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Clinical Protocol AI463189

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

Revised Protocol Number: 02
Incorporates Administrative Letters 1 and 2, and Amendment 05

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	04-Sep-2012	Incorporates Amendment 05.
Amendment 05	04-Sep-2012	Address the potential safety issues associated with extreme elevations of ALT (serum ALT > 1,000 U/L or > 20x ULN and clinical or laboratory findings suggestive of liver dysfunction) due to acute exacerbation of CHB by providing emergency access to open-label study ETV ("rescue open-label ETV") for subjects who cannot access acceptable alternative anti-HBV therapy. 1) Specify that rescue open-label ETV would be provided by the sponsor at the request of a primary investigator and approval of the Central Medical Monitor; 2) Specify that rescue therapy provided by the sponsor would be open-label ETV only, and would be provided for up to 96 consecutive weeks; 3) Specify that the management of extreme elevations of ALT are at the discretion of the primary investigator; 4) Clarify that non-serious adverse events should be documented for all LTFU subjects receiving rescue open-label ETV; 5) Change the duration of study to, "5 years, or until the last study subject treated with rescue open-label ETV for an extreme elevation of ALT completes 48-weeks of off-treatment follow-up; whichever is later"; 6) Specify that on-treatment efficacy endpoints are based on double-blind or open-label ETV therapy, and therefore exclude rescue open-label ETV: 7) Modify Figure 5.3.2.1 to provide guidance to investigators managing significant elevations of ALT due to acute exacerbation of CHB.
Administrative Letter 2	11-Jan-2012	Change in Central Medical Monitor.
Administrative Letter 1	02-May-2011	Open-label tablet bottles have a 2-panel label on them, rather than a 1-panel label.
Revised Protocol 01	23-Sep-2010	Incorporates Amendment 02.

Document	Date of Issue	Summary of Change
Amendment 02	23-Sep-2010	1) Augment the number of randomized subjects from 123 to 180 and increase the estimated number of participating study centers; 2) 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; 3) Specify the early unblinding and mechanism for doing so if subjects demonstrate significant worsening of HBV clinical symptoms or increases in ALT; 4) Specify additional analyses that will be conducted as key secondary and exploratory endpoints; 5) Modify the blood volume collected at some visits due to minimum fill volume requirements of available specimen collection tubes; 6) Summarize the plan for PK/PD analyses that will integrate Studies AI463028 and AI463189.
Original Protocol	26-Jan-2010	Not applicable.

SYNOPSIS

Clinical Protocol AI463189

Title of Study: Protocol AI463189: 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

Estimated Number of Study Centers and Countries/Regions: Approximately 50 centers in North America, South America, Asia, and Europe.

Study Phase: 3

Research Hypothesis: ETV will have superior antiviral activity compared to placebo in pediatric patients (2 to < 18 years of age) with HBeAg-positive chronic hepatitis B (CHB) who are naive to nucleoside and nucleotide antiviral agents.

Primary Objective: 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.

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. Chronic HBV-infected children and adolescents from 2 to < 18 years of age will be enrolled. Subjects will be randomized 2:1 to ETV or placebo for a maximum of 96 weeks, with the primary endpoint at Week 48. The randomization will be stratified by age group (2 to ≤ 6 yrs; > 6 to ≤ 12 yrs; > 12 to < 18 yrs). At Week 52 an assessment of HBeAg seroconversion (undetectable HBeAg and presence of anti-HBe antibodies) shall be performed based on Week 48 serology results; subjects achieving HBeAg seroconversion will continue blinded study treatment through Week 96, and 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; 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 concluding the blinded or open-label phase of the study, 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.

A subject who experiences an extreme elevation of ALT due to acute exacerbation of CHB may be eligible to receive rescue open-label ETV from the study's sponsor at the request of their principal investigator and after discussion and approval by the BMS Central Medical Monitor, for up to 96 consecutive weeks, in an effort to optimize patient safety. Rescue open-label ETV will be limited to those subjects who do not have access to acceptable alternative anti-HBV therapy. Upon completion of rescue open-label ETV, subjects will remain on study until they complete a total of 5 years of study participation from the start of blinded treatment or 48 weeks beyond the completion of rescue open-label ETV; whichever is later.

Duration of Study: 5 years, or until the last study subject treated with rescue open-label ETV for an extreme elevation of ALT due to acute exacerbation of CHB completes 48-weeks of off-treatment follow-up; whichever is later.

Number of Subjects per Group: Approximately 180 total [randomized 2:1 to ETV (120) and Placebo (60)]; the target enrollment will be 30 subjects for each age group, with a minimum requirement of 18 subjects.

Study Population: Male and female patients 2 to < 18 years of age with a history of chronic HBV infection (defined as HBsAg positive at the Screening visit and on at least one other occasion ≥ 24 weeks prior). All subjects must be nucleos[t]ide naive (< 12 weeks of prior therapy with any nucleos[t]ide antiviral agent with activity against hepatitis B virus and no anti-HBV treatment within 24 weeks of screening); have detectable HBeAg AND no detectable anti-HBe antibodies; have active viral replication and biochemical evidence of active hepatitis with compensated liver function.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): ETV dosing at 0.015 mg/kg/day up to a maximum dose of 0.5 mg/day using oral solution or tablets. During the treatment period, ETV dosing will be for a maximum of 144 weeks. Placebo (reference therapy) dosing with oral solution or tablets will be for a maximum of 96 weeks. A subject who experiences an extreme elevation of ALT due to acute exacerbation of CHB may be provided with rescue open-label ETV for up to 96 consecutive weeks at investigator's discretion and after discussion and approval by the BMS Central Medical Monitor. Rescue open-label ETV will be limited to those subjects who do not have access to acceptable alternative anti-HBV therapy.

Study Assessments and Primary Endpoints:

To test the study hypothesis, the primary endpoint of the analysis will be the proportion of subjects who achieve the composite of: 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.

Key Secondary Endpoints:

Proportion of subjects with HBV DNA < 50 IU/mL at Week 48; Proportion of subjects with HBV DNA < LOQ (29 IU/mL) at Week 48; Proportion of subjects with serum ALT ≤ 1 × ULN at Week 48; Proportion of subjects with HBe seroconversion at Week 48; and 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.

Other Secondary Endpoints:

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

Statistical Methods:

Sample Size determination:

One hundred and twenty-three (123) subjects (randomized 2:1 to ETV versus placebo) will provide 90% power to show superiority of ETV versus placebo 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 the placebo arm. A two-sided significance level of 0.05 will be used. Subjects who discontinue from study prior to Week 48 or have missing Week 48 measurement at Week 48 will be considered as failures at Week 48. This sample size will also fulfill the requirement that the ETV integrated pediatric safety database has at least 100 pediatric patients who have received ETV for at least 48 weeks; this database will be comprised of subjects currently enrolled in study AI463028 and from this study

(AI463189). The size of the overall study population has been augmented to 180 randomized subjects in order to meet the requirement of a Health Authority.

Methods:

The primary and key secondary analyses will be based on treated subjects (modified intention-to-treat [ITT]). For the analysis of the primary and key secondary endpoints at Week 48, subjects who discontinue from study prior to Week 48 or have missing Week 48 measurements will be considered failures at Week 48 (Non-completer = Failure). Sensitivity analyses will be performed in order to account for possible effects of early discontinuation, in which subjects who discontinue from study prior to Week 48 or have missing Week 48 measurements are excluded (Non completer = Missing). Treatment comparisons for the primary endpoint and key secondary endpoints will be stratified by age group using Cochran-Mantel-Haenszel (CMH) weights and NC=F. The difference in proportions (ETV - placebo), p-value, and 95% Confidence Interval (CI) will be presented. ETV will be considered superior to placebo if the p-value is < 0.05. The CI for the differences in proportions will be based on the normal approximation to the binomial distribution. On-treatment efficacy endpoints are assessed based on double-blind or open-label ETV therapy, and therefore exclude rescue open-label ETV during long-term follow-up.

Serious adverse events and deaths will be reported for enrolled subjects. Other safety analyses will be based on treated subjects. Discontinuations due to adverse events will be summarized. Adverse events will be reported by severity and relationship to study medication. Laboratory abnormalities will be summarized.

Pharmacokinetic samples will be collected at specified times to further evaluate and characterize the pharmacokinetics of ETV in pediatric subjects. The PK data collected in the study will be combined with the PK data collected in the pediatric study AI463028 to help develop a population pharmacokinetic/pharmacodynamic model in pediatric nucleos[t]ide naive subjects.

There will be an external data monitoring committee (DMC) for this study.

TABLE OF CONTENTS

Extreme elevations of ALT associated with severe acute exacerbations of CHB may represent a critical scenario with the potential for serious hepatic injury and even death.[28,29,30,31] Prior studies among adults have demonstrated significant benefit to the rapid introduction of nucleos(t)ide analogue therapy in such circumstances. [32,33]

1.4.1 Dose Selection / Pharmacokinetics

The dose selection for this study is based on PK data from Study AI463028.[34] AI463028 demonstrated that the dose of 0.015mg/kg resulted in adequate exposures of ETV in the three different age groups of nucleoside naive subjects tested (2 yrs to ≤ 6 yrs; > 6 yrs to ≤ 12 yrs; > 12 yrs to ≤ 18 yrs). The ETV exposures across all the age groups were comparable to historical PK data obtained at the dose of 0.5 mg daily in nucleoside naive adults enrolled in study AI463017; [35] a Phase 2 population pharmacokinetic/ pharmacodynamic (PK/PD) assessment in adults with chronic HBV infection.

The primary objective of Study AI463028 was to determine the doses of ETV in children and adolescents that produced drug exposures comparable to those observed in adults given the 0.5 mg and 1.0 mg doses in nucleoside naive (LVD-naive) and LVD refractory subjects respectively. For LVD-naive subjects, a dose of 0.015 mg/kg was selected by scaling the adult dose to the dose in children on the basis of body surface area. For LVD-naive subjects, an adult 0.5 mg dose scaled to approximately 0.29 mg/m^2 which extrapolated to 0.013 mg/kg in a young child of normal height and weight, therefore, a dose of 0.015 mg/kg was selected for testing in LVD-naive subjects. The target exposure selected for the study was based on achieving a geometric mean steady-state plasma AUC similar to the median AUC that was observed in the Phase 2 population pharmacokinetic/pharmacodynamic (PK/PD) assessment (Study AI463017). That analysis resulted in a median plasma AUC of 18.7 ng·h/mL for adult subjects receiving a 0.5 mg dose. The targeted median exposure for the pediatric population was anticipated to be between 13.1 and 24.3 ng·h/mL, well within the AUC range where efficacy was demonstrated in the adult Phase 2 trials. Furthermore, the PK/PD analysis demonstrated that AUC was predictive of efficacy, and an AUC of 2.22 ng·h/mL resulted in 90% of the maximal antiviral effect in the adult Phase 2 clinical trials, indicating that the targeted exposure in Study AI463028 should provide an efficacious exposure for the pediatric

1.5 Overall Risk/Benefit Assessment

The overall clinical safety profile of ETV is benign and comparable to that for LVD. The safety experience from Phase 3 clinical trials in adults reflects 1 to 2 years of ETV treatment in a broad range of patients with chronic HBV infection. This experience includes nucleoside-naïve and LVD-refractory patients, and those with HBeAg-positive as well as HBeAg-negative disease. The most common adverse events that may have been related to treatment with ETV were headache, fatigue, dizziness, nausea, increased liver enzymes, increased pancreas enzymes, upper abdominal pain and dyspepsia. Other common adverse events were diarrhea, vomiting, insomnia as well as sleepiness. These events were generally of mild to moderate severity and they occurred at similar rates for ETV as for LVD. Like all other available treatments for chronic HBV, exacerbations of hepatitis have been observed both during treatment with ETV and during post-treatment follow-up observation.[37,38] The long-term studies with extended dosing through 5 years, and the post-marketing experience with ETV both remain consistent with this overall profile.

Given its favorable clinical safety profile, the risk assessment for ETV is primarily concerned with specific findings from the pre-clinical evaluation. In rodent carcinogenicity studies using lifetime dosing, ETV was associated with statistically increased rates of tumors for both mice and rats with 2 distinct patterns observed. First, a specific pattern of lung tumor development was observed only in mice and at low exposure multiples (ranging between 4 and 5 times the exposure in humans at 0.5 mg daily, or between 2 and 3 times the exposure in humans at the 1.0 mg dose, depending on whether the multiples are calculated in relation to patients or healthy subjects respectively). Second, multiple tumor types occurred in both mice and rats, but only after lifetime exposure at high exposure multiples.[37,38] The results of investigative studies suggest that lung tumors observed in mice at low exposure multiples result from unique effects of ETV on the mouse lung; whereas tumors in rodents occurring only at high doses/exposures may result from biochemical actions that are likely to demonstrate a biological threshold (eg, are not expected to occur below a threshold dose). Observed malignancy rates for ETV- and LVD-treated patients from the ETV development program (1755 ETV patients observed for a mean of 77.6 weeks, including a mean treatment duration of 60.4 weeks; 1160 LVD patients observed for a mean of 71.6 weeks,

including a mean treatment duration of 59.5 weeks) are comparable across the 2 treatment groups and these rates fall within the expected range for malignancies based on epidemiologic studies in populations with chronic HBV infection.[39]

Additional analysis of malignancy rates for subjects enrolled in three ETV rollover studies (AI463049, AI463050, and AI463901) is conducted annually; the observation time for this analysis is restricted to time spent in the rollover studies. Subjects in the rollover studies may have been treated with LVD or ADV in prior protocols before entering the rollover studies (AI463049, -050, and -901) or with any commercially available anti-HBV therapy during the rollover study (AI463049); thus a comparison of malignancy rates by treatment arm is not possible. In the most current report of the analysis of malignancy rates from the rollover studies, a total of 1955 subjects (prior ETV n = 1193; prior LVD/ADV n = 762) were observed over 7053.5 person years of observation (prior ETV group = 4034.9; Prior LVD/ADV group = 3018.6). The results were within the expected rates for malignancies based upon epidemiological studies in the reference populations of chronic HBV infected persons.[40]

Thus there is no early safety signal for an increased rate of cancers as a result of treatment with ETV. Nevertheless, the number of ETV-treated patients and the duration of follow-up in the development program to date remain limited, and therefore the long-term risk of malignancy remains unknown. Exposure to other nucleoside/nucleotide analogues (including some for which animal carcinogenicity studies were positive) has not been associated with an increased incidence of tumors in humans. The data that address this issue are limited and derive primarily from long-term follow up studies of neonatal zidovudine exposure.[41,42]

Although HIV/HBV co-infected subjects are excluded from enrolling in this study, there is a potential risk that subjects enrolled may acquire new HIV infection during the course of the study. From subsequent observations during post marketing clinical experience, ETV use for HBV therapy in HIV/HBV co-infected persons who were not concurrently receiving anti-retroviral therapy has been documented to select for the M184V reverse transcriptase substitution, which confers resistance to anti-retroviral drugs such as LVD and emtricitabine (FTC). ETV is therefore not recommended for use in HIV/HBV co-infected persons who are not concurrently receiving effective anti-retroviral therapy.

Any subject who develops new HIV infection during participation in the study is therefore at risk for the development of HIV nucleoside/nucleotide resistance if they are not concurrently receiving effective anti-retroviral therapy while on ETV. This potential risk to patients is minimized by the fact that the protocol excludes HIV infected persons from enrollment and HIV serologies will be tested every 48 weeks while on study treatment. Additionally, the protocol strongly recommends that investigators consider HIV serologies for any subject in the observational long-term follow-up phase of the study that they decide to maintain on any anti-HBV therapy.

The clinical benefit of ETV derives from its potent activity against HBV. In the worldwide ETV development program, ETV was consistently superior to LVD across specific virologic, histologic, and biochemical endpoints. ETV was comparable to LVD for serologic endpoints. In addition, the resistance profile of ETV is favorable and is of particular note for nucleoside-naive patients among whom the cumulative probability of genotypic ETV-resistance remains low at 1.2% through 5 years of continuous ETV treatment. Small studies of adult patients with severe acute exacerbation of CHB have suggested that early initiation of nucleos(t)ide therapy, including ETV, is beneficial.[32,33] Taken together, these clinical benefits of ETV represent an important treatment advance for patients with chronic HBV infection. In weighing the overall risk/benefit, it must be noted that HBV is a human carcinogen and causes HCC;[43] chronic HBV infection is associated with a 30- to 148-fold higher relative risk for HCC compared with the background rate in uninfected individuals.[44] Among those with cirrhosis at baseline, antiviral therapy with LVD has now been shown to delay the progression to decompensated disease and to delay or prevent HCC,[45] a finding consistent with the known pathophysiology of this tumor. Thus, there is a rationale to predict that the superiority of ETV over LVD in well established 48-week efficacy endpoints may be associated with superior long-term benefit, potentially including long-term benefit with respect to HCC.

This study will have external oversight which will ensure the well-being of study participants. An external data monitoring committee (DMC) will provide review and input surrounding the benefit risk assessment throughout the duration of the study. The DMC shall act as an advisor to the sponsor and have responsibility for safeguarding the patients' 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.

In summary, chronic HBV infection carries with it the risk for serious morbidity and mortality related to the long-term risks for progression to cirrhosis and its complications, including HCC. Treatment of CHB with ETV results in demonstrable clinical benefit, which must be weighed against the potential risk posed by the rodent carcinogenicity data. The relevance of the animal carcinogenicity findings with respect to the long term risk of human malignancy is unknown. A full evaluation of the currently available data leads to a favorable benefit-risk assessment in which the proven benefit of ETV outweighs the unknown risk. Importantly, this assessment remains on-going and will be re-evaluated on a regular basis as further clinical data (including a large 10-year observational study) become available.

2 STUDY OBJECTIVES

This protocol is being developed at a time when reporting of HBV DNA has just concluded the transition from copies/mL to IU/mL. Though the use of HBV DNA categories based on IU/mL has now become a universal standard, it not inconceivable that some local labs may not have made the transition. In this protocol, the cutoff for the HBV DNA component of the primary endpoint is established as 50 IU/mL (291 copies/mL); however, the cutoff for the enrollment criteria is based on copies/mL and a conversion table for guiding the conversion between copies/mL and IU/mL can be found in Section 6.9.1.

2.1 Primary Objective

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.

2.2 Secondary Objectives

- 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.

3 ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor who is capable of forming an opinion and assessing this information to

refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

Appendix 1 contains BMS procedures on obtaining informed consent from subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative prior to participating in a clinical study. Procedures are described for all subjects, including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable (see subject selection criteria in Sections 4.2.1 and 4.2.2).

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

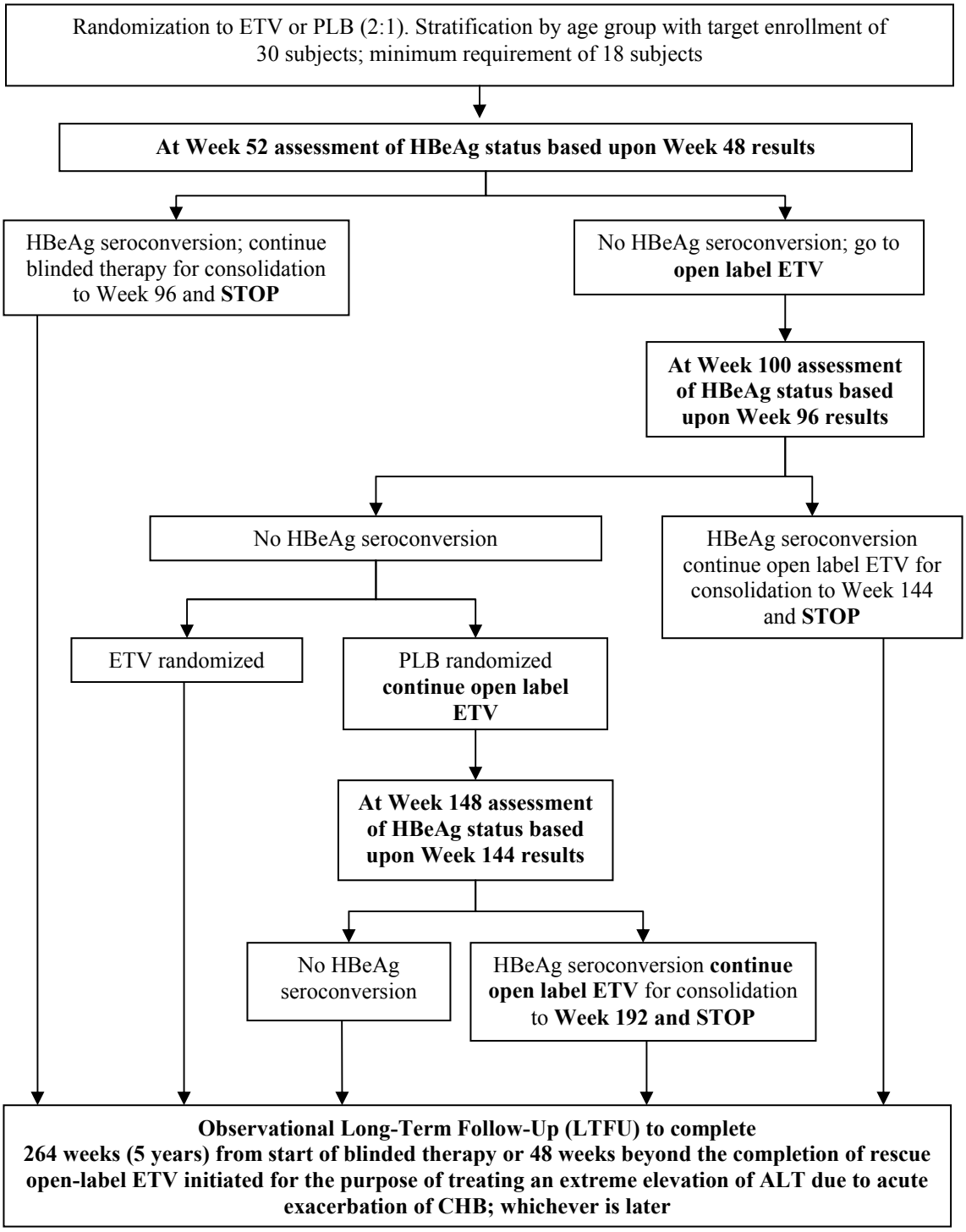
This is a comparative, randomized, double-blinded, placebo-control, multicenter study, assessing the efficacy and safety of oral ETV in pediatric subjects with chronic HBV infection who are HBeAg-positive and nucleos[t]ide naive (< 12 weeks of prior therapy with any nucleos[t]ide antiviral agent with 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 (PLB) for a maximum of 96 weeks of blinded therapy, with the analysis of the primary endpoint at Week 48 to be conducted for the first 123 treated subjects. The randomization will be stratified by age group (2 to ≤ 6 yrs; > 6 to ≤ 12 yrs; > 12 to < 18 yrs). 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. 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 (Figure 4.1).

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

A subject who experiences an extreme elevation of ALT due to acute exacerbation of CHB is eligible to receive rescue open-label ETV from the study's sponsor at the request of their principal investigator and after discussion and approval by the BMS Central Medical Monitor, for up to 96 consecutive weeks, in an effort to optimize patient safety. Rescue open-label study ETV will be limited to those subjects who do not have access to acceptable alternative anti-HBV therapy. Upon completion of rescue open-label ETV, subjects will remain on study until they complete a total of 5 years of study participation from the start of blinded treatment or 48 weeks beyond the completion of rescue open-label ETV; whichever is later.

Figure 4.1: AI463189 Study Schema



The total duration of the study will be 264 weeks (5 years) or 48 weeks beyond the completion of rescue open-label ETV initiated for the purpose of treating an extreme elevation of ALT due to acute exacerbation of CHB; whichever is later; the end of the study is defined as the date of the last follow-up visit for the last subject treated. 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 LTFU 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' or 48 weeks beyond the completion of rescue open-label ETV initiated for the purpose of treating an extreme elevation of ALT due to acute exacerbation of CHB; whichever is later.

4.1.1 Subject Management Decisions

Assessment of HBeAg seroconversion will be done, as needed, at Study Weeks:

- 52 (based upon Week 48 result);
- 100 (based upon Week 96 result); and
- 148 (based upon Week 144 result).

The investigators shall conduct the assessment of HBeAg response status at the assessment time points; this will be cross checked centrally by the BMS Medical Monitor/Protocol Manager. Subjects achieving HBeAg seroconversion shall initiate consolidation therapy for an additional 48 weeks as follows:

- At Week 52 (consolidation using blinded therapy to Week 96; 48 weeks counting from Week 48)
- At Week 100 (consolidation using open-label ETV to Week 144; 48 weeks counting from Week 96)
- At Week 148 (consolidation using open-label ETV to Week 192; 48 weeks counting from Week 144)

Subjects who achieve HBeAg seroconversion and revert back to HBeAg-positivity or develop HBeAg-negative CHB shall be managed as follows:

- Any subject who achieves HBeAg seroconversion by the Week 48 assessment and reverts to HBeAg-positive status before reaching Week 96 will be treated with open-label ETV until study Week 144, and then will stop study therapy and proceed to the LTFU phase;
- Any subject who achieves HBeAg seroconversion after the Week 48 assessment, who reverts back to HBeAg-positive status shall stop study treatment, if applicable, and be treated at the discretion of the investigator in consultation with the BMS Medical Monitor.
- Subjects who develop HBeAg-negative CHB (absence of HBeAg, presence of anti-HBe antibodies, active viral replication [HBV DNA by PCR assay ≥ 10,000 copies/mL] and biochemical or histological evidence of hepatitis) shall be managed at the discretion of the investigator in consultation with the BMS Medical Monitor.

Study treatment (ETV and placebo) shall be provided during the blinded and open-label study treatment phases. Rescue open-label ETV shall be provided to subjects who experience extreme elevations of ALT due to acute exacerbations of CHB upon investigator request and approval by the Central Medical Monitor (see section 4.1.2).

Anti-HBV treatment of study subjects during LTFU shall be at the discretion of the treating clinicians and may include marketed or investigational products. In the event that a subject in LTFU develops an extreme elevation of ALT due to acute exacerbation of CHB, rescue open-label study ETV will be made available upon investigator request and after discussion and approval by the BMS Central Medical Monitor (see section 4.1.2). If ETV is initiated during the LTFU phase, HIV testing and monitoring is strongly recommended as ETV is not recommended in subjects co-infected with HIV and HBV unless the subject is also receiving effective anti-retroviral therapy. For subjects initiated on other anti-HBV treatment during LTFU, investigators should evaluate the need for HIV testing based upon standard of care and the product label for the selected agent.

At the end of the on study treatment phase, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. The only exception is for subjects started on rescue open-label ETV as a consequence of an

extreme elevation of ALT due to acute exacerbation of CHB (see section 4.1.2). The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study, if necessary.

4.1.2 Subjects Experiencing Significant Elevations Of ALT Due To Acute Exacerbation of CHB

A subject who experiences an extreme elevation of ALT due to acute exacerbation of CHB should be carefully managed at the discretion of the primary investigator. Additional laboratory testing and frequent clinical evaluations are recommended (See Figure 5.3.2.1).

- An extreme elevation of ALT due to acute exacerbation of CHB is defined as:
  - a serum ALT > 1,000 U/L,

  OR
  - an elevation in serum ALT > 20x ULN WITH associated clinical or laboratory findings suggestive of hepatic dysfunction,
- Upon investigator request and after discussion and approval by the BMS Central Medical Monitor:
  - A subject who experiences an extreme elevation of ALT due to acute exacerbation of CHB will be provided access to rescue open-label ETV.

The choice of anti-HBV therapy to be used to treat an extreme elevation of ALT due to acute exacerbation of CHB remains at the discretion of the investigator. Only open-label ETV will be provided by the sponsor, and will be limited to those subjects who do not have access to acceptable alternative anti-HBV therapy. Subjects started on rescue open-label ETV will be provided the drug for up to 96 consecutive weeks. Upon completion of the rescue open-label ETV course, subjects will remain on study as part of the LTFU phase until they complete a total of 5 years of study participation from the start of blinded treatment or 48 weeks beyond the completion of rescue open-label ETV; whichever is later. During this time, subjects may be treated with alternative anti-HBV therapy at the discretion of their primary investigator. The sponsor reserves the right to terminate access to rescue open-label ETV if any of the following occur: a) the study is terminated due to safety concerns; b) the subject can obtain medication from a

government sponsored or private health program; or c) therapeutic alternatives become available in the local market.

Specific decisions regarding the management of an extreme elevation of ALT due to acute exacerbation of CHB remain at the discretion of the subject's primary investigator but access to rescue open-label ETV must be discussed with and approved by the BMS Central Medical Monitor.

4.2 Study Population

For entry into the study, the following criteria MUST be met.

4.2.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Freely given informed consent must be obtained prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial. Minor's parents or legally acceptable representatives must give fully informed written consent. Assent should be obtained when the minor is judged to be of an age of reason (see Appendix 1);

2) Target Population

a) History of CHB infection defined as HBsAg-positive at the Screening visit and on at least one other occasion ≥ 24 weeks prior to screening;

b) Detectable HBeAg AND no detectable anti-HBe antibodies at screening and at least once ≥ 4 weeks prior to screening;

c) Serum ALT 1.5 to < 10 x ULN at screening and at least on one other occasion within 8 to 24 weeks prior to screening;

d) HBV DNA by PCR ≥ 10^5 copies/mL at screening and evidence of the presence of HBV DNA at least once ≥ 4 weeks prior to screening;

3) Age and Sex

a) Male and females, 2 to <18 years of age.

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 6 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation,

or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause or
- For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening AND within 72 hours prior to the start of investigational product.

4.2.2 Exclusion Criteria

1) Sex and Reproductive Status

a) WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for up to 6 weeks after the last dose of investigational product;

b) WOCBP using a prohibited contraceptive method. At this time there are no known contraindicated contraceptives to entecavir;[4]

c) Women who are pregnant or breastfeeding;

d) Women with a positive pregnancy test on enrollment or prior to investigational product administration;

e) Sexually active fertile men not using effective birth control if their partners are WOCBP;

2) Target Disease Exceptions

a) Co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis D virus (HDV);

b) Other forms of acute and chronic conditions which may cause increased ALT as determined by the investigators (eg, acute viral illness, Wilson Disease, other metabolic disorders, autoimmune hepatitis, alcoholic liver disease);

c) Liver transplant recipients;

3) Medical History and Concurrent Diseases

a) Current evidence of, or history of variceal bleeding, hepatic encephalopathy, or ascites requiring diuretics or paracentesis or evidence of these on physical examination performed for this study;

b) Current evidence of, or history of pancreatitis;

c) Received bone marrow or organ transplant or therapy with an immunomodulatory, cytotoxic, or systemic corticosteroid therapies within 2 months of enrollment;

d) Evidence of current pre-malignant lesions and malignancies including HCC; (to be excluded by screening and evaluation practices standard in the country of enrollment);

e) Other serious medical conditions that might preclude completion of this study;

4) Physical and Laboratory Test Findings

a) Hemoglobin < 10.0 g/dL;

b) Platelet count < 70,000/mm^3;

c) Inadequate renal function with estimated glomerular filtration rate of < 50 mL/min/1.73m^2 (using the Schwartz formula; [k * Ht]/Cr)

d) Total serum bilirubin > 2.5 mg/dL (> 42.75 μmol/L);

e) INR > 1.5;

f) Serum albumin < 3.0 g/dL (< 30 g/L);

g) Alpha Fetoprotein ≥ 50 ng/mL;

5) Allergies and Adverse Drug Reactions

a) Known allergy to nucleoside analogues;

6) Prohibited Treatments and/or Therapies

a) ≥ 12 weeks of prior therapy with any nucleoside or nucleotide antiviral agent with activity against hepatitis B virus (including but not limited to adefovir, tenofovir, famciclovir, clevudine, lamivudine, telbivudine, or emtricitabine);

b) Therapy with interferon alpha, thymosin alpha or any nucleos[t]ide antiviral agent with activity against hepatitis B virus within 24 weeks of screening;

c) Any prior therapy with ETV;

d) Any use of illegal drugs OR use of alcoholic beverages which in the investigator's opinion is sufficient to prevent adequate compliance with study procedures or increase the risk pancreatitis or hepatotoxicty;

e) Concomitant medications which may cause immunosuppression, nephrotoxicity or hepatotoxicity or affect renal excretion or hepatic metabolism are not permitted;

f) Concomitant use of Traditional Chinese Medicines or other herbal products purported to have antiviral activity or intended for use in improving/protecting liver function;

g) During the treatment phase of the study, a subject may not be coenrolled in another clinical trial where an investigational drug is administered;

7) Other Exclusion Criteria

a) Unable to tolerate oral medication;

b) Children that are currently breastfeeding, or those who were breastfed while their mother received LVD; maternal LVD treatment during pregnancy;

c) Prisoners or subjects who are involuntarily incarcerated;

d) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

A liver biopsy prior to the start of study medication is optional. If a biopsy has been performed prior to randomization, then histological results will be collected; likewise, results from any subsequent on-study biopsies will be collected.

Subjects may be rescreened twice (for a total of three screens) if it can be reasonably expected that study criteria will be met. However, beyond this, subjects should be reevaluated only after consultation with the study team.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

4.2.3 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy (see Section 7.6.2)
- Termination of the study by Bristol-Myers Squibb (BMS)

- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Subjects who develop HIV infection after starting the study.

Study treatment should always be withdrawn in a manner that will maintain subject safety. Subjects who discontinue study treatment must be followed on study for observation, regardless of the reason for stopping study drug.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

4.3 Data Monitoring Committee

There will be a data monitoring committee (DMC) for this study. The DMC shall have access to partially unblinded data (coded treatment assignments) 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 have the right to request full unblinding of the data (codes will be decoded to reveal actual treatment assignments). The DMC shall act as an advisor to the sponsor and have responsibility for safeguarding the patients' 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 shall be developed for the DMC; this will describe the membership and activities of the DMC.

5 TREATMENTS

5.1 Study Treatment

All protocol-specified investigational and noninvestigational products are considered study drug.

5.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

In this protocol, investigational product(s) is/are: entecavir (BMS-200475) 0.5 mg tablets, matching placebo tablets, entecavir oral solution, and matching placebo solution.

5.1.2 Noninvestigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products.

In this protocol, noninvestigational product(s) is/are: not applicable.

5.1.3 Identification

ETV tablets and oral solution, and relevant placebo will be provided by Bristol-Myers Squibb. The ETV 0.05 mg/mL oral solution and placebo will be supplied as a ready-to-use, orange-flavored, clear, colorless to pale yellow, solution in a 260-mL bottle containing 210 mL of solution.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5.1.4 Packaging and Labeling of Drug

Double-Blind Phase

Entecavir 0.5 mg and matching placebo tablets will be packaged into bottles containing 30 tablets each. Each bottle will be labeled with a 1-panel blinded label with at least the following information: protocol number (or stem number), container number, batch number, quantity of tablets, dosing directions, and storage conditions.

Entecavir oral solution and matching placebo will be in 260 mL bottles (containing 210 mL oral solution) and be labeled with a 1-panel blinded label with at least the following information: protocol number (or stem number), container number, batch number, quantity of oral solution, dosing directions, and storage conditions. Each bottle of oral solution will be housed in a carton containing a plastic dosing syringe and adapter. Each carton will be labeled with a 1-panel label containing at least the following information: protocol number (or stem number), container number, batch number, dosing directions, and storage conditions.

Open-Label Phase and Rescue Open-Label ETV

Entecavir 0.5 mg tablets will be packaged into bottles containing 30 tablets each. Each bottle will be labeled with a 2-panel open label with at least the following information: protocol number (or stem number), container number, batch number, drug name and potency, quantity of tablets, dosing directions, and storage conditions.

Entecavir oral solution will be in 260 mL bottles (containing 210 mL oral solution) and be labeled with a 1-panel open label with at least the following information: protocol number (or stem number), container number, batch number, drug name and potency, quantity of oral solution, dosing directions, and storage conditions. Each bottle of oral solution will be housed in a carton containing a plastic dosing syringe and adapter. Each carton will be labeled with a 1-panel open label containing at least the following information: protocol number (or stem number), container number, product name and potency, batch number, dosing directions, and storage conditions.

5.1.5 Handling and Dispensing

Study drug supplied by the sponsor or sourced by the investigator should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that study drug is only dispensed to study subjects. The study drug must be dispensed only from official study sites by authorized personnel according to local regulations.

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. Entecavir 0.5 mg and matching placebo tablets should be stored at 15 - 25°C in a tightly closed container. Entecavir oral solution and matching placebo should be stored at 15 - 25° C, protected from light and freezing. Materials will be provided to assist in the accurate measuring the dispensation of ETV and placebo oral solution.

If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Please refer to Section 9.2.2 for information on study drug record retention and 9.3 for destruction and return instructions**.**

5.2 Method of Assigning Subjects to a Treatment

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. Details will be provided.

A randomized blocked design stratified by age group (2 to ≤ 6 yrs; > 6 to ≤ 12 yrs; > 12 to < 18 yrs) will be used. The target enrollment will be 30 subjects for each age group, with a minimum requirement of 18 subjects. It is important that the investigative staff reconfirm the subject's willingness to continue in the study prior to randomizing the subject.

Randomization should occur within 6 weeks after the screening evaluation.

5.3 Selection and Timing of Dose for Each Subject

Study medication MUST be initiated within 72 hours of randomization.

On Day 1, after all Day 1 procedures have been performed, eligible subjects will start study medication once daily. Study medication should be taken at approximately the same time each day. Study medication should be taken on an empty stomach (2 hours before OR 2 hours after food); therefore it is suggested that subjects take their study medication at bedtime or very early in the morning. Subjects participating in the semi-intense PK assessment should take study medication in the morning from Day 1 until the PK specimens are collected at a single visit between Day 14 and Week 4. On the day of the semi-intense PK assessment, subjects should take study medication, on an empty stomach, in the clinic under direct observation. Subjects who have completed the semi-intense PK assessments are permitted to take study medication at bedtime.

Note: The Summary of Product Characteristics (SmPC) for Baraclude® and product inserts in some other countries, state that ETV may be taken "with or without" food in treatment naive subjects. This labeling reflects a regulatory assessment of the pharmacokinetic/pharmacodynamic data for ETV. In developing this study, BMS has chosen to standardize study conduct worldwide using the approach that ETV should be taken on an empty stomach.

During the blinded treatment phase, ETV or the relevant placebo will be dosed once daily, as shown in Table 5.3

Table 5.3: Study Medication Dosing Table

Body Weight (kg)[a]	Body Weight (lbs)	Dose Final (mL, per 0.015 mg/kg)[b]
10.0 - 10.8	22.1 - 23.8	3.0
10.9 - 12.4	24.0 - 27.3	3.5
12.5 - 14.1	27.6 - 31.1	4.0
14.2 - 15.8	31.3 - 34.8	4.5
15.9 - 17.4	35.1 - 38.4	5.0
17.5 - 19.1	38.6 - 42.1	5.5
19.2 - 20.8	42.3 - 45.9	6.0
20.9 - 22.5	46.1 - 49.6	6.5
22.6 - 24.1	49.8 - 53.1	7.0
24.2 - 25.8	53.4 - 56.9	7.5
25.9 - 27.5	57.1 - 60.6	8.0
27.6 - 29.1	60.9 - 64.2	8.5
29.2 - 30.8	64.4 - 67.9	9.0
30.9 - 32.5	68.1 - 71.7	9.5
32.6 - 33.0	71.9 - 72.8	10.0

[a] If weight in pounds (lb) is not included in the table, use the closest higher body weight (lb.) in the table for study medication dose. The ETV dose is calculated as follows:

$$\frac{\text{weight (kg)} \times 0.015 \text{ mg/Kg}}{0.05 \text{ mg/mL}} = \text{weight (Kg)} \times 0.3 \text{ mL/Kg} = \text{mL solution.}$$

Round to the nearest 0.5 mL.

[b] Children with body weight > 32.6 kg (71.9 lb) should receive 10.0 mL of oral solution or the tablet formulation (0.5 mg) of the study medication.

During the open-label phase, ETV shall be dosed once daily at 0.015 mg/kg and should follow the dosing scheme in Table 5.3.

The need for further anti-HBV treatment of study subjects during the LTFU shall be determined by the investigator. The choice of therapy is at the discretion of the investigator and may include marketed or investigational products. In the event that a subject is treated with rescue open-label ETV as a result of an extreme elevation of ALT due to the acute exacerbation of CHB, as defined in Section 4.1.2, ETV shall be dosed once daily at 0.015 mg/kg up to 0.5mg/day and should follow the dosing scheme in Table 5.3.

If ETV is initiated during the LTFU phase, HIV testing and monitoring is strongly recommended as ETV is not recommended in subjects co-infected with HIV and HBV unless the subject is also receiving effective anti-retroviral therapy. For subjects initiated on other anti-HBV treatment during LTFU, investigators should evaluate the need for HIV testing based upon standard of care and the product label for the selected agent.

5.3.1 Dose Modifications

ETV is a nucleoside analogue that is primarily cleared by the kidneys. In patients with renal impairment, the apparent clearance of entecavir decreases as creatinine clearance decreases. In the unlikely event that a subject develops inadequate renal function while on study (estimated glomerular filtration rate of < 50 mL/min/1.73 m^2), the recommendation for dose reduction will follow the established approach used in studies of adult CHB patients. Table 5.3.1 shows the recommendation for dose reduction based upon estimated glomerular filtration rate (GFR).

Table 5.3.1: Recommended Dosing of ETV in Subjects Who Develop Renal Impairment on Study

Estimated GFR	Usual Dose (0.015 mg/kg/day up to a maximum of 0.5 mg/daily)[a]
≥ 50	Usual Dose
30 to < 50	Dose reduction by 50 % **OR** Usual dose every 48 hours
10 to < 30	Dose reduction by 70 % **OR** Usual dose every 72 hours
< 10/hemodialysis/ CAPD[b]	Dose reduction by 90 % **OR** Usual dose every 7 days

[a] For doses less than 0.5 mg daily, the oral solution is recommended.

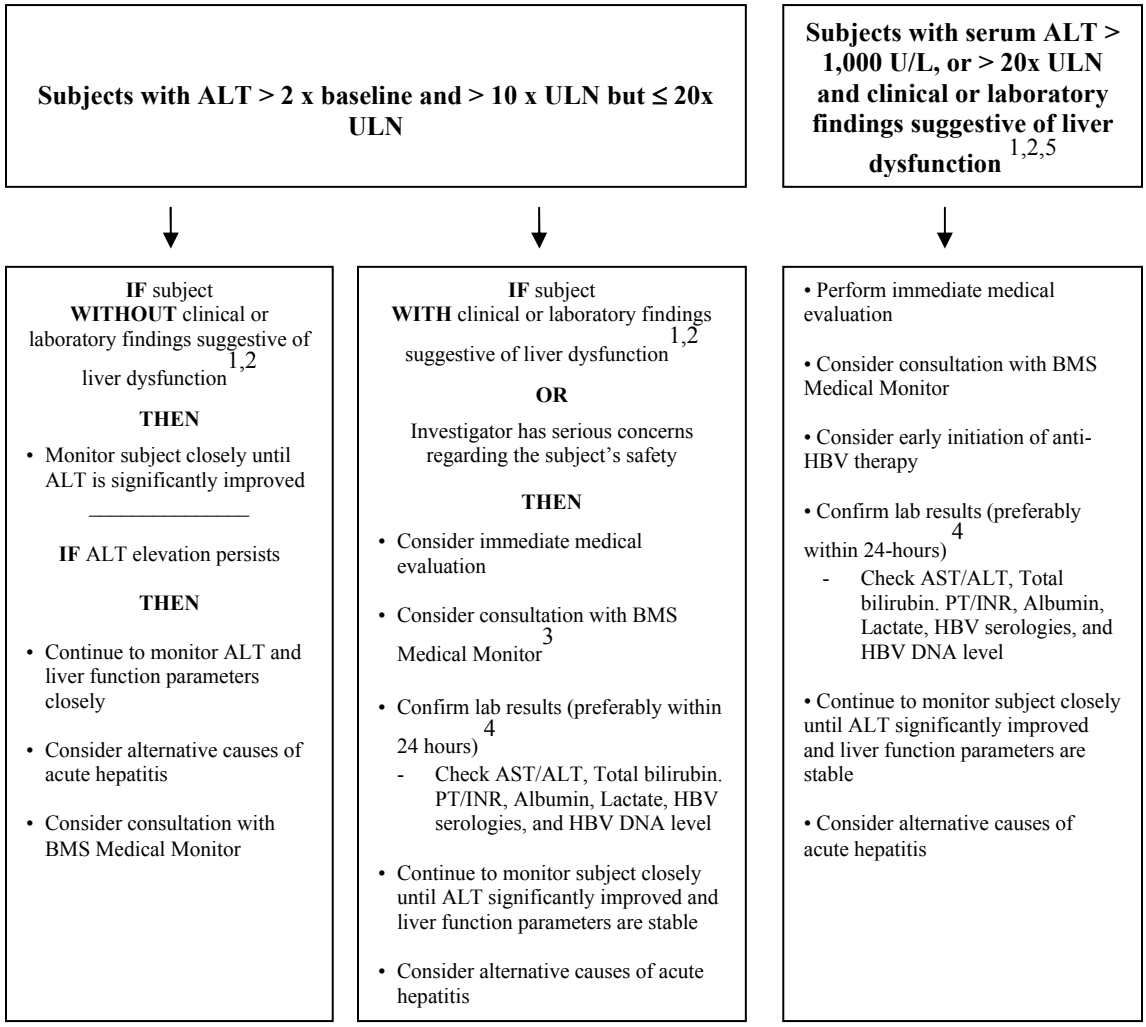
[b] Subjects receiving ETV on the day of hemodialysis should receive ETV after the session.

5.3.2 Other Guidance

5.3.2.1 Study Subject Management for ALT Elevations or Hepatic Clinical Events

Acute exacerbation of hepatitis B (ALT > 2 x baseline AND > 10 x ULN) and hepatic clinical events may represent a critical scenario with the potential for serious hepatic injury and death. Guidelines for managing these events can be found in Figures 5.3.2.1. Should an event as described occur, a blood sample for HBV DNA determination using a sensitive PCR technique should be obtained and sent to the central laboratory for this study. If results are needed urgently for patient management decisions, a sample should be also drawn and concurrently sent to a local laboratory for assessment. An unscheduled visit laboratory kit should be used for the HBV DNA sample if it is collected at a time that is not required by the protocol. Non-HBV related potential causes of worsening hepatitis also need to be considered (hepatitis A, C, D, concomitant medications, etc).

Figure 5.3.2.1: Management of Significant Elevations of Serum ALT Due to the Acute Exacerbation of Chronic Hepatitis B



[1] Clinical manifestations suggestive of hepatic complications include but are not limited to: Ascites, Hepatic encephalopathy, Increasing nausea, vomiting, or abdominal pain, Jaundice, Variceal bleeding, etc.

[2] Laboratory findings that may be suggestive of evolving liver dysfunction include but are not limited to: Increasing INR, Total bilirubin, or Serum lactate levels, or Declining serum albumin values.

[3] Subjects experiencing acute exacerbation of CHB resulting in ALT flare WITH clinical or laboratory findings suggestive of liver dysfunction or other serious safety concern may be eligible for rescue open-label ETV as determined on a case-by-case basis following consultation with the BMS Central Medical Monitor.

[4] Labs may be processed by local or central laboratory. An unscheduled visit laboratory kit should be used if labs are collected at a time that is not required by the protocol.

[5] Subjects placed on rescue open-label ETV will be immediately placed into the study's LTFU phase. Protocol visits should be scheduled as described in Section 6.1. Patients who are provided rescue open-label ETV to treat an extreme elevation of ALT due to acute exacerbation of CHB should undergo additional non-protocol visits and assessments at the discretion of the managing investigator. See section 4.1.2.

5.3.2.2 Management of Laboratory Abnormalities and Clinical Events Using Modified Toxicity Grading System.

If a subject develops a non-hepatic laboratory toxicity during the study, Table 5.3.2.2A provides guidance pending a full medical evaluation for the underlying etiology of the abnormality. The medical monitor should be consulted for the following laboratory abnormalities:

Table 5.3.2.2A: Management of Laboratory Toxicities and Clinical Events using DAIDS Toxicity Grading System

Laboratory Test	Alert Value
Lipase	> 5 times ULN (Grade 4)
ALT or AST	> 2 X baseline and > 10 x ULN (Grade 4) (see Figure 5.3.2.1)
Total Bilirubin	≥ 2 mg/dL increase from baseline and > ULN
INR	> 1.5 (Grade 2) and an increase in the INR ≥ 0.5 from baseline
Serum Albumin	Decrease ≥ 1 g/dL from baseline and < 3 g/dL
Plasma lactate[a]	Elevated: ≥ 3 mmol/L (27 mg/dL)

[a] The Central Medical Monitor must be informed

If a subject develops certain specified clinical events during the study, Table 5.3.2.2B provides guidance pending a full medical evaluation for the underlying etiology of the event. Study drug should be interrupted and the medical monitor consulted for the following clinical events:

Table 5.3.2.2B: Clinical Events Requiring Interruption of Study Drug

Grade & Events	Dose Modifications
All Grades: Pancreatitis, Acute Allergic Reaction (if it appears related to study drug), Lactic Acidosis	Interrupt study medication and inform BMS Medical Monitor
Grade 2: Shortness of breath, bronchospasm if associated with evidence of allergic reaction due to study drug	Interrupt study medication and inform BMS Medical Monitor
Grade 3: Hypotension if associated with evidence of allergic reaction due to study drug	Interrupt study medication and inform BMS Medical Monitor
Grade 4: All Clinical Events	Interrupt study medication and inform BMS Medical Monitor

All subjects who discontinue study medication, regardless of the reason off study, are to be followed to complete 5 years on study.

5.4 Blinding/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.

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, **in which knowledge of the investigational product is critical to the subject's management**, the blind for that subject may be broken by the treating physician. The primary emergency treatment arm unblinding method is through the IVRS.

In the event that a subject develops an ALT flare and/or other HBV clinical symptoms, the investigator should consult with the study medical monitor on a case by case basis. If knowledge of the subject’s HBV DNA is deemed necessary for further clinical management, as in a case of an extreme elevation of ALT due to acute exacerbation of CHB, that subject’s HBV DNA values will be unblinded; subsequent unblinding of the treatment assignment may or may not be necessary.

Before breaking the blind of an individual subject's treatment, the investigator should have determined that the information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

The DMC will be able to review unblinded HBV DNA results for individual subjects, and will inform BMS of the need to unblind data for individual subjects as appropriate; in that event the investigator will be able to make individual management decisions based on the unblinded HBV DNA.

5.5 Concomitant Treatments

5.5.1 Prohibited and/or Restricted Treatments

Subjects should be on stable doses of other medications for at least four weeks prior to first dose of study medication. If the subject is on chronic medications, a consistent dosing schedule should be maintained for the duration of the study.

In general, concomitant medications which may cause nephrotoxicity (including long-term treatment with immunosuppressive drugs); hepatotoxicity; affect renal excretion or hepatic metabolism; and agents with activity against hepatitis B are not permitted in this study (see Exclusion Criteria Section 4.2.2, number 6).

Examples of these potentially nephrotoxic or hepatotoxic agents are: amphotericin B; aminoglycosides; foscarnet; systemic corticosteroids; cyclosporin; azathioprine; carbamazepine; disulfiram; isoniazid; rifampin (rifampicin); diclofenac; troglitazone; trovofloxacin. Should a subject develop a medical need for short term therapy with any of these agents (≤ 2 weeks), such an agent may be used; longer term therapy while on study should be discussed with the central BMS Medical Monitor.

Examples of agents with anti HBV activity include: interferon alpha, thymosin alpha; any nucleos[t]ide antiviral agent with activity against hepatitis B virus (including but not limited to adefovir, tenofovir, famciclovir, clevudine, lamivudine, telbivudine, or emtricitabine); and mycophenolate mofetil.

Traditional Chinese medicines and other herbal products with purported antiviral activity or intended to improve/protect liver function are prohibited during this study and must be discontinued at the time of enrollment.

During the on study treatment phase, the subject may not be co-enrolled in another clinical trial where an investigational drug is administered.

An assessment of concomitant medication use will be performed at each on study treatment visit.

5.5.2 Other Restrictions and Precautions

Restrictions: Female subjects of childbearing potential should take measures to avoid pregnancy both during dosing and for 6 weeks after study medication has been discontinued. Male subjects should also be advised to practice barrier contraception or abstinence during the dosing period and for at least 6 weeks after dosing.

Precautions: If the subject is on chronic medications, a consistent dosing schedule is recommended for the duration of this study when medically possible.

5.6 Treatment Compliance

Assessment of study medication will be performed at each clinical evaluation visit. The subject should be instructed to bring all unused study medication in the original bottle to each visit. Partially used bottles of study medication can be returned to the subject, and dosing should continue from the in-use container until it has been emptied. The dates and number of solution/tablets dispensed and returned must be recorded in the source documents for compliance and accountability purposes.

The subject's caregiver will be provided with a diary card to record study medication and meal times preceding the semi-intense and sparse PK sampling.

Any interruptions in dosing (start and stop dates) or missed doses due to concurrent illness or toxicity will be recorded on the CRF.

Subject adherence with treatment regimens should be evaluated by the site at every visit through direct interviews with the subject's caregiver. Counseling for reinforcement of dosing instructions and importance of compliance should be provided as needed.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Flow Chart/Time and Events Schedule

Table 6.1: Flow Chart for Protocol AI463189

Procedure	Screening ≤ 6 Weeks prior to Randomization	Randomize Initiate study drug (Day 1) within 72 hours	On Study Treatment Weeks 4, 8, 12 ± 3 days, and every 12 weeks ± 5 days up to end of study drug dosing	Weeks 52, 100 and 148 ± 10 days (if needed)[a]	End of Treatment (Scheduled or Early)	Observational LTFU[b] Weeks 6, 12, and every 12 weeks ± 5 days Up to 264 weeks total study participation [or 48 weeks beyond completion of rescue open-label ETV used for treatment of an extreme elevation of ALT due to acute exacerbation of CHB; whichever is later]	Protocol Section
Eligibility Assessments							
Informed Consent	X						3.3
Inclusion/Exclusion Criteria	X						4.2
Medical & anti HBV history[c]	X						4.2
HCV, HDV serology (1 mL)	X						6.9
Alpha Fetoprotein (1 mL)	X						6.9

Table 6.1: Flow Chart for Protocol AI463189

Procedure	Screening ≤ 6 Weeks prior to Randomization	Randomize Initiate study drug (Day 1) within 72 hours	On Study Treatment Weeks 4, 8, 12 ± 3 days, and every 12 weeks ± 5 days up to end of study drug dosing	Weeks 52, 100 and 148 ± 10 days (if needed)[a]	End of Treatment (Scheduled or Early)	Observational LTFU[b] Weeks 6, 12, and every 12 weeks ± 5 days Up to 264 weeks total study participation [or 48 weeks beyond completion of rescue open-label ETV used for treatment of an extreme elevation of ALT due to acute exacerbation of CHB; whichever is later]	Protocol Section
Safety Assessments							
Physical Examination	X				X		6.3
Targeted Physical Examination (including neurologic assessment)		X	X			X[d,]	6.3
Vital Signs including height, and weight	X	X	X		X	X	6.3
Tanner Stage Assessment		X	Week 24 and every 24 weeks		X	Week 24 and every 24 weeks	App 3
Pretreatment Events Assessment		X					6.3
Adverse Events Assessment			X		X	X[e]	6.3

Table 6.1: Flow Chart for Protocol AI463189

Procedure	Screening ≤ 6 Weeks prior to Randomization	Randomize Initiate study drug (Day 1) within 72 hours	On Study Treatment Weeks 4, 8, 12 ± 3 days, and every 12 weeks ± 5 days up to end of study drug dosing	Weeks 52, 100 and 148 ± 10 days (if needed)[a]	End of Treatment (Scheduled or Early)	Observational LTFU[b] Weeks 6, 12, and every 12 weeks ± 5 days Up to 264 weeks total study participation [or 48 weeks beyond completion of rescue open-label ETV used for treatment of an extreme elevation of ALT due to acute exacerbation of CHB; whichever is later]	Protocol Section
Serious Adverse Events Assessment	X	X	X		X	X	6.3
Concomitant Medication Use	X	X	X		X		5.5
Use of anti-HBV therapies						X	5.5
Assess HBV related diagnoses						X	7.3
Hematology, Chemistry (4 - 5.5 mL)[f]	X	X	X		X	X	6.9
INR (1.8 mL)	X	X	Week 24 and every 24 weeks		X	Week 24 and every 24 weeks	6.9

Table 6.1: Flow Chart for Protocol AI463189

Procedure	Screening ≤ 6 Weeks prior to Randomization	Randomize Initiate study drug (Day 1) within 72 hours	On Study Treatment Weeks 4, 8, 12 ± 3 days, and every 12 weeks ± 5 days up to end of study drug dosing	Weeks 52, 100 and 148 ± 10 days (if needed)[a]	End of Treatment (Scheduled or Early)	Observational LTFU[b] Weeks 6, 12, and every 12 weeks ± 5 days Up to 264 weeks total study participation [or 48 weeks beyond completion of rescue open-label ETV used for treatment of an extreme elevation of ALT due to acute exacerbation of CHB; whichever is later]	Protocol Section
HIV Serology (1 mL)	X		Weeks 48, 96 and 144[g]		X	Weeks 48 and 96 after initiation of rescue open-label ETV[d]	6.9
Pregnancy Test[h]	X	X	X		X	X[i]	7.6
Efficacy Assessments							
Hepatitis B serologies (1 mL)	X	X	Week 12 and every 12 weeks		X	Week 24 and every 24 weeks	6.9
HBV DNA PCR (2 mL)	X	X	Week 4, Week 12 and every 12 weeks		X	Weeks 6, 12, 24, and every 24 weeks	6.9
HBV Genotype (HBV subtype) (2 mL)		X					6.9

Table 6.1: Flow Chart for Protocol AI463189

Procedure	Screening ≤ 6 Weeks prior to Randomization	Randomize Initiate study drug (Day 1) within 72 hours	On Study Treatment Weeks 4, 8, 12 ± 3 days, and every 12 weeks ± 5 days up to end of study drug dosing	Weeks 52, 100 and 148 ± 10 days (if needed)[a]	End of Treatment (Scheduled or Early)	Observational LTFU[b] Weeks 6, 12, and every 12 weeks ± 5 days Up to 264 weeks total study participation [or 48 weeks beyond completion of rescue open-label ETV used for treatment of an extreme elevation of ALT due to acute exacerbation of CHB; whichever is later]	Protocol Section
Specimens for Resistance Testing (3 mL)		X	Week 48, 96, 144[j]		X		6.9
Other Assessments							
Sparse PK (2 ml)[k]			Weeks 4, 12, 24, 48				
Semi-intense PK (8 ml)[l]			Week 4				
Clinical Drug Supplies							
Dispense Study Medication		X	X	X		X[d]	5.2
Assessment of Study Medication Use			X	X	X	X[d]	5.6

[a] Assessments of seroconversion will be made based on serology results at Weeks 48, 96, and 144. Study drug will be modified, continued, or discontinued according to the study schema (Section 4.1).

[b] Only protocol required visits and assessments are mentioned. Subjects placed on rescue open-label ETV to treat an extreme elevation of ALT due to acute exacerbation of CHB should undergo additional non-protocol visits and assessments at investigator discretion.

[c] Histological results will be documented for subjects who have had a prior liver biopsy.

[d] For subjects receiving rescue open-label ETV to treat an extreme elevation of ALT due to acute exacerbation of CHB only.

[e] Adverse events should be recorded at week 6 for all subjects enrolled in LTFU, and at each visit for subjects receiving rescue open-label ETV.

[f] Volume of blood to be collected may vary based on available specimen collection tubes.

[g] While on study treatment.

[h] WOCBP only. Additional home pregnancy testing will be required in between study visits starting from Week 18 and every 12 weeks thereafter while on study treatment.

[i] All subjects enrolled in LTFU should undergo pregnancy testing at week 6. Subjects receiving rescue open-label ETV should be tested every 6 weeks during treatment and 6 weeks after the last dose of study medication (home pregnancy tests should be used in between study visits).

[j] For subjects still on study ETV only (Section 6.9.2).

[k] Sparse PK assessments will be conducted in all subjects. Four samples, each drawn as a single sample, will be collected during study visits at Weeks 4 (except for subjects participating in the semi-intense PK assessment), 12, 24, and 48.

[l] Semi-intense PK assessments will be conducted at selected sites in a subset of up to 9 treated subjects in each age cohort at the Week 4 visit. For convenience, this PK assessment may be performed on any single day between Day 14 and Week 4 (Section 6.5).

6.2 Study Materials

The sponsor will provide a copy of the ETV (BMS-200475) IB and any relevant safety addendum, protocol and any amendments to the protocol, instructions for completing case report forms (CRFs; both electronic and paper), Investigator Manual from the central laboratory and serious adverse event (SAE) and pregnancy forms, etc. Materials will be provided to assist in the accurate measuring and dispensation of ETV/PLB solution. Diary cards will be provided to help record any interruptions in dosing, as well as dosing and meal time information required for the PK assessments.

6.3 Safety Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested by the sponsor.

6.3.1 Vital Signs, Physical Examination, and Targeted Physical Examination

The schedule of vital signs (seated Blood Pressure and Pulse Rate, full and targeted physical examinations) is provided in Section 6.1 (Flow Chart/ Time and Events Schedule). Targeted physical exam includes assessment of neurological system, heart, lungs, and abdomen.

6.3.2 Adverse Event Monitoring

Subjects will be closely monitored throughout the study for adverse events. Subjects who have study medication completed or discontinued permanently must be followed for the full 5 years of the study.

During the dosing phase, palatability issues with respect to the oral solution (placebo or active drug) should be reported as Adverse Events.

During the observational long-term follow up phase, Adverse Events related to the administration or discontinuation of study drug should be documented for subjects that are not receiving commercially available anti-HBV therapy. Serious Adverse Events and HBV-related diagnoses should be reported during the long-term follow up phase, regardless of whether or not the subjects are receiving commercially available anti-HBV therapy.

6.3.3 Medication Assessments

Medications taken within one month prior to study participation and while on study treatment will be reported. During the LTFU phase, anti-HBV medications will be reported.

6.4 Efficacy Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested by the sponsor.

6.4.1 Primary Efficacy Assessment

The schedule of the primary efficacy endpoint assessment, HBV DNA assay, and hepatitis B e antigen serology, is provided in Section 6.1, Flow Chart/Time and Events Schedule, Table 6.1.

6.4.2 Secondary Efficacy Assessments

The schedule of the secondary efficacy endpoint assessments, HBV DNA assay, hepatitis B serologies, and ALT is provided in Section 6.1, Flow Chart/Time and Events Schedule, Table 6.1.

6.5 Pharmacokinetic Assessments

Table 6.5A lists the sparse PK sampling schedule for all subjects for the assessment of ETV. For each subject a single sparse sample will be collected during Weeks 4, 12, 24, and 48.

In addition, a semi-intense PK assessment will be conducted at selected sites, in a subset of up to 9 treated subjects in each age cohort. Subjects providing informed consent for this PK assessment will have one pre-dose and three post-dose samples drawn during a single visit scheduled between Day 14 and Week 4 as listed in Table 6.5B.

Table 6.5A: All Subjects - Sparse PK Sampling Schedule

PK Sample Schedule	Sample No.	Time Relative to Dosing
Week 4 Visit*	1	Anytime between 1 - 24 hours after dosing
Week 12 Visit	2	Anytime between 1 - 24 hours after dosing
Week 24 Visit	3	Anytime between 1 - 24 hours after dosing
Week 48 Visit	4	Anytime between 1 - 24 hours after dosing

* The Week 4 sparse PK sample is not required for subjects participating in the Week 4 semi-intense PK assessment

Table 6.5B: Subset of Subjects - Semi-intense PK Sampling Schedule

PK Sample Schedule	Sample No.	Time Relative to Dosing
Single visit between Day 14 and Week 4	1	immediately pre-dose
	2	1.0 hours after dosing
	3	2.0 hours after dosing
	4	4.0 hours after dosing

Subjects will be directed to take their medication at the same time every day, at least 2 hours before or 2 hours after meals. The date and time of the last dose of study drug and the time of the nearest meals relative to the last study drug dose taken before sample collection should be recorded on the CRF. For each sample, the date and time of sample collection will be recorded.

In the subset of subjects who consent to the semi-intense PK assessments, study drug must be taken each day in the morning, at least 2 hours before or 2 hours after meals. On the day of the semi-intense PK assessment, subjects should take study medication, on an empty stomach, in the clinic under direct observation. The time of the meals relative to the PK dose will be recorded. Once the semi-intense PK assessment has been completed, evening dosing may begin.

6.5.1 Pharmacokinetics: Blood Collection and Processing

Tables 6.5A and 6.5B list the sampling schedule to be followed for the assessment of plasma pharmacokinetics.

Blood (2.0 mL per sample) will be collected by direct venipuncture or from an indwelling catheter (for semi-intense PK assessments). Each blood sample is to be collected into a labeled tube containing EDTA (K2 or K3 EDTA) as the anticoagulant. Immediately after collection, the tube should be gently inverted several times to completely mix the anticoagulant and placed on ice. Within 60 minutes of collection, each sample should be centrifuged for 10 minutes at ~1000 x g in a refrigerated centrifuge (~ 5°C) to separate the cellular elements from plasma. The use of a chilled rotor head (~ 5°C) in a centrifuge at room temperature is permitted. The separated plasma sample should be transferred to a labeled screw-capped polypropylene tube and stored upright and frozen at or below -20°C until shipped frozen on dry ice to the designated laboratory.

6.5.2 Pharmacokinetic Sample Shipment

The plasma samples are to be shipped by express courier with enough dry ice to maintain the samples in a frozen state until received by the Central Laboratory. Requisition slips supplied by the Central Laboratory are to be completed and included with each shipment. Do not ship to arrive over weekends or holidays. The addressee is to be notified of the air bill number in advance of the shipment via telephone or fax. Additional shipping instructions will be provided to investigators at the time of study initiation. The Central Laboratory will ship the samples to an analytical laboratory designated by Bristol-Myers Squibb. Plasma samples will be analyzed using a validated assay for ETV.

6.6 Pharmacodynamics Assessments

Not applicable.

6.7 Pharmacogenomic/Pharmacogenetic Assessments

Not applicable.

6.8 Outcomes Research Assessments

Not applicable.

6.9 Other Assessments

6.9.1 Laboratory Test Assessments

A central laboratory will be used for all testing. All serum and plasma samples, including back-up samples, will be stored by the Central Laboratory. The following testing may be performed retrospectively on any stored serum or plasma samples which have been obtained during conduct of the study: analysis for HBV resistance to study therapy and analysis for exploratory markers of HBV disease that could be influenced by study therapy but which have not previously been assessed. Laboratory test kits and a manual will be provided by the Central Laboratory designated by the Sponsor.

HBV DNA results from the Central Laboratory will be provided in both copies/mL and IU/mL. For the Roche COBAS® TaqMan - HPS assay, the conversion factor is 5.82 copies = 1 IU. Table 6.9.1 is provided to assist in interpretation of results.

Table 6.9.1: Copies/IU Conversion Table for COBAS TaqMan - HPS Assay

Copies/mL (rounded to nearest copy)	IU/mL (reported to 2 decimal places)
28	4.8
50	8.6
58	10: Lower Limit of Detection (LLD)
169	29: Lower Limit of Linearity
300	51.5

Table 6.9.1: Copies/IU Conversion Table for COBAS TaqMan - HPS Assay

Copies/mL (rounded to nearest copy)	IU/mL (reported to 2 decimal places)
1000 (10^3)	172
10,000 (10^4)	1,720
100,000 (10^5)	17,200
1,000,000 (10^6)	172,000
10,000,000 (10^7)	1,720,000
100,000,000 (10^8)	17,200,000

* Conversion Factor: 5.82 copies = 1 IU

Required laboratory tests include the following:

Hematology:

- hemoglobin;
- white blood cell count with differential (including neutrophil count);
- platelet count;
- INR.

Chemistries:

- albumin;
- AST;
- ALT;
- total bilirubin;
- creatinine;
- urea nitrogen (BUN) or urea;
- serum lipase;
- electrolytes (Na+, K+, Cl-);
- glucose;
- alpha fetoprotein (AFP).

Serologies:

- hepatitis B surface antigen;
- hepatitis B surface antibody;
- hepatitis B e antigen;
- anti-hepatitis B e antibody;
- anti-hepatitis C antibody;
- anti-hepatitis D antibody;
- HIV antibody.

Pregnancy test:

- urine or serum pregnancy test.

Other:

- HBV DNA by COBAS® TaqMan- HPS assay;
- HBV Genotype (eg, genotype A, B, C, D etc, or mixed).

Refer to Section 6.1 for details regarding at what visits the tests are required.

6.9.2 Genotypic Analysis for Drug Resistance

Blood samples shall be collected at Day 1 (prior to first study dose), Weeks 48; 96; 144; 192 for subjects on study treatment, and at the last on study treatment visit. These samples will be stored for possible HBV resistance testing.

Genotyping of HBV polymerase will be performed using the Trugene assay on stored specimens from:

1) All subjects who have received at least 12 weeks of continuous ETV treatment (blinded or open-label) immediately prior to and continuing through the Week 48, 96, 144, 192, or last on study treatment visit, and who have HBV DNA (≥ 50 IU/mL) at the specified analysis visit;
2) All subjects with a confirmed rise in HBV DNA of ≥ 1 $\log_{10}$ after achieving nadir on treatment as well as the subjects whose HBV DNA increases to ≥ 50 IU/mL after having achieved a value < 50 IU/mL. (Note: if such increase in DNA level occurs

between analysis visits, the collected specimen will be tested in addition to any evaluable specimens at the specified analysis visit as described in item 1 above), and/or

3) On a case by case basis after consultation with the BMS Central Medical Monitor.

A Central Laboratory designated by the sponsor will be used for genotypic analysis.

7 ADVERSE EVENTS

7.1 Definitions

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

7.1.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not

limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE and must be reported accordingly.

Although overdose and cancer are not always serious by regulatory definition, these events should be reported on an SAE form and sent to BMS in an expedited manner.

All pregnancies, regardless of outcome, must be reported to the sponsor on a Pregnancy Surveillance Form, not an SAE form (see Section 7.6).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

7.1.2 Nonserious Adverse Events

All AEs that are not classified as serious.

7.2 Assignment of Adverse Event Intensity and Relationship to Study Drug

The following categories and definitions of intensity as determined by a physician should be used for all BMS clinical study AEs:

- Mild (Grade 1) - Awareness of event but easily tolerated
- Moderate (Grade 2) - Discomfort enough to cause some interference with usual activity
- Severe (Grade 3) - Inability to carry out usual activity
- Very Severe (Grade 4) - Debilitating, significantly incapacitates subject despite symptomatic therapy

Refer to Appendix 2 for the Division of AIDS (DAIDS) Adult and Pediatric Toxicity Grading System.

The following categories and definitions of causal relationship to study drug as determined by a physician should be used for all BMS clinical study AEs:

- Related: There is a reasonable causal relationship to study drug administration and the AE
- Not related: There is not a reasonable causal relationship to study drug administration and the AE

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

7.3 Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs:

onset, duration, intensity, seriousness, relationship to study drug, action taken, and treatment required. If treatment for the AE was administered, it should be recorded on the appropriate CRF page. The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

7.3.1 Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing or within 30 days of the last visit for screen failures. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should notify BMS of any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

Serious Adverse Events should be reported during the long-term follow up phase, regardless of whether or not the subjects are receiving commercially available anti-HBV therapy. Any medical event that the investigator considers to be "medically important" in the context of pediatric drug exposure (for example neurodevelopmental delay), may be reported as an SAE under the category "Important Medical Event." (see Section 7.1.1)

Serious adverse events, whether related or unrelated to study drug, must be recorded on the SAE page of the CRF and reported within 24 hours to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be reported within 24 hours by confirmed facsimile transmission (fax) or scanned and reported via electronic mail. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting. The SAE electronic CRF in the electronic data capture tool should not be used.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE page of the CRF.

If an ongoing SAE changes in its intensity or relationship to study drug, a follow-up SAE report should be sent within 24 hours to the sponsor. As follow-up information becomes available it should be sent within 24 hours using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

SAE FACSIMILE TRANSMISSION:

For US Sites: Central Facsimile Station:
(609) 818-3804

Local Contact: To be provided after study initiation.

SAE Email Address: Worldwide.Safety@BMS.com

7.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting

these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. When BMS has a written agreement with a local IRB/IEC, BMS will directly submit ESR(s). The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.3.3 Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. During the long-term follow up phase, Adverse Events related to the administration or discontinuation of study drug should be documented for subjects that are not receiving commercially available anti-HBV therapy. Also during the LTFU phase, all adverse events should be documented in subjects receiving rescue open-label ETV.

If an ongoing nonserious AE worsens in its intensity or its relationship to the study drug changes, a new nonserious AE entry for the event should be completed. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 7.3.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

All identified nonserious AEs must be recorded and described on the appropriate nonserious AE page of the CRF (paper or electronic).

7.4 Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF, or be submitted electronically from a central laboratory. In addition, the following laboratory abnormalities should also be captured on the nonserious AE CRF page (paper or electronic) or SAE paper CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

7.5 Overdose

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 7.3.1 for reporting details.)

7.6 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized (see Section 4.2.1 for the definition of WOCBP).

Before enrolling WOCBP in this clinical study, investigators must review the sponsor-provided information about study participation for WOCBP. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

7.6.1 Requirements for Pregnancy Testing

All WOCBP MUST have a **negative** pregnancy test within 72 hours as specified in Section 6.1 **prior** to receiving the investigational product. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive the investigational product and must not continue in the study.

Pregnancy testing must also be performed throughout the study as specified in Section 6.1 (see flow chart/time and events schedule) and the results of all pregnancy tests (positive or negative) recorded on the CRF or transferred electronically.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

7.6.2 Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify the BMS medical monitor of this event, record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to BMS and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures described in Section 7.3.1.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

7.6.3 Specific Information Related to ETV and Pregnancy

Entecavir is classified by the US Food and Drug Administration (FDA) as Pregnancy "Category C" (Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in pregnant women).

In studies in rats and rabbits, entecavir doses producing systemic drug exposure levels approximately 28 and 212 times those expected in humans at the highest recommended dose (1 mg/day) showed no embryotoxicity or maternal toxicity, respectively. At exposures 3100 times those in humans, maternal toxicity, embryo-fetal toxicity (resorptions), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrae, and phalanges), and extra lumbar vertebrae and ribs

were observed in rats. At exposures 833 times those in humans, embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed in rabbits. In the pre- and post-natal development assessment in rats, entecavir, at maternally toxic drug exposure levels > 94 times those achieved in humans at the highest recommended dose (1 mg/day), no adverse effects on offspring were seen.

There are no adequate and well-controlled studies in pregnant women. A full description of the cumulative knowledge of ETV experience in pregnant women can be found in the Investigator Brochure.[10]

7.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the appropriate nonserious AE page of the CRF (paper or electronic) or SAE paper CRF page.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

One hundred and twenty-three (123) subjects (randomized 2:1 to ETV vs placebo) in this study will provide 90% power to show superiority of ETV versus placebo 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 arm and 1% for placebo arm. A two-sided significance level of 0.05 will be used. Subjects who either discontinue from study treatment prior to Week 48 or have having missing Week 48 HBV DNA or HBeAg serology measurement will be 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 the placebo arm 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)[13] 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 copies/mL at Week 48.

This sample size will also fulfill the requirement that the ETV integrated pediatric safety database has at least 100 pediatric patients who have received ETV for at least 48 weeks; this database will be comprised of subjects currently enrolled in study AI463028 and from this study (AI463189). Currently 24 nucleoside naive subjects are enrolled in AI463028; all 24 would have had 48 weeks of safety data collection by the time study AI463189 reaches Week 48.

Based on the original planning for study AI463189, it is estimated that 175 subjects will be enrolled to have approximately 123 subjects randomized (approximately 30% screen failure rate). Randomization will be 2:1 (ETV 82: Placebo 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 to approximately 96 the number of subjects that will be included in the integrated safety database at the end of study Week 144.

Additional safety data will be contributed by placebo randomized subjects switching to open-label ETV by study Week 52. Because it is expected to take 2 calendar years to randomize 123 subjects, and assuming even enrollment over that time frame, the last placebo 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 PLB 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 the PLB arm). 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 patients in the integrated safety database to approximately 110 subjects with at least 48 weeks of ETV exposure by study Week 144.

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.

8.2 Populations for Analyses

The enrolled cohort will include all subjects who provide informed consent and are assigned a Subject Identification number (PID).

- The enrolled cohort will be used in the analyses of all SAEs and deaths.

The treated cohort will include subjects who are randomized and received at least 1 dose of study regimen.

- The treated cohort will be used in the analyses of the efficacy endpoints; exploratory endpoints; HBV disease progression; AEs; and growth assessment.

Within the treated cohort, the primary cohort will be defined as at least the first 123 subjects treated.

- The primary cohort will be used for the primary endpoint analyses.

Some exploratory analyses will be based on 2 analysis cohorts, if not otherwise specified:

- Subjects who achieve seroconversion at Week 48 on study treatment;
- Subjects who do not achieve seroconversion at Week 48 on study treatment.

8.3 Endpoint Definitions

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.

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 HBV DNA < 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 serum ALT ≤ 1 × ULN at Week 48;
- Proportion of subjects with HBe 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.

Other Secondary Endpoints:

- The number and percent of subjects with adverse events (including palatability issues), serious adverse events, discontinuations due to adverse events, and HBV disease progression through Week 48;
- 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.

Exploratory Endpoints:

- Proportion of subjects who achieve HBV DNA < 50 IU/mL using the Roche COBAS® TaqMan HBV Test for use with the High Pure System (HPS) assay and serum ALT ≤ 1 x ULN at Week 48 of treatment;
- Proportion of subjects who achieve HBV DNA < LLD (10 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 HBsAg loss at Weeks 48 and 96 on study treatment;
- 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 96 on study treatment;
- Proportion of subjects with ALT ≤ 1 × ULN at Week 96 on study treatment;
- Proportion of subjects with HBeAg loss at Weeks 48 and 96 on study treatment;

- Proportion of subjects with HBe seroconversion at Week 96 on study treatment;
- Growth and development assessments: Height for age Z (HAZ) scores, Weight for age Z (WAZ) scores, and Tanner Stage annually while on study treatment and annually during the follow-up period;
- Cumulative probability of resistance for all patients who ever received study ETV (blinded or open-label) at treatment weeks 48, 96 and 144 of ETV;
- Subgroup analysis by age group, baseline ALT subpopulation (> 2 x ULN vs ≤ 2 x ULN), geography, genotype, and route of transmission for Primary and Key secondary endpoints;
- Subgroup analysis by age group , geography, genotype, and route of transmission for key safety endpoints including adverse events, serious adverse events, discontinuations due to adverse events, HBV disease progression or laboratory abnormalities.

The exploratory endpoints will be assessed for descriptive purposes and will be presented longitudinally every 48 weeks on treatment and during the follow-up period, unless otherwise specified.

8.4 Analyses

Binary variables will be summarized by counts and percentages. Comparisons of binary variables will be based on Cochran-Mantel-Haenszel (CMH) statistic stratified by age group. Confidence intervals (CI) for differences in proportions will be based on the normal approximation to the binomial distribution with unpooled proportions used in the computation of the standard error of the difference. The CI procedure will be used for both primary and secondary efficacy endpoints if applicable.

Continuous variables will be summarized with univariate statistics (eg, mean, median, standard deviation, minimum, and maximum).

8.4.1 Demographics and Baseline Characteristics

Baseline demography, HBV disease characteristics, prior anti-HBV (Interferon-α; ADV and TDF) treatment status, and laboratory values will be summarized and tabulated.

8.4.2 Safety Analyses

Serious adverse events and deaths will be reported for enrolled subjects regardless of treatment status. Discontinuations due to adverse events will be summarized. Other safety evaluations will be reported for Treated Subjects during the following study periods: on-study treatment (from the start of dosing until end of dosing plus 5 days), and off-treatment follow-up (from the end of dosing plus 6 days until the start of alternative anti-HBV therapy or the end of follow-up, whichever is earlier). Adverse events will be summarized by severity and relationship to study medication. Laboratory abnormalities will be summarized by modified Division of AIDS (DAIDS) or World Health Organization (WHO) grades (when pediatric specific DAIDS grading are not available). The events of HBV disease progression will be tabulated.

In addition, subgroup analysis by age group will be performed for adverse events, serious adverse events, discontinuations due to adverse events, HBV disease progression and laboratory abnormalities.

8.4.3 Efficacy Analyses

The primary and key secondary analyses will be based on randomized and treated subjects (modified intention-to-treat [ITT]). For the analysis of the primary and the key secondary endpoints at Week 48, subjects who discontinue from study prior to Week 48 or have missing measurement at Week 48 will be considered as failures at Week 48 (Non-completer = Failure). Sensitivity analyses will be performed in order to account for possible effects of early discontinuation, in which subjects who discontinue from study prior to Week 48 or have missing Week 48 measurements are excluded (Non completer = Missing). Treatment comparison for the primary endpoint and key secondary endpoints will be performed stratified by age group using Cochran-Mantel-Haenszel (CMH) weights. The difference in proportions (ETV - placebo), p-value, and 95% Confidence Interval (CI) will be presented. ETV will be considered superior to placebo if the p-value is < 0.05. The CI for the differences in proportions will be based on the normal approximation to the binomial distribution. A two-stage testing procedure will be employed for testing the primary and key secondary endpoints. In the first stage, the test for primary endpoint will be performed. Provided test result of the primary endpoint is significant (the p-value < 0.05), the second stage tests of

the key secondary endpoints will be conducted. Because the test for the key secondary endpoint will be conducted 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. In addition, treatment comparisons for the primary endpoint and key secondary endpoints will be performed within each age group. Subgroup analysis by age group will be exploratory.

For exploratory efficacy endpoints, subjects who discontinue from study prior to the analysis week or have missing analysis week measurements will be excluded (Non completer = Missing). The difference in proportions along with its 95% CI will be presented.

Genotypic resistance to ETV will be described.

8.4.4 Pharmacokinetic Analyses

Pharmacokinetic data collected in this study will be combined with data obtained from the pediatric study AI463028 to develop a Population PK/PD model which will be reported in a separate report. The population PK model will be used to provide estimates of steady state AUC which will be compared to the target exposure in adults. The median target exposure in adults of 18.7 ng·h/mL was determined based on a Phase 2 PK/PD assessment, and is reported in study AI463017. The PK/PD analysis demonstrated that AUC was predictive of efficacy, and an AUC of 2.22 ng·h/mL resulted in 90% of the maximal antiviral effect in the adult Phase 2 clinical trials. An exposure-response assessment in pediatric patients will be explored if supported by the data from study AI463189.

In addition to the population PK analysis described above, PK parameters from the intense sampling in the PK subset in Study AI463189 will be compared to the PK parameters from Study AI463028, and also combined with the intense PK data obtained in Study AI463028 to compare this exposure to the adult exposure in adults from Study AI463017. This will allow better estimation of PK parameters and variability.

8.4.5 Pharmacodynamic Analyses

Not applicable.

8.4.6 Pharmacogenomic Analyses

Not applicable.

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

Growth assessment: Height for age Z (HAZ) scores; Weight for age (WAZ) scores, and Tanner Stage scores will be summarized longitudinally by treatment group.

8.5 Interim Analyses

The primary analysis will evaluate safety and antiviral activity when the primary cohort has been treated for 48 weeks. Additional analyses will be performed when all subjects have reached Week 48, and when all subjects have completed study treatment. The final analysis will be conducted when the last randomized subjects completes the observational LTFU phase.

Additional analyses may be conducted at unscheduled intervals to support regulatory questions/interactions; and at the request of the DMC.

9 ADMINISTRATIVE SECTION

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

THE INVESTIGATOR MUST NOTIFY BMS PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, study documentation, informed consent, and enrollment of WOCBP.

For sites using the BMS electronic data capture tool, each individual making entries and/or corrections on electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

For electronic CRFs, corrections are made through the BMS electronic data capture tool that generates an automated audit trail including date and timestamp, full name of the person making the correction and original entry. The system also prompts the user to document reason for change that is also maintained in the audit trail.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

9.2 Records Retention

The investigator must retain study drug (those supplied by the sponsor or sourced by the investigator) disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.1 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the Pregnancy Surveillance Form. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

Paper CRFs must be completed legibly in ink. Subjects are to be identified by birth date and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank.

Electronic data transfer is acceptable.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

For paper CRFs, a correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialed and explained (if necessary) by the person making the correction and must not obscure the original entry.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed

electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where study drug is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number and use date
- dates and initials of person responsible for the inventory /entry/ movement of each study drug
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted, broken)
- amount returned to the sponsor
- amount destroyed at study site, if applicable
- retain samples sent to third party for bioavailability/bioequivalence, if applicable

The sponsor will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

9.3 Destruction and Return of Study Drug

9.3.1 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can

only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

9.3.2 Return of Study Drug

Upon completion or termination of the study, all unused and/or partially used study drug that was supplied by the sponsor must be returned to BMS.

All study drug returned to BMS must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original containers (eg, patient kits that have clinical labels attached). Empty containers should not be returned to BMS. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused study drug, those that were supplied by the sponsor, should be arranged by the responsible Study Monitor.

9.4 Publications

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor as related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures.
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

Term	Definition
AASLD	American Association for the Study of Liver Diseases
ADV	Adefovir
AE	Adverse event
AFP	Alpha-feto protein
Alk Phos	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma-concentration time curve
bDNA	Branched DNA hybridization assay
BID	Twice daily
BMS	Bristol-Myers Squibb
BUN	Blood urea nitrogen
CAPD	Continuous Ambulatory Peritoneal Dialysis
cccDNA	Covalently closed circular DNA
CHB	Chronic Hepatitis B
CI	Confidence Interval
Cl^-	Chloride
CLcr	Creatinine Clearance
CNS	Central Nervous System
CRF	Case Report Form
CT	Computerized Tomography
CTA	Clinical Trial Agreement
CV	Coefficient of Variation
DAIDS	Division of AIDS
D/C	Discontinue
DMC	Data Monitoring Committee

Term	Definition
DNA	Deoxyribonucleic acid
EAP	Early Access Program
EC_{50}	Effective concentration for inhibition of 50% of isolates
ESR	Expedited Safety Report
ETV	Entecavir
FDA	U.S. Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBV	Hepatitis B virus
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular Carcinoma
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HDV	Hepatitis D Virus
HIV	Human immunodeficiency virus
HPS	High Pure System
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonization
IC_{50}	Concentration which inhibits 50% of the reaction
IEC	Independent Ethics Committee
Interferon-α	Interferon Alpha
IND	Investigational New Drug

Term	Definition
INR	International Normalization Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
IU	International Units
K+	Potassium
Kg	Kilogram
KFDA	Korean Food and Drug Administration
LC/MS/MS	Liquid Chromotography - tandem mass spectrometry
LLD	lower limit of detection
LLL	lower Limit of Linearity
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantification
LTFU	Long Term Follow Up
LVD	Lamivudine
MEq/mL	Mega genome equivalents per milliliter; 1 MEq/mL = 1 million copies/mL
mg	Milligram
mL	Milliliter
Na+	Sodium
nM	Nanomolar
NR	Non-responder
Nucleos[t]ide	Nucleoside and Nucleotide
PCR	Polymerase Chain Reaction
PDR	Protocol Defined Response
PID	Subject/Patient Identification Number
pg/mL	Picograms per milliliter
PD	Pharmacodynamic
PK	Pharmacokinetic

Term	Definition
PLB	Placebo
PO	By mouth
SAE	Serious adverse event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TDF	Tenofovir
ULN	Upper Limit of Normal
USPI	United States Product Insert
μmol	Micromoles
vs	Versus
WOCBP	Women of childbearing potential
Wt	Weight

APPENDIX 1 ADDITIONAL ETHICAL CONSIDERATIONS

1 INFORMED CONSENT PROCEDURES

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

1.1 Subjects Unable to Give Written Informed Consent

1.1.1 Minors

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. (In the event that the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who

are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, eg, for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

1.1.3 Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

1.1.4 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.

In circumstances where a subject's only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for

subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

1.1.5 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.

APPENDIX 2 DAIDS TOXICITY GRADES

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

Quick Reference

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE grading table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located at the top of Page 3. For AEs that are not listed in the table but will be collected systematically for a study/trial, protocol teams are highly encouraged to define study-specific severity scales within the protocol or an appendix to the protocol. (Please see "Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-sponsored Protocols".) This is particularly important for laboratory values because the "Estimating Severity Grade" category only applies to clinical symptoms.

Grading Adult and Pediatric AEs

The DAIDS AE grading table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the table. If there is no distinction in the table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

Determining Severity Grade

If the severity of an AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

Definitions

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

Contents

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

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CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemorrhage (significant acute blood loss)		NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension					
	Adult > 17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
	Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension		NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion		Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval					
	Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
	Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

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Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

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Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

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Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	*Standard International Units are listed in italics*			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, 1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x 10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant*†, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	*Standard International Units are listed in italics*			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
URINALYSIS	*Standard International Units are listed in italics*			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

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