAEs related to study therapy and leading to death are also summarized analogously during the on-treatment period for the 3 cohorts.

Multiple on-treatment SAEs (all; related to study therapy) are also summarized for the 3 cohorts, presenting the numbers of events and exposure-adjusted incidence rates (see Section 8.10).

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation of study therapy are summarized by treatment regimen for the following cohorts and study periods:

- Through Week 48 on blinded therapy for treated subjects
- After Week 48 on blinded therapy or on open-label ETV through Week 96 for the Year 2 Safety Cohort
- On ETV treatment for the All ETV Safety Cohort

7.6.4 Other Significant Adverse Events

7.6.4.1 Events of HBV Disease Progression

Events of HBV disease progression are summarized by treatment regimen for treated subjects across the on-treatment and long-term follow-up periods combined (see Table 7.6.4.1-1).

Table 7.6.4.1-1: Events of HBV Disease Progression

Serious and non-serious AEs: preferred terms in MedDRA dictionary
Ascites, Gastric varices, Gastric varices haemorrhage, Hepatic cirrhosis, Hepatic encephalopathy, Hepatic neoplasm malignant, Hepatorenal syndrome, Oesophageal varices haemorrhage, Peritonitis bacterial, Varices oesophageal

7.6.4.2 Neoplasms and Pre-Malignant Lesions

Malignant neoplasms are summarized by treatment regimen for treated subjects across the on-treatment and long-term follow-up periods combined.

A listing of neoplasms and pre-malignant lesions is also provided for enrolled subjects regardless of diagnosis date. The listing includes exposure to treatment regimens through the event onset. Exposure is measured from the first dose of study therapy to the earlier of the event onset or the end of study therapy.

Neoplasm terms of special interest are identified from 2 sources: (1) all MedDRA preferred terms in the "neoplasms benign, malignant or unspecified" system organ class (SOC) plus the preferred term "hepatic mass"; (2) a list of selected MedDRA preferred terms which represent pre-malignant lesions (see Table 7.6.4.2-1). The list is generated by searching MedDRA for all terms containing "plasia" or "blood disorder", and adding these to all terms in the pre-neoplasm

high level term group within the skin and subcutaneous disorders SOC. The resulting list is reviewed and edited by a BMS safety clinician for appropriateness. Note some of these terms also derive from the neoplasms SOC.

All terms are further categorized as benign, malignant, pre-malignant or unclassifiable by a BMS medical monitor, with concurrence from another BMS medical monitor, who are both blinded to treatment regimen.

Table 7.6.4.2-1: Selected Pre-Malignant Lesions

Serious and non-serious AEs: preferred terms in MedDRA dictionary
Actinic keratosis, Adrenal cortex dysplasia, Anogenital dysplasia, Blood disorder, Breast dysplasia, Bronchial dysplasia, Cervical dysplasia, Dysplasia, Endometrial dysplasia, Epidermodysplasia verruciformis, Erythroplasia of lip[a], Erythroplasia of penis[a], Erythroplasia of vulva[a], Focal nodular hyperplasia[a], Gastric dysplasia, Gastrointestinal dysplasia, Hepatic dysplasia, Laryngeal dysplasia, Leukoplakia, Myeloid metaplasia[a], Nodular regenerative hyperplasia, Oesophageal dysplasia, Olfacto genital dysplasia, Palatal dysplasia, Penile dysplasia, Placental dysplasia, Precancerous skin lesion, Prostatic intraepithelial neoplasia, Queyrat erythroplasia[a], Tongue dysplasia, Vaginal dysplasia, Vulvar dysplasia.

[a]Terms derived from the neoplasms SOC.

7.6.5 Overall Adverse Events

AEs are summarized by intensity (All Grades; All Grades related; Grade 2 - 4 related; Grade 3 - 4) and treatment regimen for the following 3 cohorts:

- Through Week 48 on blinded therapy for treated subjects
- After Week 48 on blinded therapy or on open-label ETV through Week 96 for the Year 2 Safety Cohort
- On ETV treatment for the All ETV Safety Cohort

If relationship to study therapy is missing, the AE is included in summaries of AEs related to study therapy.

AEs are also summarized by intensity (All Grades) and treatment regimen during (1) off-treatment follow-up for off-treatment follow-up subjects in the Post-Year 1 Safety Cohort, (2) alternative ETV follow-up for alternative ETV follow-up subjects in the Post-Year 1 Safety Cohort, and (3) long-term follow-up for long-term follow-up subjects in the Post-Year 1 Safety Cohort.

On-treatment non-serious AEs (All Grades) occurring with incidence ≥ 5% on any treatment regimen are also summarized analogously for the 3 cohorts. Multiple on-treatment non-SAEs (All Grades) occurring with incidence ≥ 5% on any treatment regimen are also summarized for the 3 cohorts, presenting the numbers of events and exposure-adjusted incidence rates (see Section 8.10).

Multiple on-treatment AEs (All Grades) occurring with incidence ≥ 5% on any treatment regimen are also summarized for the 3 cohorts, presenting the numbers of events and exposure-adjusted incidence rates (see Section 8.10).

7.6.6 Clinical Laboratory Evaluations

Summaries are based on subjects with at least 1 laboratory measurement during the study period.

7.6.6.1 Laboratory Abnormalities

For each laboratory test, laboratory abnormalities by toxicity grade (Grade 1 - 4; Grade 3 - 4) on treatment are summarized by treatment regimen and baseline status (all, normal, abnormal, not reported) for the following 3 cohorts:

- Through Week 48 on blinded therapy for treated subjects
- After Week 48 on blinded therapy or on open-label ETV through Week 96 for the Year 2 Safety Cohort
- On ETV treatment for All ETV Safety Cohort

Laboratory tests include:

- Hematology: hemoglobin, platelets, international normalized ratio (INR), white blood cell count (WBC) and neutrophils + bands (absolute)
- Liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and albumin
- Pancreatic enzymes: lipase (colorimetric or turbidimetric assay)
- Renal function tests: creatinine and BUN/urea (BUN or urea)
- Electrolytes (low and high): chloride, potassium and sodium.

Toxicity grades are based on DAIDS, unless specified otherwise (see Protocol Appendix 2). BUN/urea and chloride are graded with modified WHO criteria.

Treatment emergent laboratory abnormalities by toxicity grade (increased to Grades 1, 2, 3 and 4) are also summarized analogously by treatment regimen and baseline status for the 3 cohorts. On-treatment emergent abnormalities are those with a higher toxicity grade than the baseline toxicity grade (including not reported baseline).

In addition, the following select laboratory elevations and abnormalities on treatment are summarized by treatment regimen for the 3 cohorts:

- Any Grade 3 - 4 laboratory abnormality (see previous list of tests)
- Liver function elevations > 2 and > 3 x baseline (ALT, AST, total bilirubin)
- Liver function elevations > 2 x baseline and Grade 4 (ALT, AST and total bilirubin; includes ALT flares, defined as ALT > 2 x baseline and > 10 x ULN)
- Simultaneous ALT and total bilirubin elevations (ALT > 2 x baseline, total bilirubin > 2 x baseline and > 2 x ULN; ie, those occurring on the same collection day).

- Albumin < 2.5 g/dL
- Lipase elevations > 3 x baseline
- Confirmed creatinine elevations ≥ 0.3 and ≥ 0.5 mg/mL from baseline (2 sequential measurement or last measurement meeting the elevation criteria)
- Glucose categories (< 50, ≥ 200 mg/dL) regardless of fasting status.

For PBO-treated subjects who receive open-label ETV, baseline is used during blinded dosing, while ETV baseline is used during open-label ETV dosing.

Laboratory abnormalities by toxicity grade (Grade 1 - 4; Grade 3 - 4) are also summarized by treatment regimen and EOD status (all, normal, abnormal) for the first 2 follow-up cohorts: (1) off-treatment follow-up for off-treatment follow-up subjects in the Post-Year 1 Safety Cohort; (2) long-term follow-up for long-term follow-up subjects in the Post-Year 1 Safety Cohort.

Laboratory abnormalities by toxicity grade (Grade 1 - 4; Grade 3 - 4) are also summarized by treatment regimen during alternative ETV follow-up for alternative ETV follow-up subjects in the Post-Year 1 Safety Cohort.

Emergent laboratory abnormalities by toxicity grade (increased to Grades 1, 2, 3 and 4) are also summarized analogously by treatment regimen and EOD status for the first 2 follow-up cohorts. Emergent abnormalities are those with a higher toxicity grade than the EOD toxicity grade.

Select laboratory elevations and abnormalities are summarized relative to the EOD value for the 3 follow-up cohorts. In addition, elevations of liver function tests (including ALT flares, defined as ALT > 2 x reference and > 10 x ULN) during the follow-up periods are summarized using the reference value (REF) (ie, minimum of the baseline and EOD values) for the 3 follow-up cohorts. Note that for PBO-treated subjects who receive open-label ETV, reference is the minimum of the ETV baseline and EOD values.

ALT multiples of ULN and HBV DNA values are plotted over time for each subject who had an ALT flare on study. The duration of an ALT flare is measured from the first ALT measurement meeting the ALT flare criteria to resolution, defined as (1) the first ALT ≤ baseline or ≤ 5 x ULN on treatment, or (2) the first ALT ≤ reference or ≤ 5 x ULN during follow-up. If (1) and (2) are not met, an ALT flare is considered unresolved, and the last ALT measurement is used to estimate duration.

The time to and duration of ALT flares (weeks) during off-treatment follow-up are summarized for off-treatment follow-up subjects in the Post-Year 1 Safety Cohort (limited to ETV, PBO OL, and All ETV). Analyses are based on the first ALT flare during off-treatment follow-up.

The laboratory value during the study period with the highest toxicity grade is reported for each test. Grade 1 abnormalities are reset to normal if the original (unconverted) values are between the lower and upper limits of normal.

7.6.6.2 Laboratory Tests over Time

Laboratory test values are summarized by treatment regimen at baseline and each scheduled visit (see Section 8.4) for the following cohorts:

- On treatment through Week 48 for treated subjects
- On treatment through Week 96 for the Year 2 Safety Cohort
- On ETV treatment for the All ETV Safety Cohort

Values are also summarized by treatment regimen at EOD and each scheduled visit during (1) off-treatment follow-up for off-treatment follow-up subjects in the Post-Year 1 Safety Cohort, and (2) long-term follow-up for long-term follow-up subjects in the Post-Year 1 Safety Cohort.

Laboratory tests include:

- Hemoglobin
- Platelets
- INR
- WBC
- ALT
- Total bilirubin
- Albumin
- Lipase (colorimetric assay only)
- Creatinine

7.6.7 Growth/Development Assessment

Growth assessment values and changes from baseline are summarized by treatment regimen at baseline and each scheduled visit (see Section 8.4) for the following cohorts:

- For treated subjects across the on-treatment and long-term follow-up periods combined
- For the Year 2 Safety Cohort across the on-treatment and long-term follow-up periods combined
- For the All ETV Safety Cohort across the ETV treatment and long-term follow-up periods combined

Growth assessment parameters include HAZ, HAP, WAZ, WAP, BMIAZ, and BMIAP. These parameters are derived using 2000 CDC growth charts.[7]

Longitudinal plots display mean growth changes from baseline in growth assessment (HAZ, HAP, WAZ, WAP, BMIAZ, BMIAP) versus visit week by treatment regimen with error bars representing ± 1 SE of the reported statistic for treated subjects across the on-treatment and long term follow-up periods combined.

Tanner stage is a development assessment parameter that is summarized analogously by age randomization strata for each staging category (pubic hair, breast/genitals) and treatment regimen (see Section 7.6.8). Stages I - V are assessed as integers 1 - 5, respectively.

7.6.8 Results by Subgroups

The following key safety endpoints are summarized by subgroups of age randomization strata, geographic region, HBV genotype and route of transmission (see Section 7.5.1) on blinded therapy through Week 48 for treated subjects, unless specified otherwise:

- SAEs
- AEs leading to discontinuation of study therapy
- Events of HBV disease progression (on-treatment and long-term follow-up periods combined)
- AEs by intensity (All Grades; Grade 2 - 4 related; Grade 3 - 4)
- Laboratory abnormalities by toxicity grade (Grade 1 - 4; Grade 3 - 4)
- Select laboratory elevations and abnormalities
- Growth/development assessment values and changes from baseline over time (on-treatment and long-term follow-up periods combined). Tanner stage is assessed only by age randomization strata for each staging category (see Section 7.6.7).

AEs are presented by system organ class and preferred term alphabetically.

7.7 Pharmacokinetic (PK) Analysis

Individual subject ETV plasma concentrations are listed and plotted versus time. Mean plasma concentration vs. time profiles in original scale as well as in log scale are provided to compare pediatric subjects by age randomization strata.

Individual subject pharmacokinetic parameter values are derived by noncompartmental methods by a validated pharmacokinetic program. Concentration data are only considered valid if complete information is available on sampling time and dosing time. Additionally, pre-dose samples for semi-intensive PK are only be considered valid if they are collected prior to the dose on the day of semi-intensive PK sampling and if sampling time and dosing time information are complete. To assess the exposure of ETV in pediatric patients, summary statistics are provided for all of the pharmacokinetic parameters of ETV by age randomization strata and treatment regimen. Geometric means and coefficients of variation as well as medians, minima, and maxima are reported for Cmax, Cmin. Medians, minima, and maxima are reported for Tmax.

8 CONVENTIONS

8.1 Missing, Unknown or Partial Dates

Rho will provide conventions for imputing values for missing or partial dates for non-study medication start and stop dates and for AE onset dates.

8.2 Unknown Study Medication End Dates

End dates of dosing that are left as 'UNKNOWN' or partial because a subject is lost to follow-up or the subject couldn't remember the exact dosing end date are assumed to be equal to the last

recorded dose start date, thus crediting the subject with 1 day of dosing. All missing dates are queried.

8.3 Partial or Missing Safety Information

A missing AE intensity is not imputed. AEs with missing intensity are included in the AE tables for All Grades. AEs with missing relationship are included in tables of "related" AEs.

8.4 Visit Week Windows

For longitudinal presentations, values are first selected within their respective study periods (see Section 6.1). Next, windows around scheduled measurement times are constructed based on the midpoint between scheduled measurement visits and the value closest to the scheduled visit for each measurement is selected from those that fall within the window.

Visit windows are defined in Table 8.4-1:

Table 8.4-1: Visit Week Windows

Week	On Treatment or ETV Treatment (Combined with or without Long-Term Follow-up)	Off-Treatment or Long-Term Follow-up	On Treatment/ETV treatment and Long-Term Follow-up Combined (Tanner Stage only)
0*	Day ≤ 1	Day ≤ Last dose + 5	Day ≤ 1
4	> 2 - 6 wks#	--	--
6	--	≤ 9 wks	--
8	> 6 - 10 wks#	--	--
12	> 10 - 18 wks	> 9 - 18 wks	--
24	> 18 - 30 wks	> 18 - 30 wks	> 12 - 36 wks
36	> 30 - 42 wks	> 30 - 42 wks	--
48	> 42 - 54 wks	> 42 - 54 wks	> 36 - 60 wks
60	> 54 - 66 wks	> 54 - 66 wks	--
72	> 66 - 78 wks	> 66 - 78 wks	> 60 - 84 wks
84	> 78 - 90 wks	> 78 - 90 wks	--
96	> 90 - 102 wks	> 90 - 102 wks	> 84 - 108 wks
108	> 102 - 114 wks	> 102 - 114 wks	--
120	> 114- 126 wks	> 114- 126 wks	> 108 - 132 wks
132	> 126 - 138 wks	> 126 - 138 wks	--
144	> 138 - 150 wks	> 138 - 150 wks	> 132 - 156 wks
156	> 150 - 162 wks	> 150 - 162 wks	--
168	> 162 - 174 wks	> 162 - 174 wks	> 156 - 180 wks
180	> 174 - 186 wks	> 174 - 186 wks	--

Table 8.4-1: Visit Week Windows

Week	On Treatment or ETV Treatment (Combined with or without Long-Term Follow-up)	Off-Treatment or Long-Term Follow-up	On Treatment/ETV treatment and Long-Term Follow-up Combined (Tanner Stage only)
192	> 186 - 198 wks	> 186 - 198 wks	> 180 - 204 wks
204	> 198 - 210 wks	> 198 - 210 wks	--
216	> 210 - 222 wks	> 210 - 222 wks	> 204 - 228 wks
228	> 222 - 234 wks	> 222 - 234 wks	
240	> 234 wks	> 234 wks	> 228 wks

* "Week 0" is formatted according to treatment period: "Baseline" for the on-treatment period; "ETV Baseline" for the ETV treatment period; "EOD" for the off-treatment and long-term follow-up periods.
# On treatment (combined with or without long-term follow-up) only.

Additional visit windows after Week 240 are defined analogously as needed.

For the on-treatment period, weeks are calculated as (measurement date - first dose date of study therapy + 1)/7. This also applies to the on-treatment and long-term follow-up periods combined.

For the ETV treatment period, weeks are calculated as (measurement date - first dose date of active ETV + 1)/7. This also applies to the ETV treatment and long-term follow-up periods combined.

For the off-treatment and long-term follow-up periods, weeks are calculated as (measurement date - last dose date of study therapy)/7.

8.5 Baseline and EOD Measurements

Baseline values are the last non-missing assessments taken prior and up to the first dose of study therapy, or the enrollment date for subject never receiving study therapy, unless specified otherwise.

HBV genotype is derived as the first non-missing assessment regardless of study period. Missing values include those that are labeled "ND" or "UAS". Indeterminate values are not considered missing.

End of dosing (EOD) values are the last non-missing assessments taken after the first dose of study therapy and up to the last dose of study therapy plus 5 days.

For analyses of ETV treatment for the All ETV Efficacy and Safety Cohorts, the baseline values are the last non-missing assessments taken prior and up to the first dose of active ETV (i.e., "ETV baseline"). For these cohorts, the following parameters are derived only at baseline and

not re-derived at ETV baseline: gender, race, ethnicity, geographic region, country, HBV genotype.

Subjects are excluded from any changes from baseline (or EOD) analysis for which they have a missing baseline (or EOD) value.

8.6 HBV DNA Below LOQ or LLD

HBV DNA < LOQ is identified by the specify field "DETECTED BUT BELOW LOQ" or NOT DETECTED".

HBV DNA < LLD is identified by the specify field "NOT DETECTED".

In analyses of HBV DNA as a continuous variable, HBV DNA < LOQ or LLD is assigned a value 1 IU less than the LOQ i.e., 28 IU/mL.

8.7 Multiple Measurements

If more than one specific test result is reported in a given visit window, the result closest to the scheduled visit week is used in the analysis (as determined by the absolute difference in days between the planned visit and the measurement date). In addition:

- For HBV DNA by PCR from multiple HBV DNA samples collected on the same date, the one assayed at an earlier date is reported in the analysis.
- For multiple ALT, HBeAg and HBeAb values obtained from the same collection date, the 'worst case' is selected in the efficacy analyses (i.e., "POSITIVE" for HBeAg and "NEGATIVE" for HBeAb for subjects who were HBeAg-positive at baseline, and the highest ALT value after start of dosing).
- For growth parameters based on height and weight, the 'worst case' is selected in the safety analyses: if values are of equal distance or there are multiple values on same date, then select the pair (height, weight) with smallest percentile across all measurements.

8.8 Indeterminate Serology Results

Serum HBeAg, HBeAb, HBsAg and HBsAb values of "INDETERMINAT", "BORDERLINE" and "EQUIVOCAL" are considered indeterminate.

For efficacy analyses in Section 7.5, indeterminate values are imputed to be "worst case", i.e., "POSITIVE" for HBeAg and "NEGATIVE" for HBeAb.

8.9 Derived Dates

Derived dates that are used commonly in analyses are defined as follows. Derivations of dose dates exclude rescue open-label ETV.

- First dose date of study therapy is the earliest start date of drug (ie, blinded therapy [ETV active or PBO] or open-label ETV) identified from valid dosing records, ie, non-missing start date and number of units per day > 0, from blinded therapy study medication CRFs. This date is used to identify treated subjects and to distinguish measurements across study periods. Note that this is also first dose date of blinded study therapy.

- Dose end date of study therapy is the latest start or end dates of drug (ie, blinded therapy [ETV active or PBO] or open-label ETV) identified from valid dosing records, ie, non-missing start or end date and number of units per day > 0 or total dose > 0. This date is is used to asses time on study therapy.
- Last dose date of study therapy is the dose end date of study therapy derived only for subjects with an end of treatment subject status CRF indicating whether the subject completed the treatment period. This date is used to exclude data in antiviral activity and safety analyses, and to distinguish measurements across study periods.
- Dose end date of blinded therapy is the latest start or end date of blinded therapy (ETV active or PBO) identified from valid dosing records, ie, non-missing start or end date and number of units per day > 0, from blinded therapy study medication CRFs. This date is used to assess time on blinded study therapy.
- First dose date of open-label ETV is the earliest start date of open-label ETV identified from valid dosing records, ie, non-missing start date and total dose > 0, from open-label study medication CRFs. This date is used to distinguish measurements across blinded vs open-label treatment, and to assess time on open-label therapy.
- Dose end date of open-label ETV is the latest start or end date of open-label ETV identified from valid dosing records, ie, non-missing start or end date and total dose > 0, from open-label study medication CRFs. This date is used to assess time on open-label therapy.
- First dose date of active ETV is the first dose date of study therapy for ETV-randomized subjects, and the first dose date of open-label ETV for PBO-randomized subjects. This date is used to identify all ETV-treated subjects and to distinguish measurements across study periods.
- Dose end date of active ETV is the dose end date of study therapy for ETV-randomized subjects and the dose end date of open-label ETV for PBO-randomized subjects. This date is used to assess time on active ETV.
- Last dose date of active ETV is the dose end date of active ETV derived only when the last dose date of study therapy is not missing.
- Start date of rescue open-label ETV is the earliest start date of rescue open-label ETV identified from valid dosing records, ie, non-missing start date and total dose > 0, from rescue open-label ETV study medication CRFs.
- Start date of alternative ETV therapy is the earliest start date of (1) rescue open-label ETV, or (2) concomitant ETV taken on treatment or during long-term follow-up.
- Start date of alternative anti-HBV therapy is the earliest start date of (1) rescue open-label ETV, or (2) concomitant anti-HBV medication taken on treatment or during long-term follow-up.
- Last contact date is the death date, if it exists, or the latest of the following dates: randomization; first or last dose of study therapy; adverse event onset or resolution; hepatitis B related diagnosis; laboratory test (safety, pregnancy, serology and virology); liver biopsy; physical measurement; physical exam; neurologic exam; vital sign; non-study medication start or stop; last contact from end of treatment or end of study subject status; Tanner staging.

8.10 Collapsed AEs and Exposure-Adjusted Incidence Rates

In order to account for AEs with multiple occurrences in the same subject, AE records are collapsed for each subject and preferred term when:

- Records have the same onset date.
- The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
- The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

The collapsed record contains the earliest onset date (and time, if collected); latest resolution date (and time, if collected); highest intensity in the following order (highest to lowest: very severe, severe, moderate, or mild); AE type of SAE, if ever reported as a SAE, AE otherwise; latest causality, as determined by the last modification time stamp (highest causality in the following order [highest to lowest: related, not related], if records contain the same last modification time stamp with different causalities); treatment required of yes, if ever required; highest action taken in the following order (highest to lowest: drug discontinued, drug interrupted, dose reduced, dose increased, none); latest reported term, as determined by the last modification timestamp.

Incidence rates per 100 person-years of exposure (IR/100 P-Y) are defined as event count * 100 / person-years of exposure (see Section 7.6.5). Exposure is defined as time on study therapy (see Section 7.4.1), plus 5 days for subjects who discontinued study therapy to account for on-treatment safety reporting.

8.11 Laboratory Test Conversion

ICON changed its chemistry testing platform from the Roche Diagnostics Hitachi Modular system to the Abbott Architect system. Thus, values from the Abbott system are converted to the Roche system for comparability.

Based on regression analyses, laboratory tests which fail to show statistical equivalence between the Roche and the Abbott systems are converted as follows: $x = (y - c)/m$, where x is the Roche value, y is Abbott value, and m and c are respectively the slope and intercept of the regression line (see table below).

Records from the Abbott system are identified with laboratory names containing “ARCHITEC”. Values are converted before applying toxicity grades.

ICON Laboratory Services Dublin Method Comparison, Version 4, 15-Apr-2015							
Method X:	Roche Hitachi Modular SN. 1234-8						
Method Y:	Abbott Architect c1600881		Approved by: R. Shukla		Date:24APR2016		
Analyte	Slope	Intercept	R Value	X-Method (Modular) Results Range	Y-Method (Architect) Results Range	Units	Statistically Equivalent
Albumin	0.870 (0.786 to 0.954)	1.9 (-1.9 to 5.8)	0.9494	38 to 53	35 to 47	g/L	N
Alkaline Phosphatase	1.011 (0.973 to 1.049)	0.2 (-2.6 to 2.9)	0.9923	40 to 121	36 to 118	U/L	Y
ALT	1.113 (1.023 to 1.203)	-1.1 (-2.7 to 0.5)	0.9655	7 to 41	6 to 45	U/L	N
AST	0.986 (0.931 to 1.041)	-1.1 (-2.3 to 0.2)	0.9822	10 to 57	9 to 57	U/L	Y
Bicarb	0.972 (0.750 to 1.193)	-0.4 (-5.2 to 4.4)	0.7074	17 to 26	16 to 24	mmol/L	N
BUN	0.982 (0.931 to 1.032)	-0.26 (-0.57 to 0.04)	0.9850	3.1 to 9.3	2.7 to 8.9	mmol/L	Y
Calcium	1.002 (0.925 to 1.079)	-0.079 (-0.266 to 0.109)	0.9612	1.57 to 3.20	1.57 to 3.18	mmol/L	Y
Cholesterol	1.081 (1.049 to 1.112)	-0.104 (-0.262 to 0.054)	0.9954	2.85 to 7.48	2.95 to 8.16	mmol/L	N
CK	1.027 (1.013 to 1.040)	-2.9 (-4.9 to -1.0)	0.9990	32 to 428	33 to 443	U/L	N
Chloride	0.949 (0.884 to 1.014)	7.0 (0.5 to 13.6)	0.9610	81 to 111	83 to 112	mmol/L	N
Creatinine (Enzymatic)	0.970 (0.932 to 1.009)	1.25 (-1.82 to 4.33)	0.9914	46.0 to 128.5	45.5 to 123.6	umol/L	Y
Direct Bilirubin	2.750 (2.007 to 3.493)	-2.28 (-3.92 to -0.65)	0.4805	0.0 to 3.0	1.1 to 5.7	umol/L	N
GGT	1.035 (1.018 to 1.052)	0.7 (0.0 to 1.3)	0.9985	6 to 126	7 to 133	U/L	N
Glucose	1.040 (1.006 to 1.074)	-0.176 (-0.465 to 0.113)	0.9943	3.20 to 14.05	3.35 to 14.19	mmol/L	N
HDL	0.824 (0.756 to 0.893)	0.161 (0.068 to 0.255)	0.9610	0.65 to 2.61	0.65 to 2.42	mmol/L	N
Potassium	0.981 (0.908 to 1.054)	-0.02 (-0.36 to 0.31)	0.9686	3.6 to 6.0	3.6 to 5.9	mmol/L	Y
LDH	0.985 (0.898 to 1.072)	-1.3 (-14.0 to 11.5)	0.9558	94 to 210	88 to 198	U/L	Y
LDL	0.953 (0.888 to 1.017)	-0.018 (-0.221 to 0.185)	0.9742	1.08 to 5.36	0.97 to 5.52	mmol/L	Y
Sodium	1.060 (0.991 to 1.129)	-11.6 (-21.5 to -1.8)	0.9652	124 to 164	120 to 161	mmol/L	N
Phosphate	0.987 (0.928 to 1.045)	0.030 (-0.037 to 0.097)	0.9800	0.57 to 1.54	0.58 to 1.59	mmol/L	Y
Total Bilirubin	1.194 (1.109 to 1.278)	0.21 (-0.45 to 0.86)	0.9716	0.0 to 15.0	2.0 to 18.9	umol/L	N
Total Protein	1.026 (0.968 to 1.083)	-6.1 (-10.3 to -1.9)	0.9689	49 to 90	46 to 90	g/L	N
Triglycerides	0.894 (0.859 to 0.929)	0.147 (0.080 to 0.214)	0.9911	0.45 to 3.97	0.61 to 3.78	mmol/L	N
Uric Acid	1.156 (1.076 to 1.237)	-0.51 (-0.90 to -0.13)	0.9726	1.3 to 7.0	1.7 to 7.8	mg/dL	N
Creatinine (Enzymatic) - Urine	0.903 (0.896 to 0.911)	-0.007 (-0.074 to 0.059)	0.9997	1.92 to 23.95	1.73 to 21.71	mmol/L	N
Glucose - Urine	1.033 (1.028 to 1.039)	-0.082 (-0.129 to -0.035)	0.9998	0.02 to 22.65	0.06 to 23.40	mmol/L	N
MicroAlbumin - Urine	1.100 (1.077 to 1.122)	1.3 (0.4 to 2.2)	0.9979	3 to 156	5 to 171	g/L	N

Tests are considered to be statistically equivalent if the following conditions are achieved:	
Slope:	1.00 (within 95% Confidence)
Intercept:	0.0 (within 95% Confidence)
R value:	≥ 0.95

Note: to calulate y, use the formula $y=mx+c$, where m = slope, and c = intercept
For the inverse, use the formula $(y-c)/m = x$

9 CONTENT OF REPORTS

The primary analysis is conducted when the Primary Cohort has been treated for 48 weeks (see Section 6.3). Longitudinal analyses present data on treatment through Week 48. Efficacy is focused on the Primary Cohort. Safety is focused on blinded therapy through Week 48 for treated subjects, as well as on all ETV therapy for the All ETV Safety Cohort. Follow-up safety is presented only if ≥ 10% of treated subjects have post-dosing follow-up data.

An additional analysis is performed when all subjects have reached Week 48. Longitudinal analyses present efficacy data on treatment through Week 48 for treated subjects, efficacy data on treatment through Week 96 for the Year 2 Primary Efficacy Cohort, safety data on treatment through Week 96 for the Year 2 Safety Cohort, and all available safety data on ETV treatment for the All ETV Safety Cohort. All safety analyses described in this plan are performed.

An additional unplanned analysis is performed when all subjects have reached Week 96. All analyses described in this plan are performed, except for pre-treatment analyses of study population and efficacy/safety analyses on blinded therapy through Week 48.

An additional analysis is performed when all subjects have completed study therapy. All analyses described in this plan are performed, except for pre-treatment analyses of study population, efficacy/safety analyses on blinded therapy through Week 48, and efficacy/safety analyses on treatment through Week 96.

The final analysis is performed when the last subject has completed long-term follow-up. At a minimum, safety analyses are reported for the off-treatment and long-term follow-up periods.

APPENDIX 1 RELEVANT PROTOCOL DEVIATIONS

The relevant protocol deviations that can be programmed from the database are identified below. The list may be updated as appropriate if, in the course of monitoring the study, additional protocol deviations are found and considered relevant. Non-study medications marked below with # are identified by a BMS physician prior to database lock from blinded listings.

Eligibility Deviations

Eligibility deviations (ie, protocol deviations of entry criteria) are listed below.

- Inclusion 2b: HBeAg negative or missing, or HBeAb positive or missing at screening
- Inclusion 2c: ALT < 1.5 x ULN or ≥ 10 × ULN or missing at screening
- Inclusion 2d: HBV DNA < 10^5 c/mL or missing at screening
- Inclusion 3a: Age < 2 or ≥ 18 years
- Exclusion 1d: Women with positive pregnancy test at screening
- Exclusion 2a: Positive test for HIV, HCV or HDV at screening.
  - HCV positive is defined as both HCV antibody positive and detectable HCV RNA.
  - HIV positive is defined as having a positive result for HIV-1 and HIV-2 screen and either HIV-1 confirmation or the HIV-2 confirmation immunoblot.
- Exclusion 4a: Hemoglobin < 10.0 g/dL or missing at screening
- Exclusion 4b: Platelets count < 70,000/mm^3 or missing at screening
- Exclusion 4c: Glomerular filtration rate < 50 mL/min/1.73 m^2 or missing at screening. This is estimated using Schwartz formula.
- Exclusion 4d: Total bilirubin > 2.5 mg/dL (> 42.75 μmol/L) or missing at screening
- Exclusion 4e: INR > 1.5 or missing at screening
- Exclusion 4f: Albumin < 3 g/dL (< 30 g/L) or missing at screening
- Exclusion 4 g: Alpha fetoprotein ≥ 50 ng/mL or missing at screening
- Exclusion 6a: Prior therapy ≥ 12 weeks with any anti-HBV nucleoside or nucleotide. This includes, but is not limited to adefovir, tenofovir, famciclovir, clevudine, lamivudine, telbivudine or emtricitabine (#)
- Exclusion 6b: Prior therapy with interferon alpha, thymosin alpha or any anti-HBV nucleos[t]ide antiviral agent within 24 weeks of screening (#)
- Exclusion 6c: Prior ETV

On-Treatment Protocol Deviations

Protocol deviations during the on-treatment period are as follows:

- Incorrect study therapy received: subjects randomized to active ETV who received PBO or the incorrect active dose; subjects randomized to PBO who received blinded active ETV. Subjects who received the incorrect study therapy during the entire treatment period are further identified.

- Blinded therapy received after not seroconverting at Week 48 (defined as receiving blinded therapy after 54 weeks and not seroconverting at Week 48 based on NC = M)
- Open-label ETV received after seroconverting at Week 48 without seroreversion (defined as receiving open-label ETV after 54 weeks, seroconverting at Week 48 based on NC = M, and seroreverting after Week 48 based on NC = M)
- Average daily dose < 80% of target dose
- Treatment continued after positive pregnancy test (defined as not discontinuing study therapy or discontinuing study therapy > 2 weeks after positive pregnancy test)
- Treatment continued after positive HIV test (defined as not discontinuing study therapy or discontinuing study therapy > 2 weeks after positive HIV test)
- Prohibited concomitant medications (#)

Protocol deviations related to semi-intensive PK data:

- At least one of the sampling time, dosing time or meal time is missing
- Sampling time ≥ 10% different from scheduled time
- Meal taken within 2 hours before or within 2 hours after the previous day's dose (inclusive)