Official Title: Phase IIIb, Randomized, Open-Label Study of Pegylated Interferon Alfa-2A in Combination With Lamivudine or Entecavir Compared With Untreated Control Patients in Children With HBeAg Positive Chronic Hepatitis B in the Immune-Tolerant Phase

NCT Number: NCT02263079

Document Date: Protocol Version 13: 26-October-2018

PROTOCOL

TITLE: **PHASE IIIB, RANDOMIZED, OPEN-LABEL STUDY OF PEGYLATED INTERFERON ALFA-2A IN COMBINATION WITH LAMIVUDINE OR ENTECAVIR COMPARED WITH UNTREATED CONTROL PATIENTS IN CHILDREN WITH HBEAG-POSITIVE CHRONIC HEPATITIS B IN THE IMMUNE-TOLERANT PHASE**

PROTOCOL NUMBER: NV25361

VERSION NUMBER: 13

EUDRACT NUMBER: 2006-000977-31

IND NUMBER: 10,144

TEST PRODUCT: Pegasys® (RO 25 8310)

MEDICAL MONITOR: [redacted], *Ph.D.*

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 22 February 2006

DATES AMENDED:
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Version 1 (6): 2 January 2013
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Version 8: 22 August 2013
Version 9: 3 February 2014
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Version 11: 31 July 2015
Version 12: 15 February 2016
Version 13: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	26-Oct-2018 15:36:53

PROTOCOL AMENDMENT, VERSION 13: RATIONALE

The results from two multicenter clinical trials (sponsored by the National Institutes of Health [NIH]) evaluating the entecavir plus Pegasys® treatment regimen in patients with immune-tolerant chronic hepatitis B (CHB) were made available in October 2017 at the American Association for the Study of Liver Diseases Congress in Washington, USA (Rosenthal et al. 2017 [pediatric patients]; Feld et al. 2017 [adult patients]). These two NIH studies demonstrated minimal to no efficacy of the intervention in both adult and pediatric patient populations with immune-tolerant CHB. Moreover, both studies had a similar design to Study NV25361. The conclusion was that the combination of entecavir with Pegasys®, administered for up to 48 weeks, rarely led to loss of hepatitis B envelope antigen with sustained suppression of hepatitis B virus (HBV) DNA levels and was associated with frequent but not serious adverse events. The authors also concluded that more potent and more broadly targeted regimens against HBV are needed to treat children in the immune-tolerant phase of chronic HBV infection. Because of the similar study design, treatment regimen and efficacy assessments compared with these two NIH-sponsored studies, Study NV25361 is not expected to demonstrate efficacy in the target patient population.

Based on the results of the NIH pediatric study and following a Pediatric Investigational Plan (PIP) modification procedure, the PDCO agreed in March 2018 to modify the PIP for Pegasys® and remove Study NV25361 from the PIP commitments. After this decision, the Sponsor terminated recruitment in the study on 28 March 2018 after enrollment of 62 patients (26 patients had been randomized to the active combination treatment, and 3 patients had been randomized to Pegasys® monotherapy before Roche became the study sponsor). This decision to terminate recruitment was also in accordance with the recommendation from the Data Safety Monitoring Board on 22 March 2018 based on the NIH results demonstrating minimal efficacy and a changed benefit–risk assessment. No specific safety concerns were identified in their scheduled review of the study.

The protocol for Study NV25361 has been amended because of the expected lack of efficacy of the treatment regimen and the premature termination of recruitment, as follows:

- The background section on Pegasys® has been updated to summarize the recently disclosed data from the two NIH studies in patients with immune-tolerant CHB, which demonstrated minimal efficacy with a similar treatment intervention (see Section 1.2).
- The background section on Pegasys® has been updated with the results of the primary analysis of Study YV25718 in pediatric patients with immune-active CHB (see Section 1.2).
- The benefit–risk assessment has been updated (see Section 1.5).

- The protocol has been updated to reflect that recruitment into the study was prematurely terminated (see Section 1.5).
- The duration of patient follow-up has been modified from up to 5 years to 1 year after the end of treatment (see revised Figure 1). This modification is due to the low number of patients enrolled and that the small amount of data that would now be collected during the long-term follow up would limit the interpretation of any long-term effects of Pegasys®. Consequently, study objectives associated with the long-term follow-up period have been removed (see Section 2).
- Clarification has been made to highlight that the final analysis from the study will be reported when the last patient completes the last study visit at 1-year of follow up (see Sections 3.2 and 6).
- Language regarding post-study access to study drug has been removed as no clinical benefit is expected (see Section 4.3.4).
- The total volume of blood that will be collected during the study has been updated to reflect the shorter duration of the follow-up period (see Sections 4.5.1 and 4.5.1.7).
- Pharmacokinetic and anti-drug antibody sample collection has been removed (see Appendix 1B) and the planned pharmacokinetic analysis has been updated.
- The Medical Monitor of the study has changed (see Section 5.4.1).

Additional minor changes have been made to improve clarity and consistency and to align the protocol with the Sponsor's current internal guidelines and standard operating procedures. The Protocol Amendment Acceptance Form page has also been added to the document. Substantive new information appears in italics.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	***PHASE IIIB, RANDOMIZED, OPEN-LABEL STUDY OF PEGYLATED INTERFERON ALFA-2A IN COMBINATION WITH LAMIVUDINE OR ENTECAVIR COMPARED WITH UNTREATED CONTROL PATIENTS IN CHILDREN WITH HBEAG-POSITIVE CHRONIC HEPATITIS B IN THE IMMUNE-TOLERANT PHASE***
PROTOCOL NUMBER:	*NV25361*
VERSION NUMBER:	*13*
EUDRACT NUMBER:	*2006-000977-31*
IND NUMBER:	*10,444*
TEST PRODUCT:	*Pegasys® (RO 25 8310)*
MEDICAL MONITOR:	[redacted], *Ph.D.*
SPONSOR:	*F. Hoffmann-La Roche Ltd*

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature *Date*

Please return the signed original of this form as instructed by your local study monitor. Please retain a signed copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**PHASE IIIB, RANDOMIZED, OPEN-LABEL STUDY OF PEGYLATED INTERFERON ALFA-2A IN COMBINATION WITH LAMIVUDINE OR ENTECAVIR COMPARED WITH UNTREATED CONTROL PATIENTS IN CHILDREN WITH HBEAG-POSITIVE CHRONIC HEPATITIS B IN THE IMMUNE-TOLERANT PHASE**
PROTOCOL NUMBER:	NV25361
VERSION NUMBER:	13
EUDRACT NUMBER:	2006-000977-31
IND NUMBER:	10,144
TEST PRODUCT:	Pegasys® (RO 25 8310)
PHASE:	IIIb
INDICATION:	Chronic Hepatitis B
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Recruitment into the study was terminated prematurely; therefore, the data collected will be descriptively summarized. No formal statistical hypothesis testing or formal treatment group comparisons will be performed.

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of Pegasys® + lamivudine or entecavir for 48 weeks compared with an untreated control in children with CHB, as measured by loss of HBsAg 24 weeks post-treatment/end of untreated observation

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of Pegasys® + lamivudine or entecavir compared with an untreated control in children with CHB, as measured by seroconversion to anti-HBs, seroconversion to anti-HBe, loss of HBeAg, and HBV DNA levels, at 24 weeks post- treatment/end of untreated observation
- To evaluate the efficacy of Pegasys® + lamivudine or entecavir in children with CHB, as measured by seroconversion to anti-HBs, seroconversion to anti-HBe, loss of HBsAg, loss of HBeAg, HBV DNA levels, at *1 year* post-treatment

Safety Objective

The safety objective for this study is as follows:

- To evaluate the safety of the Pegasys® + lamivudine or entecavir group compared with *the* untreated control group in children with CHB, by assessment of adverse events (including neuropsychiatric assessment), laboratory test results (including thyroid function), vital signs and growth, up to 24 weeks post-treatment/end of untreated observation *and up to 1 year post-treatment*

Pharmacokinetic Objective

The pharmacokinetic objective for this study is as follows:

- To evaluate the pharmacokinetics of Pegasys® in children with CHB treated with Pegasys®+lamivudine or entecavir following administration of a body surface area (BSA)–based dosing regimen

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To explore the relationship between quantitative HBsAg/quantitative HBeAg and treatment response in children with CHB
- To explore lamivudine or entecavir viral resistance in children with CHB
- To explore the incidence of anti-drug antibodies (ADAs) in children with CHB treated with Pegasys®+lamivudine or entecavir

Study Design

Description of Study

Study NV25361 *was planned as* a randomized, controlled, parallel group, open-label, multicenter superiority study in approximately 114 children, aged 3 to less than 18 years with immune-tolerant CHB.

To allow for the varying response rates associated with different genotypes, patients will be stratified by HBV genotype A vs. B/C vs. D/other) and randomized 1:1 to one of two groups:

- Lamivudine or entecavir alone for 8 weeks followed by Pegasys®+lamivudine or entecavir for 48 weeks
- Untreated control

The screening period will be up to 6 weeks. All treated patients will be followed for *up to 1 year* after the end of treatment. Primary analysis will be performed at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80).

Pegasys® will be given subcutaneously once weekly with dosing based on BSA categories. Lamivudine or entecavir will be given as a film-coated tablet or oral solution once daily with dosing based on weight. Once the nucleoside analog is chosen, the patient must continue on that nucleoside analog throughout the study.

The study will comprise evaluation of efficacy (seroconversion to anti-HBe/anti-HBs, loss of HBeAg/HBsAg, and HBV DNA levels), safety (adverse events, laboratory abnormalities, dose modifications/discontinuations, vital signs, and growth), and pharmacokinetics (measurement of Pegasys® blood levels), as well as exploratory measures (quantitative HBsAg/HBeAg, lamivudine or entecavir viral resistance, and ADAs).

Patients will be enrolled from approximately 55 sites worldwide.

Number of Patients

n ~ 114

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Male and female patients age 3 to less than 18 years of age at baseline (12 to < 18 years of age at baseline in Russia and India)
- Positive for HBsAg and HBeAg for more than 6 months prior to baseline
- Detectable HBV-DNA (>20,000 IU/mL, as measured by PCR or hybridization) on at least 2 occasions at least one month apart with the latest determination obtained ≤42 days prior to baseline.
- Compensated liver disease (Child-Pugh Class A clinical classification)
- Either

Liver biopsy performed within 2 years prior to baseline showing no or minimal fibrosis (Liver Biopsy Scores) and stable normal ALT levels ($\leq$ upper limit of normal [ULN]) during the 6 months leading up to baseline (including two separate occasions at least 1 month apart over the 6 months prior to baseline). Screening ALT levels must be normal ($\leq$ ULN).

OR

Stable normal ALT levels ($\leq$ ULN), during the 1-year leading up to baseline (including three separate occasions at least 1 month apart over the 1 year prior to baseline) and no signs of HCC, advanced fibrosis/cirrhosis, or splenomegaly on liver abdominal ultrasound at screening. Screening ALT levels must be normal ($\leq$ ULN).

- Signed informed consent from parent/legal guardian and willingness of parent/legal guardian to abide by the requirements of the study, and signed informed consent or assent from child where appropriate. Patients $<$ 18 years of age at baseline who are legally considered to be adults according to their national legislation must consent in their own right if required.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Patients who have received investigational drugs or licensed treatments with anti-HBV activity (e.g., IFNs, lamivudine, tenofovir, emtricitabine, adefovir, entecavir, telbivudine, systemic acyclovir, systemic famciclovir) (Exception: Patients who have had a limited [$\leq$ 7-day] course of acyclovir for herpetic lesions more than 1 month before the study baseline visit are not excluded)
- Patients who have participated in any other clinical trial or who have received any investigational drug within 6 months prior to baseline
- Known hypersensitivity to IFN, Pegasys®, lamivudine, or entecavir
- BSA $<$ 0.51 m^2 (based on Mosteller formula)
- Positive test results at screening for HAV immunoglobulin M (IgM) antibody (Ab), anti-HCV Ab, anti-HDV Ab, or anti-HIV Ab
- History or other evidence of bleeding from esophageal varices
- Decompensated liver disease (e.g., Child-Pugh Class B or C clinical classification or clinical evidence such as ascites or varices)
- Advanced fibrosis or cirrhosis (assessed by liver biopsy or ultrasound)
- Suspicion of HCC on liver abdominal ultrasound (all patients to have liver abdominal ultrasound within 6 months prior to baseline)
- History or other evidence of a medical condition associated with chronic liver disease other than CHB, including metabolic liver diseases such as hemochromatosis, Wilson's disease, or α-1 anti-trypsin deficiency
- Screening alfa-fetoprotein (AFP) $\geq$ ULN
- Screening neutrophil count $< 1.5 \times 10^9$ cells/L, platelet count $< 90 \times 10^9$ cells/L, or hemoglobin $<$ lower limit of normal (LLN)
- Screening albumin of $<$ LLN or direct and indirect bilirubin of $>$ ULN (Exception: patients with non-hepatitis related factors which may elevate bilirubin such as Gilbert's disease where screening indirect bilirubin must be $\leq$ 3.0 mg/dL.)
- Evidence of renal impairment
- History of immunologically mediated disease to include, but not limited to autoimmune hepatitis, inflammatory bowel disease, idiopathic thrombocytopenic purpura, lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis, or clinical evidence of rheumatoid arthritis
- Major depression or history of psychiatric disorder, such as major psychoses, suicidal ideation, and/or suicide attempt, for which clinical trial participation would be inappropriate

- Evidence or history of chronic pulmonary or cardiac disease associated with clinically significant functional limitation
- History of thyroid disease that was poorly controlled on prescribed medications, or clinically relevant abnormal thyroid function tests (thyroid-stimulating hormone [TSH], free triiodothyronine [FT3], free thyroxin [FT4], thyroid peroxidase [TPO] antibodies, and TBG) at screening
- Poorly controlled diabetes
- History of solid organ or bone marrow transplantation
- Evidence of an active or suspected cancer or a history of malignancy in which the risk of recurrence was/is $>$20% within 2 years
- History of having received any systemic anti-neoplastic (including radiation) or immunomodulatory treatment (including systemic corticosteroids) $\leq$6 months prior to the study baseline visit or the expectation that such treatment will be needed at any time during the study (Exception: topical corticosteroids, corticosteroids prescribed as physiological replacement therapies, or short courses [$\leq$7 days] of systemic corticosteroids)
- Coagulopathy (screening international normalized ratio $>$1.5), hemoglobinopathy, hemophilia, or history of severe illness or other blood disorders that would make patient unsuitable for the study
- History of seizure disorder requiring treatment with anticonvulsant medication (excluding febrile seizures)
- History or other evidence of severe retinopathy
- History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the investigator, unsuitable for the study
- Active substance abuse within 6 months prior to screening
- Sexually active females of childbearing potential and sexually active males who are not willing to utilize effective contraceptive measures (with abstinence being considered a satisfactory method), during treatment and for 90 days following the end of treatment
- Females who are pregnant or breastfeeding. (Females of childbearing potential who have a positive urine or serum pregnancy test result at screening or at the baseline visit are excluded).

Length of Study

The study originally commenced as a single-site investigator–led study (i.e., investigator-sponsored trial [IST]) in November 2006. The length of the Roche-sponsored global multicenter study from screening of first patient to end of study will be approximately 10 years.

For treated patients, the approximate study length is *2* years and 2 months (with up to 6 weeks screening, 8 weeks of lamivudine or entecavir treatment, 48 weeks of Pegasys®+lamivudine or entecavir treatment [i.e., 56 weeks of treatment], 24 weeks of initial follow-up, *28 weeks of additional follow-up [i.e., 52 weeks total or 1 year of* follow-up*]*).

For untreated patients, the approximate study length is 1.5 years (with up to 6 weeks screening and 80 weeks untreated observation).

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) for the final analysis occurs.

LPLV for primary analysis *was planned* at 24 weeks after end of treatment/end of untreated observation is expected to occur approximately 1 year and 8 months after last patient is enrolled.

LPLV for final analysis at *1 year* after the end of treatment is expected to occur approximately *2* years and 2 months after the last patient is enrolled.

Efficacy Outcome Measures

The primary efficacy outcome measure for this study at 24 weeks post- treatment/end of untreated observation is as follows:

- Loss of HBsAg

The secondary efficacy outcome measures for this study at 24 weeks post–treatment/end of untreated observation are as follows:

- Loss of HBeAg
- Seroconversion to anti-HBs (loss of HBsAg and presence of anti-HBs)
- Seroconversion to anti-HBe (loss of HBeAg and presence of anti-HBe)
- HBV DNA < 20,000 IU/mL, < 2000 IU/mL, undetectable and change from baseline (by polymerase chain reaction [PCR] or hybridization)
- Combined endpoints: HBeAg seroconversion and HBV DNA < 20,000 IU/mL
- Combined endpoints: HBeAg seroconversion and HBV DNA < 2000 IU/mL

The secondary efficacy outcome measures for this study at $1\ year$ post-treatment are as follows:

- Loss of HBeAg
- Loss of HBsAg
- Seroconversion to anti-HBs (loss of HBsAg and presence of anti-HBs)
- Seroconversion to anti-HBe (loss of HBeAg and presence of anti-HBe)
- HBV DNA < 20,000 IU/mL< 2000 IU/mL, undetectable and change from baseline (by PCR or hybridization)
- Combined endpoints: HBeAg seroconversion and HBV DNA < 20,000 IU/mL
- Combined endpoints: HBeAg seroconversion and HBV DNA < 2000 IU/mL

Safety Outcome Measures

The safety outcome measures for this study at 24 weeks post–treatment/end of untreated observation are as follows:

- Incidence, nature, and severity of serious and non-serious adverse events (including neuropsychiatric assessment)
- Reasons for the discontinuation of any study medication
- Dose modifications for laboratory abnormalities and clinical adverse events
- Changes in vital signs and laboratory tests from screening/baseline, including thyroid function
- Effect on growth (height, weight and sexual maturity status)

The safety outcome measures for this study at $1\ year$ post–treatment are as follows:

- Incidence, nature, and severity of persisting adverse events, new-onset related serious adverse events/non-serious adverse events of special interest
- Changes in thyroid function from screening/baseline
- Effect on growth (height, weight and sexual maturity status)

Pharmacokinetic Outcome Measures

Pharmacokinetic samples will be collected from all patients treated with Pegasys® + lamivudine or entecavir for measurement of Pegasys®.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Quantitative HBsAg and quantitative HBeAg
- Presence of lamivudine or entecavir viral resistance
- Incidence of ADAs from all patients treated with Pegasys® + lamivudine or Pegasys® + entecavir

Investigational Medicinal Products

Test Product

Pegasys® for 48 weeks subcutaneously once weekly with dosing based on the following body surface area (BSA) categories:

Dose (µg)	BSA Range (m^2)
45	0.51–0.53
65	0.54–0.74
90	0.75–1.08
135	1.09–1.51
180	>1.51

Pegasys® will be used in combination with lamivudine or entecavir.

Treated patients will receive lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg), or entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks. The first dose of lamivudine or entecavir should be taken at the study site during the baseline visit. Pegasys® will be given subcutaneously once weekly with dosing based on BSA categories. Pegasys® injection instructions will be provided for the parent/legal guardian and patients, if applicable. A container will also be provided for disposal of all used needles. The first dose of Pegasys® should be taken at the study site during the Week 8 visit (after approximately 8 weeks of lamivudine or entecavir monotherapy).

Statistical Methods

Primary Analysis

The primary efficacy endpoint is defined as loss of HBsAg at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80). The number of observations, percentage of responders (response rate) and 95% CI (using the Clopper-Pearson method) for the response rate will be presented for each group.

The primary analysis *was planned as* the comparison of the response rate in the Pegasys®+lamivudine or entecavir group with that in the untreated control group. Testing of the primary endpoint *was planned as* a superiority test based on the ITT population, which *would* comprise all randomized patients who received at least one dose of study medication and patients randomized to no treatment. The test *would* be using Fisher's exact test, stratified by HBV genotype (A vs. B/C vs. D/other), and the significance level taken at 5% two-sided. Patients with missing data will be treated as non-responders. Sensitivity analyses *would* include a last observation carried forward approach for missing data. The Cochran Mantel Haenszel test stratified by genotype *would* also be provided.

Determination of Sample Size

Taking into account the comparable entecavir and lamivudine early viral kinetics and the low resistance rates observed during Pegasys®-combination therapy with entecavir or lamivudine, the efficacy of Pegasys®+lamivudine and Pegasys®+entecavir regimens in this study are expected to be comparable. The assumptions for the expected loss of HBsAg rates after 24 weeks after the end of treatment/end of untreated observation are 17% in the Pegasys®+lamivudine arm and 0.6% in the untreated control group. These assumptions are based on the observed rate on conventional Interferon in a pilot study (D'Antiga et al. 2006) and observed spontaneous rates (Hsu 1992), respectively.

With a two-sided 5% significance level, Fisher's Exact test would have 80% power to detect a difference between a treated group and untreated control with 50 evaluable patients per group. Approximately 114 patients *were planned to be* recruited (57 per group) to ensure at least 50 evaluable patients in each group.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Ab	antibody
ADA	anti-drug antibody
AE	adverse event
AFP	α-fetoprotein
anti-HBe	hepatitis B envelope antibody
anti-HBs	hepatitis B surface antibody
AUC	area under curve
BSA	body surface area
CDI	Children's Depression Inventory
CHB	chronic hepatitis B
CHC	chronic hepatitis C
CL/F	clearance
CRF	Case Report Form
CSR	clinical study report
DAIDS	Division of AIDS
DAP	data analysis plan
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assays
EU	European Union
FDA	U.S. Food and Drug Administration
FT3	free triiodothyronine
FT4	free thyroxin
G-CSF	granulocyte colony-stimulating factor
HAV	hepatitis A virus
HbeAg	hepatitis B envelope antigen
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
ICH	International Conference on Harmonization
IFN	interferon
IgM	immunoglobulin M

Abbreviation	Definition
IMC	Internal Monitoring Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IST	investigator sponsored trial
ITT	intent to treat
IxRS	interactive voice or Web response system
LLN	lower limit of normal
LPLV	last patient last visit
PCR	polymerase chain reaction
PK	pharmacokinetic
PRO	patient-reported outcome
RCR	Roche Clinical Repository
SAE	serious adverse event
SMT	Study Management Team
SVR	sustained virological response
TBG	thyroxine-binding globulin
TP	triphosphate
TPO	thyroid peroxidase
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UTC	coordinated universal time
V/F	volume of distribution
YMDD	tyrosine-methionine-aspartate-aspartate

1. BACKGROUND

1.1 BACKGROUND ON CHRONIC HEPATITIS B

Hepatitis B virus (HBV) infection is a major public health problem with an estimated 300 million hepatitis B surface antigen (HBsAg) carriers worldwide. In endemic areas like China and Africa, where the HBsAg carrier rate is as high as 15%–20%, hepatitis B is primarily a disease of childhood, acquired either perinatally from HBsAg-positive mothers or horizontally from infected mates or family members (Beasley et al. 1982; Kiire 1990). In areas of intermediate endemicity (Italy, Japan, Spain, Greece, and Portugal), where 2%–10% of the population are HBsAg carriers, infection occurs in both adults and children. In low endemicity areas, including the United Kingdom, infection during infancy and childhood is uncommon and $<$1% of the population has chronic HBV infection (Maynard et al. 1988), which usually, though not exclusively, affects ethnic minorities originating from endemic countries or travelers to endemic areas. These epidemiological data are, however, changing with the introduction of effective vaccination in some countries whereas in others, prevalence is maintained by either incomplete vaccination coverage or an increase in travel and international adoption from countries with less successful prevention strategies.

The virus is highly infectious, much more than hepatitis C virus (HCV) or HIV, and chronically infected individuals readily infect unvaccinated family members, mates, and sexual partners. The probability of becoming a chronic HBV carrier is correlated to age at infection and the efficiency of the immune system, being highest in children infected within the first year of life who tend to become “tolerant” to the virus. Thus, more than 90% of infected infants, including the 5% who do not respond to HBV vaccination, become chronic carriers, as compared with 6%–10% if the infection occurs after the 6th year of life (Chu et al. 1985; Chang et al. 1989). Chronically infected children are usually asymptomatic with normal or minimally abnormal liver function tests, but their liver histology can show progressive inflammatory changes (Bortolotti et al. 1986).

Chronic HBV infection in children is typically characterized by three phases: 1) the immune-tolerant phase, 2) the immune-active phase, and 3) the inactive carrier state. Most children with perinatally acquired HBV infection and hepatitis B envelope antigen (HBeAg)–positive disease are considered to be in the immune-tolerant phase. This phase of disease is associated with minimal or no evidence of clinical symptoms, normal ALT levels, high serum HBV DNA, and minimal activity or injury (e.g., minimal or mild inflammation and fibrosis) on liver biopsy (see Appendix 3). This phase can persist throughout childhood, with disease becoming active with consequent liver damage in a proportion of patients only later in life. Importantly, this immune-tolerant phase of the disease in childhood is when most person-to-person transmission of HBV occurs in sub-Saharan African and Mediterranean countries (Lok and McMahon 2009). The immune-active phase normally follows the immune-tolerant phase. Early in this phase, there may be high HBV DNA levels, but these may decrease to $<$10,000 copies/mL. It is characterized by varying degrees of liver inflammation and fibrosis and increased levels

of AST and ALT. Seroconversion with loss of HBeAg and production of hepatitis B envelope antibody (anti-HBeAb) may occur, leading to the next phase: the inactive carrier state. In the inactive carrier state, patients are HBeAg negative, AST and ALT levels return to normal, and HBV DNA levels remain very low.

Besides posing a serious infection risk to the community, chronically HBV infected children, particularly if male, have a high risk of progressing to cirrhosis and hepatocellular carcinoma (HCC) (Bortolotti et al. 1986; Hsu et al. 1987, 1988; de Potter et al. 1987; Leuschner et al. 1988), the likelihood of developing these complications being correlated to the length of time to achieve anti-HBe seroconversion. Spontaneous HBeAg loss in chronically infected children occurs at an annual rate of 10% -16% (Bortolotti et al. 1986; Moyes et al. 1993), whereas spontaneous loss of HBsAg is as low as 0.6% per year (Hsu et al. 1992), the children achieving earlier seroconversion being those with biochemical and/or histological evidence of active disease. Moreover, the annual HBsAg clearance rate is significantly higher in those children who are already anti-HBe positive (i.e., low viral load) than in those with HBeAg (i.e., high viral load) (1.7% vs. 0.4%).

1.2 BACKGROUND ON PEGASYS®

Roche has chemically modified the interferon alfa-2a molecule by covalently attaching a branched methoxy polyethylene glycol moiety. Pegasys® has a decreased systemic clearance rate and an approximately 10-fold increase in serum half-life compared with interferon alfa-2a; as a result, Pegasys® circulates in the blood much longer than the parent compound.

A development program exploring the use of Pegasys® in the treatment of chronic hepatitis B (CHB) was initiated with a Phase II study using 90-, 180-, and 270-μg doses of Pegasys®, which were compared against the licensed dose of conventional α-interferon (IFN) for 24 weeks of therapy (Study NV16037). This pilot trial showed a two-fold improvement in efficacy of Pegasys® over non-pegylated IFN and the 270-μg dose did not show any indication of additional benefit over the 180-μg dose. Two large Phase III studies were performed and showed that 180 μg of Pegasys® was superior to lamivudine in both HBeAg-positive and HBeAg-negative disease when assessed 24 weeks after stopping 48 weeks of therapy. Furthermore, both studies contained a third arm containing the combination of Pegasys® with lamivudine. Although this combination showed significantly greater HBV DNA suppression on treatment than lamivudine monotherapy, it did not show any improvement over Pegasys® monotherapy at 24 weeks after the end of therapy (Study WV16240, Study WV16241). These HBV studies included more than 1500 patients and led to regulatory approval of Pegasys® use in CHB in the European Union, United States, and many other countries with high incidence of HBV disease. The safety profile of 180-μg of Pegasys® in patients with CHB was no worse and possibly slightly better tolerated than in HCV patients treated with Pegasys®, particularly with regards to the incidence of depression.

The NEPTUNE study (Clinical Study Report WV19432) was a Phase IV trial that examined two doses of Pegasys® (90 and 180 μg/week), and two durations (24 and 48 weeks) in adults with HBeAg-positive chronic HBV infection. This trial incorporated a non-inferiority study design and showed that the highest response rate was achieved in the 180-μg/week, 48-week treatment group, confirming the registered dose and duration of the 180-μg/week, 48-week treatment as the most efficacious regimen. For the secondary endpoints tested, the overall trends were consistent with the primary endpoint, with the highest response rates being achieved in the 180-μg/week, 48-week treatment group. The results confirmed that the overall safety profile of Pegasys® in patients with HBeAg-positive CHB was consistent with the currently approved label, with no new signals identified.

Study YV25718 *is a prospective, open-label, randomized pediatric study* evaluating the efficacy and safety of Pegasys® monotherapy compared with untreated control in children *with immune-active,* HBeAg-positive CHB *disease. The study met the primary efficacy endpoint of HBeAg seroconversion at 24 weeks after the end of the treatment (principal) observation period. At this timepoint, 26 patients treated with Pegasys® achieved HBeAg seroconversion (25.7%; 95% CI: 17.6%, 35.4%) compared with 3 patients in the untreated control group (6%; 95% CI: 1.3%, 16.6%), which was statistically significant (p =0.0043). Safety data were consistent with the known safety profile of Pegasys® and the patient population (Wirth et al. 2018). After completion of the 24-week follow-up period, patients entered into a long-term follow-up (LTFU) period for up to 4.5 years after the study visit for the primary analysis. The study is currently ongoing.*

The present study (NV25361) aims to assess the safety and efficacy of Pegasys® in combination with lamivudine or entecavir versus untreated control, in a randomized trial evaluating treatment of the immune-tolerant pediatric HBV population.

Following pivotal Phase III Study NV17424 conducted in 114 children with HCV aged 5 to 17 years, Pegasys® is indicated in the European Union and the United States for treatment of chronic hepatitis C in treatment-naive children and adolescents 5 years of age and older with compensated liver disease. The most common adverse reactions in pediatric patients were similar to those seen in adults, with the exception of growth inhibition during the course of treatment with Pegasys® and Ribavirin (see Section 5.1.1.4). Safety and efficacy in pediatric patients younger than 5 years of age have not been established.

During the recruitment period of the present study, results from a large National Institutes of Health (NIH) study evaluating Pegasys® in combination with entecavir in 60 pediatric patients with CHB in the immune-tolerant phase were presented at the 2017 American Association for the Study of Liver Diseases (AASLD) Congress in Washington, DC (Rosenthal et al. 2017). In this study, entecavir was given for 8 weeks followed by combination therapy with entecavir and Pegasys® for an additional

40 weeks. Two of 60 patients (3%) met the primary endpoint of lack of HBeAg and HBV DNA levels less than 1000 IU/mL and also achieved HBsAg loss. HBsAg loss was achieved by 3 of 60 patients (5%) by the end of the treatment period at Week 48. The conclusion from this study was that the combination of entecavir and Pegasys®, administered for up to 48 weeks, rarely led to loss of HBeAg with sustained suppression of HBV DNA levels and was associated with frequent though not serious adverse events.

The results of a second NIH study in adults with immune-tolerant CHB, with the same design and treatment regimen as the above pediatric study, were also presented at the 2017 AASLD Congress (Feld et al. 2017). In this 28-patient adult study, no patients achieved the primary endpoint of HBeAg loss and HBV DNA levels below 1000 IU/mL. In addition, no patients achieved HBsAg loss.

See the Pegasys® Investigator's Brochure for details on nonclinical and clinical studies.

1.3 BACKGROUND ON LAMIVUDINE

Lamivudine is a potent synthetic nucleoside analog reverse transcriptase inhibitor with activity against HBV and HIV. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B. It is phosphorylated to active metabolites that compete for incorporation into viral DNA. The active metabolites inhibit the HIV/HBV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis (Epivir-HBV U.S. Package Insert). Viral resistance to lamivudine has been observed after prolonged therapy in patients infected with hepatitis B and was mapped to amino acid changes in the HBV polymerase region (tyrosine-methionine-aspartate-aspartate [YMDD or YMDD motif]) (Lai et al. 2003).

Lamivudine is currently approved for the treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation in adults, and some health authorities have approved the use of lamivudine in children and/or adolescents infected with hepatitis B (e.g., in the United States for children ≥ 2 years old); it improves the seroconversion of e–antigen-positive hepatitis B and also improves histology staging of the liver. The safety and efficacy of lamivudine in pediatric patients with HBV were evaluated in a double-blind clinical trial in 286 patients aged 2–17 years of age with elevated ALT levels (immune active phase). The combination of loss of HBeAg and reduction of HBV DNA to below the assay limit of the research assay, evaluated at Week 52, was observed in 23% of lamivudine patients and in 13% of placebo patients. Normalization of serum ALT was achieved and maintained to Week 52 more frequently in patients treated with lamivudine compared with placebo (55% vs. 13%, respectively) (Epivir-HBV U.S. Package Insert). A previous study in adult HBV population (Study WV16241) has shown no effect of lamivudine on the pharmacokinetics of Pegasys®.

For more information on lamivudine, see local prescribing information.

1.4 BACKGROUND ON ENTECAVIR

Baraclude® is the tradename for entecavir, a guanosine nucleoside analogue with activity against HBV polymerase. It is efficiently phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine TP, entecavir-TP functionally inhibits the three activities of the viral polymerase: 1) priming of the HBV polymerase, 2) reverse transcription of the negative strand DNA from the pregenomic messenger RNA, and 3) synthesis of the positive strand HBV DNA. Entecavir inhibited HBV DNA synthesis (50% reduction, EC50) at a concentration of 0.004 µM in human HepG2 cells transfected with wild-type HBV. The median EC50 value for entecavir against LVDr HBV (rtL180M and rtM204V) was 0.026 µM (range: 0.010–0.059 µM). An analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical HIV-1 isolates using a variety of cells and assay conditions yielded EC50 values ranging from 0.026 to >10 µM; the lower EC50 values were observed when decreased levels of virus were used in the assay. In cell culture, entecavir selected for an M184I substitution at micromolar concentrations, confirming inhibitory pressure at high entecavir concentrations. HIV variants containing the M184V substitution showed loss of susceptibility to entecavir fully susceptible to entecavir. (BARACLUDE® SmPC).

Entecavir is approved for the treatment of hepatitis B in adults, and, since 2014, in children of 2 years of age and older in both Europe and U.S.

Entecavir was evaluated in two clinical trials of pediatric subjects 2 years of age and older with HBeAg-positive chronic HBV infection and compensated liver disease. The exposure of entecavir in nucleoside-inhibitor, treatment-naïve, and lamivudine-experienced pediatric subjects 2 years of age and older with HBeAg-positive chronic HBV infection and compensated liver disease receiving 0.015 mg/kg (up to 0.5 mg once daily) or 0.03 mg/kg (up to 1 mg once daily), respectively, was evaluated in Study AI463028. Safety and efficacy of the selected dose in treatment-naïve pediatric subjects were confirmed in Study AI463189, a randomized, placebo-controlled treatment trial. The pharmacokinetics, safety, and antiviral activity of entecavir in pediatric subjects were initially assessed in Study AI463028. Twenty-four treatment-naïve and 19 lamivudine-experienced HBeAg-positive pediatric subjects aged 2 to less than 18 years with compensated CHB and elevated ALT were treated with entecavir 0.015 mg/kg (up to 0.5 mg) or 0.03 mg/kg (up to 1 mg) once daily. Fifty-eight percent (14/24) of treatment-naïve subjects and 47% (9/19) of lamivudine-experienced subjects achieved HBV DNA <50 IU/mL at Week 48 and ALT normalized in 83% (20/24) of treatment-naïve subjects and 95% (18/19) of lamivudine-experienced subjects.

Safety and antiviral efficacy were confirmed in Study AI463189, an ongoing study of entecavir among 180 nucleoside-inhibitor, treatment-naïve pediatric subjects 2 to less than 18 years of age with HBeAg-positive chronic hepatitis B infection, compensated liver disease, and elevated ALT. Subjects were randomized 2:1 to receive blinded

treatment with entecavir 0.015 mg/kg up to 0.5 mg/day (N = 120) or placebo (N = 60). The randomization was stratified by age group (2 to 6 years; > 6 to 12 years; and > 12 to < 18 years). Baseline demographics and HBV disease characteristics were comparable between the 2 treatment arms and across age cohorts. At study entry, the mean HBV DNA was 8.1 $\log_{10}$ IU/mL and mean ALT was 103 U/L. The primary efficacy endpoint was a composite of HBeAg seroconversion and serum HBV DNA < 50 IU/mL at Week 48 assessed in the first 123 subjects reaching 48 weeks of blinded treatment. Twenty-four percent (20/82) of subjects in the entecavir-treated group and 2% (1/41) of subjects in the placebo-treated group met the primary endpoint. Forty-six percent (38/82) of entecavir-treated subjects and 2% (1/41) of placebo-treated subjects achieved HBV DNA < 50 IU/mL at Week 48. ALT normalization occurred in 67% (55/82) of entecavir-treated subjects and 22% (9/41) of placebo-treated subjects; 24% (20/82) of entecavir-treated subjects and 12% (5/41) of placebo-treated subjects had HBeAg seroconversion.

Entecavir has a high barrier to resistance as it requires at least three codon substitutions, including rtL180M, rtM204I/V, plus a substitution at one of the following amino acids: rtT184S/G, rtS202I/G and/or rtM250V (Zoulim F, Locarnini S., 2013). Among treatment-naïve adult patients, entecavir resistance is very rare; in the long-term follow up of the international trial on HBeAg-positive and HBeAg-negative patients and in a long-term follow-up study in Hong Kong, the cumulative probability of entecavir resistance was 1.2% after 5 years of entecavir treatment (Seto et al., 2015).

No pharmacokinetic (PK) interactions between Pegasys® and entecavir have been reported.

For more information on entecavir, see local prescribing information.

1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Given the low spontaneous HBeAg/HBsAg loss and seroconversion rates observed in children infected with chronic HBV (spontaneous HBeAg loss of 10%–16% per year [Bortolotti 1986; Moyes et al.1993], spontaneous loss of HBsAg ~0.6% per year [Hsu 1992]) and the fact that spontaneous HBsAg seroconversion rates are significantly higher in those who have HBeAg seroconverted (anti HBeAg positive and lower HBV DNA viral load) than in those who have not (1.7% vs. 0.4%), any treatment that can speed up the HBeAg/HBsAg loss and seroconversion rate would avoid the long-term complications of chronic infection such as cirrhosis and cancer and have a major impact on reducing the spread of infection of Hepatitis B in the population. This would bring added benefits of reducing the stigma of carrying an infectious disease, avoiding the other potential social sequelae of impaired career choices, and reducing the impact on personal relationships/marriages. An additional consideration is that because most pediatric patients are in the immune-tolerant phase of disease, they have lower HBeAg seroconversion rates than those in the immune-active phase and therefore a lower chance of HBsAg seroconversion. Annual rates of spontaneous HBeAg seroconversion

in immune-tolerant children with CHB of 0.8% in children <6 years of age, 1.4% in children 6–11 years of age, and 5.6% in children 12–17 years of age have been reported (Park et al. 2012).

Hepatitis B virus infection in children presents a therapeutic challenge for the practitioner. Decisions regarding selection of patients who may benefit from treatment, appropriate timing of treatment, and the choice of antiviral therapy are complex and are compounded by the limited number of drugs that have been studied in children.

Current consensus statements and reviews in the treatment of HBV-infected children and adult HBV treatment guidelines (Murray et al. 2008; Kurbergov and Sokol 2009; Lok and McMahon 2009; Giacchino and Cappelli. 2010; Jonas et al. 2010; Papatheodoridis et al. 2012) favored treatment of children in the immune-active phase of pediatric HBV disease, with non-pegylated IFN-α as the first-line agent of choice (outside of clinical trials) because of the higher HBeAg seroconversion response rates achieved and higher HBsAg seroconversion rates seen in comparison with lamivudine. These recommendations have been based upon current indications for therapy in adults with chronic HBV infection since there are limited therapeutic options that have been studied and licensed for use in children. Because of the lack of robust data regarding treatment of children with CHB, this has resulted in a lack of consensus among international experts regarding the need for HBV therapy during childhood and the subsequent lack of pediatric HBV guidelines. However, these review articles agree that further studies are necessary to generate robust pediatric data. *Study YV25718 evaluated Pegasys® as a treatment for pediatric patients with* immune-active *HBV infection. This study established Pegasys® for the* treat*ment of* CHB in children and *has provided an additional* therapeutic option *for this population.*

Although the consensus statements and reviews in the treatment of HBV-infected children and adult HBV treatment guidelines (Murray et al. 2008; Kurbegov and Sokol 2009; Lok and McMahon 2009; Giacchino and Cappelli 2010; Jonas et al. 2010; Papatheodoridis et al. 2012; Terrault et al. 2015; Sarin et al. 2015) favored treatment of children in the immune-active phase of pediatric HBV disease, there is no established benefit of treatment of children in the immune-tolerant phase. Historical clinical trial data of immune-active patients suggest that patients with normal or minimally elevated ALT respond poorly to current therapies (Jonas et al. 2002), or showed lower efficacy response rates with lower ALT levels in pegylated-IFN studies (Liaw et al. 2011). Therefore, the current recommendations are not to treat immune-tolerant adult and pediatric patients with CHB.

However, two literature references from small pilot studies treating pediatric patients with CHB in the immune-tolerant phase reported results for the treatment groups showing impressive HBeAg and HBsAg loss, seroconversion, and sustained virological responses, compared with controls (D'Antiga et al. 2006; Poddar et al. 2013), but also compared with historical spontaneous loss and seroconversion rates. The rate of

HBsAg loss and hepatitis B surface antibody (anti-HBs) seroconversion reported by Poddar et al. (2013) is the highest observed in immune-tolerant children and similar if not better than that observed within treatment trials of HBV-infected children with active disease.

In the pilot study (D'Antiga et al. 2006), 23 immune-tolerant children, all infected during the first year of life and HBsAg, HBeAg, and HBV DNA positive, 17 of Asian (China and South East Asia) ethnicity, 21 with normal transaminase levels, and 15 with high viral load (HBV DNA $>$1000 pg/mL [Digene test]) at baseline, were treated for 8 weeks with lamivudine (3 mg/kg, maximum 100 mg daily), and then for 10 months with lamivudine (same dose) and Viraferon (5 Mu/m^2 subcutaneously three times per week). At the end of treatment, 19 patients (82%) were HBV DNA negative and 3 months later, 5 (22%) continued to be HBV DNA negative. All 5 (22%) seroconverted to anti-HBe during a 6-month follow-up, and 4 (17%) cleared HBsAg and become persistently anti-HBs positive (latest follow-up, 36–48 months). No patients developed resistant HBV (YMDD) mutations at the end of treatment, and the authors suggested that IFN in this regimen may protect from lamivudine-induced YMDD mutations. No serious adverse events were reported by the authors, but all patients reported influenza-like symptoms during the first few weeks of treatment. Reported adverse events comprised decreased appetite in 7 of 23 (30%) patients, epistaxis or menorrhagia in 7 of 23 (30%) patients, tiredness 5 of 23 (22%) patients, headache 4 of 23 (17%) patients, hair loss 4 of 23 (17%) patients, abdominal pain 2 of 23 (9%) patients, arthralgia 1 of 23 (4%) patients, rash 1 of 23 (4%) patients, and sleepiness 1 of 23 (4%) patients. The authors reported raised transaminases in 3 of the 5 responders, but also in 9 of 18 non-responders. Persistent loss of height but not weight was reported at 1 year after treatment, consistent with reports in HCV interferon trials.

The other pilot study examined the treatment of immune-tolerant pediatric patients with HBV using the same sequence of lamivudine followed by a combination of lamivudine and non-pegylated interferon (Poddar et al. 2013). Twenty-eight children were treated in a prospective cohort of clinic patients, and these were compared against 34 untreated controls. HBeAg seroconversion was reported in 11 of 28 (39.3%) patients in the treatment group versus 2 of 34 (5.9%) patients in the control group. Six patients (21.4%) achieved HBsAg loss 6 months after the end of treatment and remain HBsAg seroconverted after a mean follow-up period of 21.1 $\pm$ 11.9 months, compared with 0 of 34 controls. Viral resistance to lamivudine was not assessed. No serious adverse events were reported in this study, although 2 children (2 of 28 [7%]) developed leukopenia that required dose modification but not discontinuation. Other adverse events reported were fever in all patients, anorexia in 15 of 28 (54%) patients, malaise in 8 of 28 (29%) patients, and recurrent oral apthous ulcers in 1 of 28 (4%) patients. No growth effects were reported in this study.

Low response rates to treatment with IFN monotherapy have been seen in two randomized controlled trials (Lai et al. 1987, 1991) using IFN in children with CHB. Of

the 110 immune-tolerant children enrolled across the two studies, 70 received IFN and 40 received placebo. Sustained off-treatment response (from 15 to 18 months after treatment) was observed in only 3 of 70 (4%) patients and 1 of 70 (1%) patients for HBeAg and HBsAg loss, respectively in IFN group compared with 0 of 40 (0%) for both HBeAg and HBsAg in the control group. Similar findings were observed in adults with CHB (Lok et al. 1992), where 1 of 40 (2.5%) immune tolerant patients achieved HBeAg or HBsAg loss at 12 months post-end of 16-weeks of IFN treatment compared with 0 of 20 (0%) untreated immune-tolerant patients for HBeAg or HBsAg loss. Although these trials employed non-pegylated IFN (alfa-2a and alfa-2b) and shorter treatment duration (12–16 weeks), the results showed no improvement in efficacy for IFN treatment compared with control groups.

Prevalence of viral resistance to lamivudine at baseline in untreated patients has been reported from low (~1%) to high (~20%) in several studies, depending mainly on the population studied and the sequencing methodologies used to detect the resistance (Akarsu et al. 2006; Salpini et al. 2011; Lee et al. 2012; Zhao et al. 2012). Early emergence of lamivudine resistance in treated patients has not been well studied thus far, and only a few reports have been published showing lamivudine resistance emergence in some patients at the first time point analyzed, which was still 5–6 months after the beginning of treatment (Chayama et al. 1998; Zöllner et al. 2004; Natsuizaka et al. 2005). Efficacy of treating lamivudine-resistant patients with a combination of Pegasys® and lamivudine has not been widely reported: 3 patients who enrolled in Study WV16240 and for whom lamivudine resistance was detected at baseline (2 receiving the Pegasys® and lamivudine combination, and 1 receiving lamivudine monotherapy) had no detectable HBV DNA at Week 48 (CSR WV16240).

Combining the antiviral effect of lamivudine or entecavir with the immune-boosting action of IFN in sequence may be a more appropriate therapeutic approach for children, particularly in those who are less likely to respond to IFN alone because of infection at a very young age, who have normal transaminase levels, high HBV DNA and who are "tolerant" to the virus. The use of a lead-in phase consisting of 8 weeks of lamivudine or entecavir monotherapy to lower the viral load, followed by interferon-containing combination therapy that has both antiviral and immune-stimulatory effects, is hypothesized to produce better effects than previous treatment strategies on antigen loss, seroconversion rates, and sustained virological control in the immune-tolerant population.

However, during the recruitment period of the present study, the results from two NIH trials that were conducted with an 8-week, lead-in period of treatment with entecavir followed by 40 weeks of treatment with entecavir plus Pegasys® showed minimal efficacy for this intervention in both pediatric and adult patients with immune-tolerant CHB (see Section 1.2). The available data together suggest that this novel strategy of sequential use of a nucleoside analogue followed by the combination of this nucleoside analogue with an interferon is *not* a *suitable* strategy for *the* management of pediatric

immune-tolerant HBV disease. *The* data *from both studies* showed *a minimal* chance *for* both HBeAg and HBsAg loss and seroconversion through lowering viral load in patients.

The adverse event profile of interferons is predictable, well established, and clinically manageable. Adverse events reported in the literature with combination therapy (nucleoside analogues and IFN) in children are commonly associated with interferon treatment, and include fever, influenza-like symptoms, fatigue, depression, thyroid dysfunction, and bone marrow toxicity with no evidence of nucleoside resistance detected. Effects on growth have been reported in a proportion of patients, and this is class effect reported with all interferons (see Section 5.1.1.4).

The incorporation of a pegylated interferon into this combination regimen would be expected to provide much improved tolerability for pediatric patients (one weekly injection compared with three weekly injections), in addition to more reliable exposures, and no change in the adverse event profile.

The primary efficacy endpoint for Study NV25361 is HBsAg loss, which is the "ideal endpoint of treatment in patients with CHB with or without seroconversion to anti-HBs" (Papatheodoridis et al.2012).

Based on an evaluation of the *recently disclosed data from the NIH, as well as data from* other *previous studies, the Sponsor considers that the NIH trial provides a more relevant and reliable assessment* of *the efficacy* of Pegasys® in *combination with a nucleoside analogue in pediatric patients with CHB in the* immune-tolerant *stage. Study NV25361 is expected to show similar efficacy results* to *those of* the *two NIH studies and the likelihood of patients achieving HBsAg loss is anticipated to be minimal. Therefore, the expected benefit–risk profile has changed* in the immune-tolerant population *treated with Pegasys® in combination with nucleoside analogue. The minimal treatment benefit that is now expected should be weighed against the known* risks *related to Pegasys® and nucleoside analogue treatment.*

The assessment of current guidelines is that there is no urgency for treatment *intervention in patients with immune-tolerant CHB because of the low risk of disease progression and the minimal or no liver necroinflammation. Moreover, patients in this phase of the disease can afford to wait for better treatment options with new agents that will become available in the near future (Sokal et al. 2013).*

For these reasons the Sponsor has prematurely terminated recruitment into Study NV25361. This decision was in accordance with the recommendation from the Data Safety Monitoring Board (DSMB) on 22 March 2018 to terminate recruitment on the basis of low efficacy and a changed benefit–risk assessment in light to the NIH studies, although no specific safety concerns were identified in their scheduled review of the study.

2. OBJECTIVES

Recruitment into the study was terminated prematurely (see Section 1.5); therefore, the data collected will be descriptively summarized. No formal statistical hypothesis testing or formal treatment group comparisons will be performed.

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of Pegasys® + lamivudine or entecavir for 48 weeks compared with an untreated control in children with CHB, as measured by loss of HBsAg 24 weeks post-treatment/end of untreated observation

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of Pegasys® + lamivudine or entecavir compared with an untreated control in children with CHB, as measured by seroconversion to anti-HBs, seroconversion to anti-HBe, loss of HBeAg, and HBV DNA levels, at 24 weeks post- treatment/end of untreated observation
- To evaluate the efficacy of Pegasys® + lamivudine or entecavir in children with CHB, as measured by seroconversion to anti-HBs, seroconversion to anti-HBe, loss of HBsAg, loss of HBeAg, HBV DNA levels, at *1 year* post-treatment

2.2 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To evaluate the safety of the Pegasys® + lamivudine or entecavir group compared with *the* untreated control group in children with CHB, by assessment of adverse events (including neuropsychiatric assessment), laboratory test results (including thyroid function), vital signs and growth, up to 24 weeks post-treatment/end of untreated observation *and up to 1 year post-treatment*

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic objective for this study is as follows:

- To evaluate the pharmacokinetics of Pegasys® in children with CHB treated with Pegasys® + lamivudine or entecavir following administration of a body surface area (BSA)–based dosing regimen

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore the relationship between quantitative HBsAg/quantitative HBeAg and treatment response in children with CHB
- To explore lamivudine or entecavir viral resistance in children with CHB
- To explore the incidence of anti-drug antibodies (ADAs) in children with CHB treated with Pegasys® + lamivudine or entecavir

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

Study NV25361 *was planned as* a randomized, controlled, parallel group, open-label, multicenter superiority study in approximately 114 children, aged 3 to less than 18 years with immune-tolerant CHB.

To allow for the varying response rates associated with different genotypes, patients will be stratified by HBV genotype A vs. B/C vs. D/other) and randomized 1:1 to one of two groups (see Figure 1):

- Lamivudine or entecavir alone for 8 weeks followed by Pegasys®+lamivudine or entecavir for 48 weeks
- Untreated control

The screening period will be up to 6 weeks. All treated patients will be followed for *up to 1 year* after the end of treatment. Primary analysis will be performed at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80).

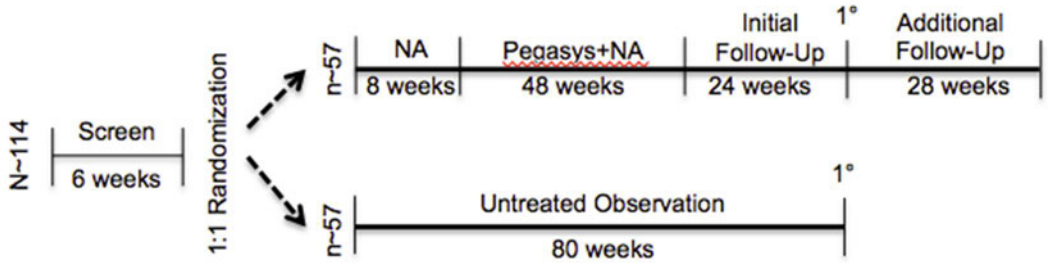
Pegasys® will be given subcutaneously once weekly with dosing based on BSA categories. Lamivudine or entecavir will be given as a film-coated tablet or oral solution once daily with dosing based on weight. Once the nucleoside analog is chosen, the patient must continue on that nucleoside analog throughout the study.

The study will comprise evaluation of efficacy (seroconversion to anti-HBe/anti-HBs, loss of HBeAg/HBsAg, and HBV DNA levels), safety (adverse events, laboratory abnormalities, dose modifications/discontinuations, vital signs, and growth), and pharmacokinetics (measurement of Pegasys® blood levels), as well as exploratory measures (quantitative HBsAg/HBeAg, lamivudine or entecavir viral resistance, and ADAs).

Patients will be enrolled from approximately 55 sites worldwide.

A schedule of assessments is provided in Appendix 1.

Figure 1 Schematic of Study Design



NA = nucleoside analog (lamivudine or entecavir).

Notes: The primary endpoint will be measured at 24 weeks after the end of the treatment period or the end of the untreated observation period.

3.1.2 Length of Study

The study originally commenced as a single-site investigator–led study (i.e., investigator-sponsored trial [IST]) in November 2006. The length of the Roche-sponsored global multicenter study from screening of first patient to end of study will be approximately 10 years.

For treated patients, the approximate study length is 2 years and 2 months (with up to 6 weeks screening, 8 weeks of lamivudine or entecavir treatment, 48 weeks of Pegasys® + lamivudine or entecavir treatment [i.e., 56 weeks of treatment], 24 weeks of initial follow-up, *28 weeks of additional follow-up [i.e., 52 weeks total or 1 year of* follow-up*]*).

For untreated patients, the approximate study length is 1.5 years (with up to 6 weeks screening and 80 weeks untreated observation).

3.1.3 Data Safety Monitoring Board

An external DSMB will periodically review accrued safety data approximately every 6 months on an advisory basis. A separate DSMB Charter will be prepared that will define the DSMB membership and role, meeting outlines and schedule, communication plan, and data outputs to be provided to the DSMB.

3.1.4 Internal Monitoring Committee

To enhance safety monitoring in this study, an Internal Monitoring Committee (IMC) will review safety data on a routine basis (IMC Agreement).

The IMC will be an internal committee comprising study team members: Biostatistician, Drug Safety Scientist, Statistical Programming Analyst, and Clinical Scientist. The IMC will review the accumulating safety data for in this study population according to a predefined schedule.

A separate IMC Agreement will be prepared, which defines the roles and responsibilities of the IMC, including its membership, scope, the timing of meetings, and communication plan.

3.1.5 Patients Previously Randomized to Investigator-Sponsored Trials including Pegasys® Monotherapy Group

The study originally commenced as a single-site IST with three arms (i.e., Pegasys® monotherapy, Pegasys® + lamivudine, and untreated control). Safety data will be collected from all patients previously randomized to the IST; all other data will be collected only from those patients who subsequently consent to allow Roche to analyze those data. In addition, any patients who have not yet completed the study will be asked to consent to continue in the Roche-sponsored study.

Some differences exist between the IST Schedule of Assessments (Protocol NV25361, Version 5) and the Roche-sponsored study Schedule of Assessments, including certain assessments required as part of the IST study that were not required as part of the Roche-sponsored study. However, all data collected on patients as part of the IST study, which are also part of assessments defined in the Roche-sponsored study, will be recorded in the Roche electronic Case Report Form (eCRF). Certain assessments included in the Roche-sponsored study may not have been undertaken as part of the IST (e.g., PK and ADA), hence data on these assessments will not be available for previous IST patients and will not be collected from previous IST patients continuing in the Roche-sponsored study.

Patients in the Pegasys®+lamivudine arm will follow the current protocol Schedule of Assessments for their remaining visits, with the caveats mentioned above. All patients in the untreated have now completed the study, per the Roche-sponsored study design.

Any patient who was randomized to the Pegasys® monotherapy treatment arm under the IST and continuing in the Roche-sponsored study (all of whom have now completed treatment) will follow the Pegasys® monotherapy follow-up Schedule of Assessments in Appendix 1 for their remaining visits. Where possible, the Pegasys® monotherapy Schedule of Assessments in Appendix 1, is consistent with the original IST Schedule of Assessments (Protocol NV25361, Version 5), while also incorporating differences required by the Roche-sponsored study. Details on how these data will be reported will be described in the data analysis plan (DAP).

All laboratory data collected for patients to date as part of the IST have been collected by a local laboratory; local laboratory ranges will be provided to Roche.

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) for the final analysis occurs.

LPLV for primary analysis *was planned* at 24 weeks after end of treatment/end of untreated observation is expected to occur approximately 1 year and 8 months after last patient is enrolled.

LPLV for final analysis at *1 year* after the end of treatment is expected to occur approximately *2* years and 2 months after the last patient is enrolled.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Test Product Dosage

The NEPTUNE study (Study WV19432) was a Phase IV trial that examined two doses of Pegasys® (90 and 180 μg/wk) and two durations (24 and 48 weeks) in adults with HBeAg-positive chronic HBV infection. This trial incorporated a non-inferiority study design and demonstrated that the highest response rate was achieved in the 180-μg/48-week treatment group, confirming the registered dose and duration of 180-μg and 48-week treatment as the most efficacious regimen. For the secondary endpoints tested, the overall trends were consistent with the primary endpoint, with the highest response rates being achieved in the 180-μg/48-week treatment group. The results confirmed that the overall safety profile of Pegasys® in patients with HBeAg-positive CHB was consistent with the currently approved label, with no new signals identified. The dose confirmed by the NEPTUNE study has been modified for pediatric use in order to achieve similar exposures to the adult dosing of 180-μg (see Section 3.3.1.1).

The present study aims to evaluate the efficacy and safety of treating children with immune-tolerant CHB disease in an open-label, randomized study of Pegasys® + lamivudine or entecavir compared with untreated control in children with HBeAg-positive CHB. Therapy duration in the treatment arm is based on those used in the 2 pilot studies where this particular treatment strategy was first tested and benefit shown (D'Antiga et al. 2006; Poddar et al. 2013).

3.3.1.1 Pediatric Dosing

This study will use the dose and duration of PEG-IFN established in the NEPTUNE study but modified for pediatric use. Study NR16141 (Schwarz et al. 2006) demonstrated that adequate levels of PEG-IFN were achieved in a PK/PD study involving 14 children between 2 and 8 years of age infected with CHC when a PEG-IFN dose of 180 μg/1.73 $m^2 \times$ BSA was used for 48 weeks of treatment. When pediatric PK data were compared with PK data in adults, it was revealed that mean predicted exposure (area under the curve [AUC_{0-t}]) to PEG-IFN in children was 25%–70% higher than that observed in adults receiving a weekly dose of 180-μg of PEG-IFN (5,667 ng • h/mL vs. a range of mean values from 3,334 to 4,348 ng • h/mL). There was a higher incidence of neutropenia in children compared with adults, which may reflect the higher exposure in children. However, predicted exposures in children were still within the range of individual adult exposures reported (maximum exposure of

11,125 ng • h/mL), decreases in neutrophil counts reversed after the end of treatment, no patients had neutrophil counts less than 0.25×10^9 cells/L, and neutropenia events were not associated with serious infections or premature withdrawal and were clinically manageable with appropriate dose modification. In addition, dose modifications appeared to have no impact on sustained virological response (SVR), indicating that dosing may be slightly reduced to improve exposure-related adverse events while maintaining viral response.

The dosing regimen for this study is based on formula dosing of 180 μg/1.73 $m^2 \times$ BSA used in the pivotal Phase III HCV pediatric study (Study NV17424) and in the PK/PD Study NR16141 (Schwarz et al. 2006). BSA categories, based on the formula 180 μg/1.73 $m^2 \times$ BSA, have been provided to facilitate the calculation of the dose by clinicians and to minimize the risk of dosing errors (see Table 1).

This approach has been accepted by the EMA for Pegasys® pediatric dosing in HCV disease (EMEA-000298-PIP01-08). This also aligns with the approved Pegasys® pediatric prescribing information in the United States, where the dose for children between the ages of 5 and 18 years is 180 μg × BSA/1.73 m^2. Utilizing the same dosing regimen and the same BSA categories will help align pediatric dose recommendations for Pegasys® across both HCV and HBV indications.

Since it has been established that there are no differences in the dosing regimen between hepatitis C versus and hepatitis B in adults, no differences are anticipated in the pediatric doses for the two indications. Based on this assumption, it is reasonable to use the same bridging approach employed in treatment of HCV from adult to pediatric doses for hepatitis B. The doses resulting from the BSA categories have deviations from −20% to +19% from the formula dose. This difference in doses relative to the formula dose is similar to the deviation in several adult HCV studies (−17% to +24%). The range of deviation in adults is computed from the variance resulting from a fixed dose given to adult patients of various sizes (BSAs) participating in six HCV clinical trials with Pegasys®. It is calculated by comparing the ratio of the 180 μg dose per adult BSA of the 5th and 95th percentile adult BSA (n = 1940) to the reference (180/median adult BSA).

Table 1 Pegasys® Pediatric Dosing Regimen

Dose (μg)	BSA Range (m^2)
45	0.51–0.53
65	0.54–0.74
90	0.75–1.08
135	1.09–1.51
180	>1.51

The pediatric lamivudine dose of 3-mg/kg/day used in HBV was established in 2−12 year old children when this dose showed maximal antiviral effects in a dose-ranging study evaluating the pharmacokinetics, safety and efficacy of lamivudine monotherapy (Sokal et al. 2000). In this study, adolescents from 12 years of age received 100 -mg daily doses. Therefore, the recommended pediatric dosing is 3 mg/kg (maximum of 100 mg daily).

The recommended once-daily dose of entecavir in pediatric patients weighing at least 10 kg is presented in Table 2. Patients may be dosed with or without food. The oral solution should be used for patients with body weight less than 32.6 kg. Pediatric patients with body weight of at least 32.6 kg should be administered 10 mL (0.5 mg) of the oral solution or one 0.5 mg tablet once daily (BARACLUDE® SmPC).

Table 2 Entecavir Dosing for Nucleoside Naïve Pediatric Patients Aged 2 to < 18 Years

Body Weight [a]	Recommended Once Daily Dose of Oral Solution [b]
10.0 – 14.1 kg	4.0 mL
14.2 – 15.8 kg	4.5 mL
15.9 – 17.4 kg	5.0 mL
17.5 – 19.1 kg	5.5 mL
19.2 – 20.8 kg	6.0 mL
20.9 – 22.5 kg	6.5 mL
22.6 – 24.1 kg	7.0 mL
24.2 – 25.8 kg	7.5 mL
25.9 – 27.5 kg	8.0 mL
27.6 – 29.1 kg	8.5 mL
29.2 – 30.8 kg	9.0 mL
30.9 – 32.5 kg	9.5 mL
At least 32.6 kg	10 mL

[a] Body weight should be rounded to the nearest 0.1 kg

[b] Children with body weight at least 32.6 kg should receive 10 mL (0.5 mg) or oral solution or one 0.5 mg tablet once daily

3.3.2 Rationale for Patient Population

Hepatitis B is a major public health problem, with infected children being at risk of serious complications in later life as well as posing a risk of spread of infection to others. Most children with chronic HBV are in the immune-tolerant phase of infection and have high viral loads as well as no or minimal signs of liver disease.

Historically, the consensus among clinicians has been to avoid treating children infected with certain baseline characteristics (e.g., patients with normal transaminase levels, high HBV DNA, or mild changes on liver biopsy) on the grounds that the published results in these children did not justify the cost and the particularly demanding nature of non-pegylated IFN treatment (i.e., three injections per week) (Jara and Bortolotti 1999). However, despite the low reported rates of success historically using IFN and/or lamivudine treatment in immune-tolerant HBV patients, two small studies (D'Antiga et al. 2006; Poddar et al. 2013) have shown impressive HBeAg and HBsAg seroconversion and sustained virological responses, both compared with controls and compared historical spontaneous seroconversion rates, when sequential and then combination therapy using non-pegylated interferon and lamivudine were evaluated. These data suggest this novel strategy is a promising alternative strategy for management of pediatric immune-tolerant HBV disease, since an increased chance of

both HBeAg and HBsAg seroconversion through lowering viral load in a proportion of patients has been reported in both studies.

Any treatment that can speed up the HBeAg/HBsAg loss and seroconversion rate would avoid the long-term complications of chronic infection such as cirrhosis, cancer, and have a major impact on reducing the spread of infection of hepatitis B in the population. Successful treatment in the immune-tolerant population would bring added benefits of reducing the stigma of carrying an infectious disease, and would avoid the other potential social sequelae of impaired career choices, and an impact on personal relationships/marriages.

3.3.3 Rationale for Untreated Control Group

This study will use an untreated control group in order to assess the benefit-risk balance of anti-HBV treatment in this immune-tolerant population, across a treated group (Pegasys® and lamivudine or entecavir sequential combination) versus an untreated observation control group.

An untreated control will be used, because the use of a placebo control is not considered appropriate for several reasons. First, the use of placebo injections would not effectively blind treatment, because the known adverse effects of IFN therapy would not occur, particularly influenza-like illness. It would therefore be likely that patients/parents would become aware the patient is not receiving IFN resulting in a potential risk of noncompliance. Secondly, it would be unethical to administer weekly placebo injections for 48 weeks, because there is an associated risk of injection-site infections without any associated benefit. A further benefit of using an untreated control arm is that the study burden for the untreated patients is reduced because their visit schedule is less frequent compared with that of the treated patients, which they would have to match in a placebo-controlled study. Importantly, an open–label study design does not introduce significant bias in the primary analyses, because the primary efficacy endpoints are objective and unaffected by presence of blinding. The risk of bias being introduced is further minimized with current procedures, including use of a central randomization, use of a central laboratory and standardized assays, and the choice of intent-to-treat (ITT) population for the primary analysis.

Because treatment up until now has been reserved for those with immune-active HBV disease, there is no standard-of-care therapy for the immune-tolerant HBV population (Murray et al. 2008; Kurbegov and Sokol 2009; Jonas et al. 2010). Therefore, any evaluation of treatment strategies requires a comparison with an untreated control in order to clearly assess the benefit risk of the treatment strategy. Use of an untreated control group has advantages over use of a historical control since randomization can reduce differences in baseline factors, and provide a robust assessment of the benefit risk of the treatment, thereby increasing the chance that the research question will be satisfactorily answered. The untreated control group will not be at any disadvantage as treatment of pediatric patients is not normally required in this group.

The analysis *planned* a superiority assessment of loss of HBsAg of sequential combination Pegasys® + lamivudine or entecavir treatment against the control group. The study design *allowed* a comparison of various serological and virological markers across the groups during treatment and at the primary endpoint.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The primary efficacy outcome measure for this study at 24 weeks post- treatment/end of untreated observation is as follows:

- Loss of HBsAg

The secondary efficacy outcome measures for this study at 24 weeks post–treatment/end of untreated observation are as follows:

- Loss of HBeAg
- Seroconversion to anti-HBs (loss of HBsAg and presence of anti-HBs)
- Seroconversion to anti-HBe (loss of HBeAg and presence of anti-HBe)
- HBV DNA < 20,000 IU/mL, < 2000 IU/mL, undetectable and change from baseline (by polymerase chain reaction [PCR] or hybridization)
- Combined endpoints: HBeAg seroconversion and HBV DNA < 20,000 IU/mL
- Combined endpoints: HBeAg seroconversion and HBV DNA < 2000 IU/mL

The secondary efficacy outcome measures for this study at *1 year* post-treatment are as follows:

- Loss of HBeAg
- Loss of HBsAg
- Seroconversion to anti-HBs (loss of HBsAg and presence of anti-HBs)
- Seroconversion to anti-HBe (loss of HBeAg and presence of anti-HBe)
- HBV DNA < 20,000 IU/mL< 2000 IU/mL, undetectable and change from baseline (by PCR or hybridization)
- Combined endpoints: HBeAg seroconversion and HBV DNA < 20,000 IU/mL
- Combined endpoints: HBeAg seroconversion and HBV DNA < 2000 IU/mL

3.4.2 Safety Outcome Measures

The safety outcome measures for this study at 24 weeks post–treatment/end of untreated observation are as follows:

- Incidence, nature, and severity of serious and non-serious adverse events (including neuropsychiatric assessment)
- Reasons for the discontinuation of any study medication
- Dose modifications for laboratory abnormalities and clinical adverse events

- Changes in vital signs and laboratory tests from screening/baseline, including thyroid function
- Effect on growth (height, weight and sexual maturity status)

The safety outcome measures for this study at $1\ year$ post–treatment are as follows:

- Incidence, nature, and severity of persisting adverse events, new-onset related serious adverse events/non-serious adverse events of special interest
- Changes in thyroid function from screening/baseline
- Effect on growth (height, weight and sexual maturity status)

3.4.3 Pharmacokinetic Outcome Measures

Pharmacokinetic samples will be collected from all patients treated with Pegasys®+lamivudine or entecavir for measurement of Pegasys®.

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Quantitative HBsAg and quantitative HBeAg
- Presence of lamivudine or entecavir viral resistance
- Incidence of ADAs from all patients treated with Pegasys®+lamivudine or Pegasys®+entecavir

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients in this study will be children 3 to less than 18 years of age with immune-tolerant CHB of any genotype, with positive HBsAg and HBeAg, and detectable HBV DNA (>20,000 IU/mL). Patients who have had any previous anti-HBV treatment, or who are co-infected with hepatitis A virus (HAV), HCV, hepatitis D virus (HDV), HIV, or who have decompensated liver disease will be excluded.

During study conduct, the Sponsor may postpone or stop the enrollment of patients in certain age ranges in order to ensure that a broad age distribution and representative dosing categories be adequately studied.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Male and female patients age 3 to less than 18 years of age at baseline (12 to<18 years of age at baseline in Russia and India)
- Positive for HBsAg and HBeAg for more than 6 months prior to baseline
- Detectable HBV-DNA (>20,000 IU/mL, as measured by PCR or hybridization) on at least 2 occasions at least one month apart with the latest determination obtained ≤42 days prior to baseline.

- Compensated liver disease (Child-Pugh Class A clinical classification [see Appendix 2])
- Either

  Liver biopsy performed within 2 years prior to baseline showing no or minimal fibrosis (Liver Biopsy Scores [see Appendix 3]) and stable normal ALT levels (≤ upper limit of normal [ULN]) during the 6 months leading up to baseline (including two separate occasions at least 1 month apart over the 6 months prior to baseline). Screening ALT levels must be normal (≤ ULN).

  OR

  Stable normal ALT levels (≤ ULN), during the 1-year leading up to baseline (including three separate occasions at least 1 month apart over the 1 year prior to baseline) and no signs of HCC, advanced fibrosis/cirrhosis, or splenomegaly on liver abdominal ultrasound at screening. Screening ALT levels must be normal (≤ ULN).

- Signed informed consent from parent/legal guardian and willingness of parent/legal guardian to abide by the requirements of the study, and signed informed consent or assent from child where appropriate. Patients < 18 years of age at baseline who are legally considered to be adults according to their national legislation must consent in their own right if required.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Patients who have received investigational drugs or licensed treatments with anti-HBV activity (e.g., IFNs, lamivudine, tenofovir, emtricitabine, adefovir, entecavir, telbivudine, systemic acyclovir, systemic famciclovir) (Exception: Patients who have had a limited [≤ 7-day] course of acyclovir for herpetic lesions more than 1 month before the study baseline visit are not excluded)
- Patients who have participated in any other clinical trial or who have received any investigational drug within 6 months prior to baseline
- Known hypersensitivity to IFN, Pegasys®, lamivudine, or entecavir
- BSA < 0.51 m^2 (based on Mosteller formula; see Appendix 4)
- Positive test results at screening for HAV immunoglobulin M (IgM) antibody (Ab), anti-HCV Ab, anti-HDV Ab, or anti-HIV Ab
- History or other evidence of bleeding from esophageal varices
- Decompensated liver disease (e.g., Child-Pugh Class B or C clinical classification [see Appendix 2] or clinical evidence such as ascites or varices)
- Advanced fibrosis or cirrhosis (assessed by liver biopsy or ultrasound)
- Suspicion of HCC on liver abdominal ultrasound (all patients to have liver abdominal ultrasound within 6 months prior to baseline)

- History or other evidence of a medical condition associated with chronic liver disease other than CHB, including metabolic liver diseases such as hemochromatosis, Wilson's disease, or α-1 anti-trypsin deficiency
- Screening alfa-fetoprotein (AFP) $\geq$ ULN
- Screening neutrophil count $< 1.5 \times 10^9$ cells/L, platelet count $< 90 \times 10^9$ cells/L, or hemoglobin $<$ lower limit of normal (LLN)
- Screening albumin of $<$ LLN or direct and indirect bilirubin of $>$ ULN (Exception: patients with non-hepatitis related factors which may elevate bilirubin such as Gilbert's disease where screening indirect bilirubin must be ≤ 3.0 mg/dL.)
- Evidence of renal impairment
- History of immunologically mediated disease to include, but not limited to autoimmune hepatitis, inflammatory bowel disease, idiopathic thrombocytopenic purpura, lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis, or clinical evidence of rheumatoid arthritis
- Major depression or history of psychiatric disorder, such as major psychoses, suicidal ideation, and/or suicide attempt, for which clinical trial participation would be inappropriate
- Evidence or history of chronic pulmonary or cardiac disease associated with clinically significant functional limitation
- History of thyroid disease that was poorly controlled on prescribed medications, or clinically relevant abnormal thyroid function tests (thyroid-stimulating hormone [TSH], free triiodothyronine [FT3], free thyroxin [FT4], thyroid peroxidase [TPO] antibodies, and TBG) at screening
- Poorly controlled diabetes
- History of solid organ or bone marrow transplantation
- Evidence of an active or suspected cancer or a history of malignancy in which the risk of recurrence was/is $>$ 20% within 2 years
- History of having received any systemic anti-neoplastic (including radiation) or immunomodulatory treatment (including systemic corticosteroids) ≤ 6 months prior to the study baseline visit or the expectation that such treatment will be needed at any time during the study (Exception: topical corticosteroids, corticosteroids prescribed as physiological replacement therapies, or short courses [≤ 7 days] of systemic corticosteroids)
- Coagulopathy (screening international normalized ratio > 1.5), hemoglobinopathy, hemophilia, or history of severe illness or other blood disorders that would make patient unsuitable for the study
- History of seizure disorder requiring treatment with anticonvulsant medication (excluding febrile seizures)
- History or other evidence of severe retinopathy

- History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the investigator, unsuitable for the study
- Active substance abuse within 6 months prior to screening
- Sexually active females of childbearing potential and sexually active males who are not willing to utilize effective contraceptive measures (with abstinence being considered a satisfactory method), during treatment and for 90 days following the end of treatment
- Females who are pregnant or breastfeeding. (Females of childbearing potential who have a positive urine or serum pregnancy test result at screening or at the baseline visit are excluded).

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. Assignment to study arms will be performed by use of an interactive voice or web-based response system (IxRS). Patients will be stratified by HBV genotype A vs. B/C vs. D/other and randomized in a 1:1 ratio.

The choice of nucleoside analog (lamivudine or entecavir) to be used in combination with Pegasys® (if applicable) will be made by the investigator and prior to the assignment to study arms by IxRS. Once the nucleoside analog is chosen, the patient must continue on that nucleoside analog throughout the study (8-week lead-in phase and the subsequent 48-week Pegasys®-combination phase).

Although this study is open-label, dummy randomization groups will be assigned in a ratio 2:1 for the development of statistical outputs to limit availability of aggregated data summaries during study conduct.

As of 28 March 2018, recruitment into the study was terminated and no additional patients have been randomized.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Pegasys®

Formulation: 180 µg/mL; 1 mL solution in 2-mL vials

Packaging: Two vials of Pegasys® will be packed per box

Storage: Refrigerate at 2°C–8°C (36°F–46°F).

For further details, see the local prescribing information for Pegasys®.

4.3.1.2 Lamivudine Tablets

Formulation: 100 mg tablets

Packaging: Each kit will contain one blister pack with 14 tablets.

Storage: Do not store above 30°C (86°F).

Oral Solution

Formulation: 10 mg/mL oral solution

Packaging: Each kit will contain one bottle with 240 mL oral solution, one syringe adapter, and one 10 mL oral dosing syringe.

Storage: Do not store above 25°C (77°F).

For further details, see the local prescribing information for lamivudine.

4.3.1.3 Entecavir

Tablets

Formulation: 0.5 mg film-coated tablets

Packaging: Each kit will contain blistered pack with 10 tablets.

Storage: Do not store above 30 °C (86 °F).

Oral Solution

Formulation: 0.05 mg/mL oral solution

Packaging: Each kit will contain one bottle with 210 mL oral solution, with a measuring spoon.

Storage: Do not store above 30 °C (86 °F). Keep the bottle in the outer carton in order to protect from light.

For further details, see the local prescribing information for entecavir.

4.3.2 Dosage, Administration, and Compliance

Treated patients will receive lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks. A single nucleoside analogue (lamivudine or entecavir) must be administered throughout the study treatment period and must not be used interchangeably. The first dose of lamivudine or entecavir should be taken at the study site during the baseline visit. Pegasys® will be given subcutaneously once weekly with dosing based on BSA categories. Pegasys® injection instructions will be provided for the parent/legal guardian and patients, if applicable. A container will also be provided for disposal of all used needles. The first dose of

Pegasys® should be taken at the study site during the Week 8 visit (after approximately 8 weeks of lamivudine or entecavir monotherapy).

Prior to starting treatment and at the time points indicated in the Schedule of Assessments (see Appendix 1), a system will be in place to confirm the patient's intended dose of Pegasys® based on the patient's weight and height provided by the investigator. Investigators may reassess the patient's dose at other interim time points if they are concerned that the BSA and therefore Pegasys® dose may have changed (see Appendix 4).

As for Pegasys®, investigators may reassess the patient's dose of lamivudine or entecavir at other interim time points if they are concerned that weight and therefore lamivudine or entecavir dose may have changed (see Appendix 4).

Each patient will be provided with a medication diary. It is mandatory that each weekly Pegasys® injection is recorded in the diary (date and volume/dose) and initialed by the person administering the treatment. Any modified/missed doses of Pegasys®, lamivudine, or entecavir must be recorded in the diary, including the reason. Patients must bring completed drug diaries to each visit during the treatment period and it will be reviewed by the investigator. Each modified/missed dose of Pegasys®, lamivudine or entecavir must be entered onto the eCRF.

All trial medication should be returned at the next scheduled visit (see Appendix 1) and reconciled against the patient's diary. The quantities returned should be documented in the drug accountability forms. Please note that any unused lamivudine or entecavir blister pack or bottles can be redispensed if unopened and will not expire. Please note that once a lamivudine bottle is opened it should not be used after 30 days. A new bottle should be opened and used.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 4.6.1.2 and Appendix 4.

4.3.3 Study Treatment Accountability

All study treatments required for completion of this study (Pegasys® and lamivudine or entecavir) will be provided by the Sponsor. The investigational site will acknowledge receipt of study treatments, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Study treatments will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of study treatment destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any study treatment is destroyed, and study treatment destruction must be documented on the appropriate form.

Accurate records of all study treatments received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 *Continued* Access to Pegasys®

The Sponsor does not have any plans to provide the Roche IMP Pegasys® or any other study treatments or interventions to patients who have completed the study.

4.3.4.1 Patients who Become Immune Active

Patients treated in the active arm of the study and untreated control patients who complete the study and subsequently meet the criteria for immune-active disease (sustained ALT elevation for at least 6 months), should be managed per investigators judgment and standard of care.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient up to follow-up Week 24/end of untreated observation. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF, including any significant concomitant medications taken within 2 years prior to baseline.

During follow-up of treated patients (i.e., after follow-up Week 24), only concomitant medications for CHB need to be recorded, which includes licensed or investigational immunomodulatory or antiviral therapy, and herbal, botanical, and other agents (e.g., ursodeoxycholic acid) that are traditionally used for CHB.

Topical corticosteroids, or corticosteroids prescribed as physiological replacement therapies are permitted.

Short courses (≤7 days) of systemic corticosteroids are permitted.

Short courses (≤1 month) of topically applied acyclovir are permitted.

Herbal, botanical, and other agents (e.g., ursodeoxycholic acid) that are traditionally used for chronic HBV disease are discouraged.

Patients who use oral contraceptives should continue their use.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited:

- Any investigational drugs as a result of participation in another clinical study during the study including the follow-up period.

- Any other investigational drugs (e.g., compassionate use), immunomodulatory treatments (e.g., interferons, systemic corticosteroids), growth factors (e.g., erythropoietin, granulocyte colony-stimulating factor [G-CSF]) or antiviral treatments with anti HBV activity (e.g., tenofovir, emtricitabine, adefovir, telbivudine, systemic acyclovir, systemic famciclovir) other than those specifically allowed by this protocol prior to follow-up Week 24/end of untreated observation. (Exception: patients with significant deterioration in hepatic function [e.g., decompensation] who permanently discontinue study treatment and need to consider alternative therapies).

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

Patients will be assessed according to the Schedule of Assessments (see Appendix 1). Baseline assessments are those assessments taken on the first day of administration of study drug and should be performed prior to administration of study drug, unless otherwise noted in the Schedule of Assessments.

Demographic data to be collected will include age, sex, and race/ethnicity (as reported by parent/legal guardian). The racial and ethnic differences in drug responses have now been well described for a range of drugs and appear to be based on the varying distributions of polymorphisms in drug receptors or drug-metabolizing enzymes among different racial and ethnic groups.

In order to help estimate the patients' growth potential, height will be collected from consenting biological parents. This information may be entered directly onto the eCRF, and the eCRF may be considered as the source document. Sexual maturity status will be monitored by collecting the date of menarche for female patients and assessing Tanner Staging for both male and female patients (see Appendix 6).

If feasible and upon agreement with the investigator, certain visits, as indicated in the Schedule of Assessments (see Appendix 1), may be conducted by appropriately qualified personnel (e.g., mobile nurse) in the patient's home, if this is more convenient for the patient. The investigator will still remain responsible for all trial-related medical decisions. If weight measurement is required at the visit, then the same brand of scales must be used by both the site and the mobile nurse. If height measurement is required at the visit, then a stadiometer must still be used.

The total volume of blood taken throughout the *whole* study is up to approximately *340* mL (excluding Roche Clinical Repository [RCR] samples) depending on the age of the child and the study group. Monovette tubes will be used in younger children to reduce blood draws, and less blood will be taken from the untreated control group since they have fewer study visits.

4.5.1.1 Safety Assessments

Assessments of safety are summarized in Table 3, including those required for study entry.

Any abnormality identified during screening or baseline assessments should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities from baseline should be recorded as adverse events on the adverse event eCRF (see Sections 5.2.1 and 5.3.5.8).

Table 3 Safety Assessments

Assessment	Parameter
Medical history	Clinically significant diseases within the previous 2 years and HBV history
Concomitant medication	All significant medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements), including any significant concomitant medications taken within 2 years prior to baseline. During follow-up of treated patients, only concomitant medications for CHB need to be recorded (see Section 4.4).
Surgeries/procedures	All surgeries/procedures, including any significant surgeries/procedures prior to baseline; during follow-up of treated patients, only surgeries/procedures associated with reportable adverse events (see Section 5.3.1).
Complete physical examination	Should include an evaluation of the head, eye, ear, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.
Symptom-directed physical examination	Signs, symptoms, and concerns reported by the parent/legal guardian/patient should be considered.
Liver biopsy	If applicable (Section 4.1.1).
Liver abdominal ultrasound [a]	Must show no signs of HCC; for patients without study entry liver biopsy, must also show no signs of cirrhosis or splenomegaly
Vital signs	Blood pressure, heart rate, temperature
Electrocardiogram [a]	Section 4.5.1.3.
Growth	Weight (kg) and height (cm), using the same instruments in the same individual [b]. A stadiometer with mean of three readings should be used for height measurement. Collect the date of menarche for female patients and assess Tanner Staging for both male and female patients.
Ophthalmological examination [a]	Completed by an ophthalmologist; includes fundoscopic examination with dilation, visual acuity assessment, visual field testing, and color visual testing. Eye examination by a pediatric ophthalmologist is recommended. Visual field testing by confrontation is recommended in younger patients. Any patient who develops ocular symptoms should receive a prompt eye examination by an ophthalmologist and additional examinations as necessary.
Neuropsychiatric questionnaire	Section 4.5.1.2
Adverse events	Section 5.3.1

CHB = chronic hepatitis B; HBV = hepatitis B virus; HCC = hepatocellular carcinoma

[a] Within 6 months prior to baseline; repeat at screening only if any change in the medical condition. Assessment does not need to be repeated at re-screening if performed within 6 months prior to baseline, unless dictated by a change in the patient's medical condition or the assessment accounted for the original screen failure.

[b] Exception to using the same instruments in the same individuals is if patients are measured at home by a mobile nurse (see Section 4.5.1).

4.5.1.2 Neuropsychiatric Questionnaire

As part of the overall assessment of patients and their mental state, and collation of neurological and psychiatric adverse events, the Children's Depression Inventory (CDI) (Kovacs 2010) will be used in patients ≥7 years of age to evaluate the presence and severity of specific depressive symptoms. It is stressed that use of the CDI should not replace the overall assessment of patient's mental state that should be undertaken before and during treatment, and investigators should consider these assessments in the context of previous medical and psychiatric history. The CDI will be performed at screening and baseline for all patients and then post-baseline for treated patients as per the schedules in Appendix 1. CDI should be performed prior to the completion of other study assessments. If a patient is <7 years old, but turns 7 years old during the study and within the scheduled CDI administration period, the CDI should be administered from that point onward. For [redacted]-year-old patients who turn [redacted] years old during the study, the CDI should continue to be administered.

Parents or patients may not be comfortable with certain sentences or question the sensitive or personal nature of some sentences; therefore, it should be clearly explained that the CDI is just a tool that all patients in the study are required to complete as part of the assessment of mood disorder problems.

The CDI Item Form will be provided in the patient's own language, if available. All patients should complete the form themselves. For younger children or those with reading difficulties or who are unable to read, the instructions and items should be read aloud to the child, and then the child will select an answer by themselves. If the CDI Item Form is not available in the patient's own language, a translator may read the instructions and items to the child and then the child will select an answer by themselves. The mode of administration (self-administered or translator/caregiver administered) should be clearly documented in the clinical records. If patients feel none of the sentences for an item applies to them, then they should be instructed to choose as best they can. Patients should be debriefed after the CDI has been completed to address any questions or concerns.

Once the patient has finished the item form, investigational site staff will then complete the CDI Scoring Page and transfer the five subscale scores to the eCRF. Site staff will then add up the five subscale scores to obtain the total CDI score. If >10% of items (i.e., more than 3 items) are unanswered, the assessment should be considered invalid/incomplete, and the data should not be entered onto the eCRF.

Follow-up of Patients with Symptoms of Major Depression or Potential Children's Depression Inventory Indicators

Whether the CDI is administered or not, investigators should still assess the mental state of their patients per their standard clinical practice. If any patient exhibits symptoms of major depression, and/or if CDI total score is >19 and/or the patient fails to complete all items on the CDI, then the investigator will perform a more thorough evaluation to

determine if major depression has developed. If major depression is confirmed by the investigator, then the patient will be referred to a mental health professional (e.g., counselor). If this is at screening or baseline, then the patient will be excluded from the study. While in the study, the investigator will determine whether adverse event criteria have been met and report as an adverse event on the eCRF, if appropriate (see Section 5.2.1). If while in the study the patient is found to have severe depression Pegasys® must be permanently discontinued and the patient referred for psychiatric intervention (Section 5.3.5.12).

4.5.1.3 Electrocardiograms

Single 12-lead ECGs will be collected locally and assessed at screening. For safety monitoring purposes, ECG abnormalities will be documented on the eCRF General Medical History and Baseline Conditions. The investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at site.

4.5.1.4 Laboratory Assessments

The list of laboratory tests is provided in Table 4. Except where specified, samples will be sent to one or more central laboratories or to the Sponsor for analysis.

At certain visits outlined in the Schedule of Assessments in Appendix 1, and at any unscheduled visit that is required for safety reasons, hematology and biochemistry may be undertaken at the patient's primary physician clinic/local hospital/home, if this is feasible and more convenient for the patient, and upon agreement with the investigator. The primary physician/local hospital laboratory must be accredited and local laboratory ranges must be provided. If the visit occurs at the primary physician clinic/local hospital, adverse events will then be recorded via a telephone call from investigator site to patient's parent/legal guardian.

Upon agreement with the Sponsor, samples can be analyzed by local laboratories if deemed required by local regulations.

Prior to screening, local laboratory test values will be used. The following parameters are required to be recorded in CRF:

- ALTs results within 6 months (for patients with liver biopsy) and within 1 year prior to baseline
- HBsAg results with more than 6 months prior to baseline
- HBeAg results with more than 6 months prior to baseline
- HBV DNA results prior to screening

Normal ranges (age-specific where available) for the local site study laboratory parameters must be supplied to Roche prior to study initiation.

Table 4 Laboratory Assessments

Laboratory Assessment	Parameters
Hematology and coagulation	Complete blood count [hemoglobin, hematocrit, reticulocytes, total WBC count, differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count], INR
Serum chemistry	ALT, AST, GGT, bilirubin (total, direct and indirect), alkaline phosphatase, total protein, albumin, BUN/urea, creatinine [a], uric acid, total calcium, phosphorus, cholesterol, triglycerides, random glucose, sodium, chloride, potassium, lactate [b]
Urinalysis [c]	Dipstick with subsequent microscopic evaluation if positive for blood.
Pregnancy test [c]	Females of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests may be performed at subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test. The result of the baseline pregnancy test must be available prior to randomization and commencement of treatment. Urine pregnancy test to be performed by site.
Thyroid function tests [d]	FT3, FT4, TSH, TPO antibodies, TBG
HBV serology and virology [d]	HBsAg, HBeAg, anti-HBs, anti-HBe, HBV DNA, HBV genotype
Special chemistry [d]	AFP, anti-HAV IgM Ab, anti-HCV Ab, anti-HDV Ab, anti-HIV Ab
Plasma samples for PK analysis (Section 4.5.1.5)	
Immunoglobulins and autoantibodies [d]	ASMA, ALKM1, ANA, A1AT
Exploratory testing [d]	Quantitative HBsAg, quantitative HBeAg, lamivudine or entecavir viral resistance [b] (Section 4.5.1.6), ADA [e]

A1AT=α-1 antitrypsin; ADA=anti-drug antibody; AFP=α-fetoprotein; ALKM1= anti–liver-kidney microsome-1 antibody; ANA= anti-nuclear antibody, ASMA=anti-smooth muscle antibodies FT3=free triiodothyronine; FT4=free thyroxin ; GGT= gamma-glutamyl transpeptidase; HAV=hepatitis A virus; TBG=thyroxine-binding globulin; TPO=thyroid peroxidase; TSH=thyroid-stimulating hormone.

[a] Estimated creatinine clearance to be calculated by sites during lamivudine or entecavir treatment any time creatinine is abnormal (see Appendix 5) and internally by Roche at baseline and end of treatment/Week 48 of untreated observation.

[b] Treated patients only post-baseline.

[c] To be performed by site/local laboratory.

[d] Parameters do not need to be repeated at re-screening if performed within 6 months prior to baseline, unless dictated by a change in the patient's medical condition or the parameter accounted for the original screen failure.

[e] Patients treated with Pegasys®+lamivudine or entecavir only.

Additional serum bank samples will be collected during the course of this study in order to perform or repeat any scheduled laboratory tests should there be a problem with the original sample. If patients have consented to a RCR sample collection, any serum bank

samples that are no longer required for repeat testing will be converted to RCR serum samples at the end of the study (see Section 4.5.1.7).

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

4.5.1.5 Pharmacokinetic Analysis

Blood samples will be collected in all patients treated with Pegasys® + lamivudine or entecavir to evaluate the pharmacokinetics of Pegasys® following administration of a BSA-based dosing regimen. See Section 4.5.2.5 for timing of PK assessments.

The exact date and time of Pegasys® dosing and collection of PK blood samples will be recorded in the source document (see Section 4.5.2.4). The procedure for the collection and handling of blood samples for PK analysis is specified in the laboratory manual.

The serum concentrations of Pegasys® will be assessed by a quantitative enzyme-linked immunosorbent assays (ELISA). PK parameters, such as C_{max}, AUC, clearance (CL/F) and volume of distribution (V/F), if possible, will be estimated using a population approach.

4.5.1.6 Lamivudine and Entecavir Resistance

Blood samples will be collected from all patients for lamivudine or entecavir viral resistance testing (sequencing of the HBV polymerase reverse transcriptase region where the YMDD motif and other resistance mutations are located). For untreated patients, a blood sample for lamivudine or entecavir viral resistance testing will be taken at baseline only. For treated patients, a blood sample for lamivudine or entecavir viral resistance testing will be taken at baseline (prior to the first dose of lamivudine or entecavir) and Week 8 (end of lamivudine or entecavir monotherapy treatment and prior to dose of lamivudine or entecavir during that visit), per the Schedule of Assessments in Appendix 1. Samples will be batched and sent to the sequencing laboratory. Therefore, results from baseline and Week 8 lamivudine or entecavir viral resistance testing may not be obtained before the start of the lamivudine or entecavir monotherapy and the Pegasys® + lamivudine or entecavir combination, respectively. In the event of baseline lamivudine or entecavir viral resistance or emergence of lamivudine or entecavir viral resistance after 8 weeks of monotherapy, the investigator will be informed. After consultation with the Medical Monitor, the decision to continue treatment will be at the discretion of the investigator.

A blood sample for lamivudine or entecavir viral resistance testing will be taken at follow-up Week 4 for all treated patients. If lamivudine or entecavir viral resistance is detected or the test is unsuccessful, a blood sample to assess for lamivudine or entecavir viral resistance should be taken at follow-up Week 24. If lamivudine or entecavir viral resistance is detected at follow-up Week 24, then testing should continue *up to* the *last* time *point* of the follow-up period.

If HBV DNA measurement was negative at follow-up Week 4 but becomes positive at follow-up Week 24, an unscheduled blood sample may be requested for lamivudine or entecavir viral resistance testing, preferably within 2 to 4 weeks. If lamivudine or entecavir viral resistance is detected *before the last time point of follow up*, lamivudine or entecavir viral resistance testing should *be performed* at the *last* time *point* of the follow-up period

The procedure for the collection and handling of blood samples for lamivudine or entecavir viral resistance is specified in the laboratory manual.

Population sequencing will be used as the primary methodology for the detection of the lamivudine or entecavir viral resistance mutation(s). For the purposes of sequence determination, an HBV DNA $\geq$200 IU/mL is required. Additional sequencing analyses may be performed on those samples for which viral resistance mutation(s) cannot be detected by population sequencing.

4.5.1.7 Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent/assent to participate in this optional research (provided parents/legal guardians also provide consent). RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent/Assent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

The following samples will be collected as per the Schedule of Assessments (see Appendix 1) for identification of dynamic (non-inherited) biomarkers:

- Serum samples (if patients consent/assent to RCR samples, residual serum bank samples will be converted into RCR serum samples at the end of the study)
- Whole blood samples for RNA extraction

The following sample will be collected at baseline for identification of genetic (inherited) biomarkers:

- Whole blood samples for DNA extraction

The total volume of blood taken for RCR samples is up to approximately *29* mL depending on the study group.

For all samples, dates of consent/assent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens, which includes any residual serum bank samples, will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent/Assent Form (or separate authorization for use and disclosure of personal health information) signed by the parent/legal guardian/patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Roche Clinical Repository

The Informed Consent and Assent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient and their parent/legal guardian the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's and their parent/legal guardian’s agreement for provision of optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient and their parent/legal guardian has given consent/assent to participate by completing the RCR Research Sample Informed Consent/Assent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

Withdrawal from the Roche Clinical Repository

Patients who give consent/assent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a parent/legal guardian or patient wishes to withdraw consent/assent to the testing of the patients specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent/Assent eCRF. The parent/legal guardian/patient will be provided with instructions on how to withdraw consent/assent after the trial is closed. A patient's withdrawal from Study NV25361 does

not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study NV25361.

Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent/Assent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

Written informed consent signed by the patient's parent/legal guardian and written informed consent or assent (if applicable) signed by the patient, for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent/Assent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations should be performed within 6 weeks prior to baseline (Day 1), unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent/assent and within 6 weeks prior to baseline (Day 1) may be used; such tests do not need to be repeated for screening. Extensions to the screening period of up to 7 days may be permitted under exceptional circumstances if information concerning eligibility is outstanding and upon approval from the Medical Monitor. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Assessments scheduled for baseline (Day 1) should be performed prior to administration of study treatment, unless otherwise noted in the Schedule of Assessments.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Re-Testing Laboratory Inclusion/Exclusion

If a patient fails any laboratory Inclusion/Exclusion criteria at screening, the investigator may repeat the test twice within the screening period. (This will not be considered as re-screening; see Section 4.5.2.3) If the patient fails the laboratory criteria on the third assessment, he or she will not be able to enter the study. It will not be considered a

retesting if blood samples have to be redrawn because of sample handling problems, breakage or sample integrity.

4.5.2.3 Re-Screening

Patients who fail to meet the entry criteria may be screened on one more occasion, provided that enrollment remains open. Rescreening refers to repeating the whole screening process (except potentially for those assessments/parameters indicated in Table 3 and Table 4). Rescreening is required if a patient has not met all of the eligibility criteria within 6 weeks from the original screening visit. Prior to rescreening, approval from the Medical Monitor is required. It will not be considered a rescreening if blood samples have to be redrawn because of sample handling problems, breakage or sample integrity. Only the data for a successful screening visit will be recorded in the eCRF.

4.5.2.4 Assessments during Treatment and Untreated Observation

All assessments must be performed on the day of the specified visit, unless a time window is specified in the Schedule of Assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the Schedule of Assessments. CDI should be performed prior to the completion of other study assessments.

Please see Appendix 1 for the Schedule of Assessments performed during the treatment and untreated observation period.

4.5.2.5 Pharmacokinetic Assessments

A PK blood sample will be taken at baseline (prior to the first dose of lamivudine or entecavir) and on Day 1 of subsequent PK sampling weeks as per the Schedule of Assessments in Appendix 1. The pre-dose PK sample will be collected prior to (anytime between 6 hours to immediately before) administration of Pegasys® and lamivudine or entecavir on that day. Pegasys® dosing (if scheduled to occur) on the day of PK sampling should happen in the clinic. If a particular visit is taking place outside the clinic via mobile nursing then the mobile nurse will ensure the dosing takes place after PK sampling. The exact date and time of Pegasys® dosing and collection of PK blood samples will be recorded.

At Week 32 samples will be taken at pre-dose (any time between 6 hours to immediately before), and at post doses at 24–48 hours, 72–96 hours, and 168 hours. For scheduling purposes, time windows are provided for the first two post-dose blood samples. The first post-dose blood sample should be collected within 24 to 48 hours after the dose. The second post-dose blood sample should be collected between 72 and 96 hours after the dose. There must be at least 48 hours between the two blood samples. The 168-hour blood sample will be collected within 6 hours before the next dose is administered.

The procedure for the collection and handling of blood samples for PK analysis is specified in the Lab Manual and Lab Flowchart. The exact date and time of dosing and collection of blood samples will be recorded in the source document and eCRF. If an unscheduled PK sample is taken, the exact day and time that the sample was taken relative to the latest dose of Pegasys® needs to be recorded in the source document.

4.5.2.6 Lamivudine or Entecavir Viral Resistance Assessments

A blood sample for lamivudine or entecavir viral resistance testing will be taken at baseline for all patients (prior to the first dose of lamivudine or entecavir for treated patients) and at subsequent weeks per the Schedule of Assessments in Appendix 1 and as described in Section 4.5.1.6.

4.5.2.7 Assessments at Study Drug Discontinuation

For patients in the Pegasys®+lamivudine or entecavir group who prematurely discontinue study drug, the assessments as per the Week 56 visit should be completed.

All patients should then continue onto the follow-up visit schedule (see Appendix 1).

4.5.2.8 Assessments at Study Completion or Early Termination

Patients who complete the study will be those treated patients who complete the full *1*-year follow-up and those untreated patients who complete the full 80-week untreated observation. All patients who withdraw from the study early will be asked to return to the clinic for a final visit.

For treated patients withdrawing from the study prior to the end of treatment, the assessments as per the Week 56 visit should be completed.

For treated patients withdrawing from the study after the end of treatment but prior to follow-up Week 24, the assessments as per the follow-up Week 24 visit should be completed.

For treated patients withdrawing after follow-up Week 24, the assessments as per follow-up Year *1* visit should be completed.

For patients in the untreated control group withdrawing prior to Week 80, the assessments as per the Week 80 visit should be completed.

Please see Appendix 1 for the Schedule of Assessments performed at the study completion/early termination visit.

4.5.2.9 Follow-Up Assessments

Please see Appendix 1 for the Schedule of Assessments for initial and follow-up of treated patients.

After the study completion or early termination visit, adverse events should be followed (see Section 5.5 and 5.6).

4.5.2.10 Assessments at Unplanned Visits

Assessments at unplanned visits should be clinically indicated as determined by the investigator.

4.5.3 Assessment of Sexual Maturity

The age of onset of menarche will be collected for all female patients. Depending on approval by the Institutional Review Board / Ethics Committee (IRB/EC), the relevant health authority, and patient/guardian consent, Tanner Stage for all patients will be determined at baseline. Patients deemed to be at Tanner Stage 5 at baseline will require no further Tanner Stage assessments. Patients deemed to be below Tanner Stage 5 at baseline will be assessed annually as outlined in the schedule of assessments (see Appendix 1). Guidance on the Tanner Stages is provided in Appendix 6.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include but are not limited to the following:

- Parent/legal guardian or patient withdrawal of consent/assent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with study requirements

4.6.1.1 Untreated Control Patients who become Immune-Active

Untreated control patients who progress to immune-active disease (sustained ALT elevation for at least 6 months) should remain in the study until their completion (Week 80), per investigator's judgment. If the investigator wishes to initiate treatment per standard of care, this should first be discussed with the Medical Monitor. If such treatment is started, the patient would have been deemed to have been withdrawn from the study (see also Section 1.1).

4.6.1.2 Discontinuation from Study Drug

Individual patient treatment with Pegasys® + lamivudine or entecavir must be discontinued in the event of any of the following:

- Severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchoconstriction)

- Severe depression
- Absolute neutrophil count $< 0.25 \times 10^9$ cells/L or febrile neutropenia
- Platelets $< 25 \times 10^9$ cells/L

Discontinuation of individual patient treatment with Pegasys® + lamivudine or entecavir should be considered in the event of any of the following:

- Evidence of hepatic decompensation (e.g., Child-Pugh Class B or C clinical classification [Appendix 2] or clinical evidence such as ascites or varices)
- Thyroid abnormalities that cannot be effectively controlled by medication
- Hypoglycemia, hyperglycemia, or diabetes mellitus that cannot be effectively controlled by medication
- New or worsening visual disorders such as field deficits, decrease or loss of vision
- Persistent or unexplained pulmonary infiltrates or pulmonary function impairment
- Worsening of psoriatic lesion
- Development of autoimmunity, including autoimmune hepatitis
- Pregnancy

Discontinuation of individual patient treatment with lamivudine or entecavir should be considered in the event of the following:

- Clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations)

In the event that Pegasys® treatment has to be permanently discontinued, patients must also cease lamivudine or entecavir.

In the event that lamivudine or entecavir treatment has to be discontinued, patients may continue to receive Pegasys® monotherapy for the rest of the planned treatment period.

Patients who discontinue study drug permanently will be asked to return to the clinic for a study drug discontinuation visit (see Section 4.5.2.7) and should continue into follow-up. The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

4.6.1.3 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study (see Section 4.5.2.7). The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent/assent has been withdrawn.

4.6.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

As of 28 March 2018, recruitment into the study was terminated due to questionable efficacy and a change in the benefit–risk profile of the trial, although no specific safety concerns were identified in the DSMB scheduled review of the study (see Section 1.5).

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Pegasys® is associated with adverse effects such as neuropsychiatric events, cytopenias (including neutropenia, lymphopenia, and thrombocytopenia), influenza-like symptoms, infections, and cardiovascular, thyroid, metabolic, autoimmune, respiratory, ophthalmic, and other conditions. Significant adverse effects of Pegasys® are highlighted in Section 5.1.1.

The safety profiles of lamivudine and entecavir are summarized in Section 5.1.2 and Section 5.1.3, respectively.

For other adverse effects associated with lamivudine or entecavir, see local prescribing information.

Specific exclusion criteria aim to exclude patients who are at risk for increased toxicity based on the potential and identified risks of Pegasys® and lamivudine or entecavir, such as patients with pre-existing cardiac disease, significant anemia, abnormal thyroid function, severe retinopathy, and severe mood or psychiatric disorder.

Regular monitoring of laboratory parameters, growth parameters, vital signs, and adverse events will occur as per the Schedule of Assessments in Appendix 1 and will ensure that any adverse effects are detected early and treated promptly. Appropriate study drug and study stopping rules based on safety will be instituted (see Sections 4.6.1.2 and 4.6.2).

Dose adjustment guidance for Pegasys® is provided in Appendix 4, including guidance for management of the specific effects listed below. All missed, reduced, or withheld doses of Pegasys® or lamivudine or entecavir, including the reason, must be recorded on the eCRF.

- Neutropenia
- Thrombocytopenia
- Elevated serum ALT
- Severe mood or psychiatric disorder
- Change of BSA category

A DSMB and IMC will review the safety data at regular intervals (see Sections 3.1.3 and 3.1.4).

5.1.1 Risks Associated with Pegasys®

5.1.1.1 Neutropenia, Lymphopenia, and Thrombocytopenia

Pegasys® is associated with the development of neutropenia, lymphopenia, and thrombocytopenia through dose-related suppression of the bone marrow. Neutropenia is the most common reason for dose modification of Pegasys® and is managed clinically with dose reduction in approximately one quarter of patients.

5.1.1.2 Elevated ALT

Transient elevations in ALT (2-fold to 5-fold above baseline) have been observed in some patients receiving Pegasys® and were not associated with deterioration of other liver function tests.

5.1.1.3 Thyroid

α-interferons, including Pegasys®, may cause or aggravate hypothyroidism and hyperthyroidism. The most common thyroid function abnormalities during studies with Pegasys® were hypothyroidism (low T3 and elevated TSH) as well as hyperthyroidism (elevated T4). Female patients appear to be more likely than male patients to develop significant thyroid abnormalities with Pegasys® treatment. Most patients who developed thyroid abnormalities during treatment were generally adequately managed with medication without the need for stopping Pegasys® treatment, and in most, thyroid function had normalized or improved by the end of an untreated follow-up period.

5.1.1.4 Growth

Growth inhibition was observed in pediatric patients. Pediatric patients with HCV treated with Pegasys® plus ribavirin combination therapy (Study NV17424, [PEDS-C] Phase III study) showed a delay in weight and height increases after 48 weeks of therapy compared with baseline. Both weight and height for age z-scores as well as the percentiles of the normative population for patient weight and height decreased during treatment. At the end of 2 years of follow-up after treatment, most patients had returned to baseline normative growth curve percentiles for weight and height (mean weight for age percentile was 64% at baseline and 60% at 2 years after the end of treatment; mean height percentile was 54% at baseline and 56% at 2 years after the end of treatment). At the end of treatment, 43% of patients experienced a weight percentile decrease of 15 percentiles or more and 25% of patients experienced a height percentile decrease of 15 percentiles or more on the normative growth curves. At 2 years after the end of treatment, 16% of patients remained 15 percentiles or more below their baseline weight curve and 11% of patients remained 15 percentiles or more below their baseline height curve. In addition, 38 of 114 patients who participated in Study NV17424 continued into the long-term follow-up study, whose data demonstrated that recovery in growth at the 2-year follow-up was maintained at 5–6 years after treatment. In the few patients who did not return to baseline height for age percentiles by 5–6 years post-treatment, an alternative causative factor was identified.

5.1.1.5 Neuropsychiatric

Effects on mood have been reported in adults treated with interferons. In Study NV17424 (PEDS-C), a Phase III study of HCV-infected children treated with Pegasys®, insomnia, depression, and anxiety were reported.

Life-threatening or fatal neuropsychiatric reactions may manifest in patients receiving therapy with Pegasys® and include suicide, suicidal ideation, homicidal ideation, depression, relapse of drug addiction, and drug overdose. These reactions may occur in patients with and without previous psychiatric illness.

Neuropsychiatric AEs observed with Pegasys® treatment include aggressive behavior, psychoses, hallucinations, bipolar disorders, and mania. Physicians should use their clinical judgment to monitor young pediatric patients for evidence of depression and other psychiatric symptoms.

5.1.1.6 Ophthalmic

Decrease or loss of vision, retinopathy (including macular edema), retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema are induced or aggravated by treatment with Pegasys® or other α-interferons.

5.1.1.7 Fertility

Pegasys® has not been studied for its effect on fertility and should not be used in pregnant women.

5.1.2 Risks Associated with Lamivudine

The safety profile of lamivudine has been established in adult patients with HBV, and also in adult and pediatric patients with HIV. The dose of lamivudine used to treat adults with HIV as part of combination therapy is 150 mg twice daily, whereas in adults with chronic HBV the dose is 100 mg four times daily. Similarly a lower lamivudine dose is recommended for pediatric patients with HBV than in pediatric patients with HIV, and therefore it is anticipated that the safety profile in pediatric patients with HBV will be no worse given the lower exposure, and very likely better, than that observed in pediatric patients with HIV who have been treated with regimens containing lamivudine. Some safety data are available on lamivudine use in pediatric HBV treatment (Sokal et al. 2000, 2006; Jonas et al. 2002, 2008), and most reported events were not different from placebo and included ear, nose, and throat symptoms, gastrointestinal symptoms, and non-specific AEs such as malaise and fatigue. Few safety issues, other than the development of lamivudine viral resistance with long-term monotherapy, have been reported relating to lamivudine.

In a review of therapies used in pediatric HBV (Jonas et al. 2010), it was concluded that the safety profile of nucleoside and nucleotide analogues used in pediatrics was generally well tolerated, while serious sequelae such as lactic acidosis were rare. Cases of lactic acidosis, sometimes fatal, and usually associated with severe hepatomegaly with steatosis, have been reported rarely with the use of nucleoside analogues.

Investigators should refer to the prescribing information for lamivudine indicated for HBV for additional information on the safety profile of lamivudine in HBV.

5.1.3 Risks Associated with Entecavir

The safety profile of entecavir has been established in adult and pediatric patients with HBV. In clinical studies in adult patients with compensated liver disease, the most common adverse reactions of any severity with at least a possible relation to entecavir were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%). Exacerbations of hepatitis during and after discontinuation of entecavir therapy have also been reported. Assessment of adverse reactions in adults is based on experience from postmarketing surveillance and four clinical studies in which 1720 patients with chronic hepatitis B infection and compensated liver disease received double-blind treatment with entecavir (n = 862) or lamivudine (n = 858) for up to 107 weeks. In these studies, the safety profiles, including laboratory abnormalities, were comparable for entecavir 0.5 mg daily (679 nucleoside-naive HBeAg positive or negative patients treated for a median of 53 weeks), entecavir 1 mg daily (183 lamivudine-refractory patients treated for a median of 69 weeks), and lamivudine.

Cases of lactic acidosis have been reported, often in association with hepatic decompensation, other serious medical conditions or drug exposures.

The safety of entecavir in pediatric patients from 2 to < 18 years of age is based on two clinical trials in subjects with chronic HBV infection: one Phase II PK trial and one Phase III trial. These trials provide experience in 173 HBeAg-positive nucleoside-analog treatment-naïve subjects treated with entecavir for a median duration of 60 weeks. The adverse reactions observed in pediatric subjects who received treatment with entecavir were consistent with those observed in clinical trials of entecavir in adults (BARACLUDE® SmPC).

Adverse drug reactions reported in greater than 1% of pediatric subjects included abdominal pain, rash events, poor palatability ("product taste abnormal"), nausea, diarrhea, and vomiting (BARACLUDE®. U.S. Package Insert).

Investigators should refer to the prescribing information for entecavir for additional information on the entecavir safety profile.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including serious adverse events (SAEs) and non-serious AEs of special interest, measurement of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, measurement of height and weight, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor (see Section 5.4).

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition [see Section 5.3.5.9]).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., invasive screening procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life-threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE that had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to the Division of AIDS [DAIDS] criteria [see Section 5.3.3]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; [see Section 5.4.2]).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

In addition to SAEs, non-serious AEs of special interest must be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2]). AEs of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug. Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1) are recorded on the AE eCRF and reported to the Sponsor in accordance with instructions (see Sections 5.4 and 5.6).

For each AE recorded on the AE eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the AE eCRF.

After informed consent/assent has been obtained but prior to initiation of study drug /baseline visit, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies).

After initiation of study drug/baseline visit, all AEs, regardless of relationship to study drug, will be reported until follow-up Week 24/end of untreated observation. After this period (i.e., during follow-up for treated patients), investigators should report any persisting AEs, new-onset SAEs or non-serious AEs of special interest that are believed to be related to prior treatment with study drug, and any deaths (see Section 5.6).

At certain visits outlined on the Schedule of Assessments in Appendix 1, AEs may be recorded via a telephone call from investigator site to the patient or the patient's parent/legal guardian as appropriate.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The DAIDS Table for Grading the Severity of Adult and Pediatric AEs should be used to assist in the assessment of severity:

http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf

Note that events that are considered life-threatening should be reported as an SAE (see Section 5.2.2), and the severity would be reported as “severe” on the eCRF.

Table 5 will be used for assessing severity for AEs that are not specifically listed in the DAIDS Table.

Table 5 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of an SAE (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the AE eCRF; the use of colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field on the AE eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., record only appendicitis rather than abdominal pain, vomiting,

sweating and elevated white blood cell count). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the AE eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should be recorded only once on the AE eCRF. The initial severity of the event should be recorded in the initial severity field of the AE eCRF page, and the most extreme severity field should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the AE eCRF should be updated to reflect it.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the AE eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. In this study, a laboratory test result should be reported as an AE if it meets any of the following criteria:

- Considered an SAE
- Results in a discontinuation of study treatment

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a laboratory abnormality meeting the above criteria is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the AE eCRF.

If a laboratory abnormality meeting the above criteria is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, a decreased neutrophil level below 0.6 x 10^9 cells/L should be recorded as "Neutropenia".

Observations of the same laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless the etiology changes. The

initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$baseline value) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$baseline value in combination with total bilirubin $>2\times$ULN (of which $\geq$35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the AE eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or a non-serious AE of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the study including follow-up of treated patients (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the AE eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of CHB.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. Generally, only one such event should be reported. The term **"**sudden death**"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"**unexplained death**"** should be recorded on the AE eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of CHB, "Chronic hepatitis B progression" should be recorded on the AE eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Lack of Efficacy or Worsening of CHB

Medical occurrences or symptoms of deterioration that are anticipated as part of CHB should be recorded as an AE if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of CHB on the AE eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “worsening of chronic hepatitis B”).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not suffered an AE.

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All overdoses or incorrect administration of study drug should be recorded on the AE eCRF. If the associated AE fulfils serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event [Section 5.4.2]).

5.3.5.12 Patient-Reported Outcome Data

AE reports will not be derived from patient-reported outcome (PRO) data (CDI [see Section 4.5.1.2]). However, if any patient responses are suggestive of a possible AE and are identified during site review of the CDI questionnaires, site staff will alert the

investigator, who will determine if the criteria for an AE have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an AE, it will be reported on the AE eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs
- Non-serious AEs of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Note: The Study Monitor should be contacted for any routine and administrative queries such as patient eligibility queries.

Medical Monitor Contact Information

Medical Monitor (UTC+01):	[redacted], *Ph.D.*
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted], *M.D. (Secondary)*
Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will be available to access the appointed Roche Medical Monitors, escalate emergency

medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Help Desk will be available 24 hours per day, 7 days per week, 52 weeks per year. Help Desk numbers will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Administration

For reports of SAEs and non-serious AEs of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the AE eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper SAE/Non-Serious AE of Special Interest Case Report Form (CRF) and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant at any time during the study or within 90 days after the last dose of study drug for any treated patients that withdraw from the study early. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the AE eCRF.

The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the

pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE eCRF.

In addition, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent/Assent Form to immediately inform the investigator if their partner becomes pregnant during the treatment period or within 90 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will be required to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. After the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; [see Section 5.4.2]).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; [see Section 5.4.2]).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent/assent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the AE eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, the appropriate AE outcome should be recorded on the AE eCRF and in the patient's medical record.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For SAEs, non-serious AEs of special interest, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

At the study completion/early termination visit, the investigator should instruct each patient to report to the investigator any subsequent AEs that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, SAE, or non-serious AE of special interest occurring at any time after a patient has discontinued study participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a treated patient that participated in this study.

The investigator should report these events to Roche Safety Risk Management on the AE eCRF. If the AE eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management using the telephone number provided.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Pegasys® Investigator's Brochure
- Local prescribing information for lamivudine and entecavir

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Recruitment into the study was terminated prematurely (see Section 1.5). Therefore, the data collected will be summarized using descriptive statistics. No formal statistical hypothesis testing or formal treatment group comparisons will be performed. The data from this study will be descriptively summarized and reported in a clinical study report after the last patient has completed the last study visit at 1 year post-end of treatment.

The efficacy analyses and summaries will be presented for the ITT population, which will comprise all randomized patients who receive at least one dose of study medication and patients randomized to no treatment who report any efficacy or safety data. Patients will be analyzed according to the group assigned at randomization.

Patients with missing data for the primary endpoint will be considered non-responders for the purpose of statistical analysis.

The safety population will be used for the reporting of all safety information and will comprise all patients who report any safety data. For safety summaries, patients will be summarized according to treatment received.

6.1 DETERMINATION OF SAMPLE SIZE

Taking into account the comparable entecavir and lamivudine early viral kinetics and the low resistance rates observed during Pegasys®-combination therapy with entecavir or lamivudine, the efficacy of Pegasys®+lamivudine and Pegasys®+entecavir regimens in this study are expected to be comparable. The assumptions for the expected loss of HBsAg rates after 24 weeks after the end of treatment/end of untreated observation are 17% in the Pegasys®+lamivudine arm and 0.6% in the untreated control group. These assumptions are based on the observed rate on conventional Interferon in a pilot study (D'Antiga et al. 2006) and observed spontaneous rates (Hsu 1992), respectively.

With a two-sided 5% significance level, Fisher's Exact test would have 80% power to detect a difference between a treated group and untreated control with 50 evaluable patients per group. Approximately 114 patients *were planned to be* recruited (57 per group) to ensure at least 50 evaluable patients in each group.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study drug administration, patient disposition, and important protocol deviations will be summarized by group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics will be summarized descriptively by group. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized using frequencies and percentages.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as loss of HBsAg at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80). The number of observations, percentage of responders (response rate) and 95% CI (using the Clopper-Pearson method) for the response rate will be presented for each group.

The primary analysis *was planned as* the comparison of the response rate in the Pegasys® + lamivudine or entecavir group with that in the untreated control group. Testing of the primary endpoint *was planned as* a superiority test based on the ITT population, which *would* comprise all randomized patients who received at least one dose of study medication and patients randomized to no treatment. The test *would* be using Fisher's exact test, stratified by HBV genotype (A vs. B/C vs. D/other), and the significance level taken at 5% two-sided. Patients with missing data will be treated as non-responders. Sensitivity analyses *would* include a last observation carried forward approach for missing data. The Cochran Mantel Haenszel test stratified by genotype *would* also be provided.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study at 24 weeks post-treatment/end of untreated observation are as follows:

- Seroconversion to anti-HBs (loss of HBsAg and presence of anti-HBs)
- Seroconversion to anti-HBe (loss of HBeAg and presence of anti-HBe)
- Loss of HBeAg
- HBV DNA $<$ 20,000 IU/mL 2000 IU/mL, undetectable and change from baseline (by PCR or hybridization)
- Combined endpoints: HBeAg seroconversion and HBV DNA 20,000 IU/mL
- Combined endpoints: HBeAg seroconversion and HBV DNA $<$ 2000 IU/mL

Categorical endpoints will be summarized and analyzed in the same way as the primary efficacy endpoint. Continuous endpoints will be summarized using descriptive statistics (n, mean, median, SD, minimum, and maximum) and comparisons between the treated

and untreated control groups *were planned* using an analysis of variance, adjusted for HBV genotype (A vs. B/C vs. D/other).

In order to control the Type I error rate for the multiple secondary endpoints, a hierarchical testing approach *would* be used.

The secondary efficacy endpoints for this study at 1 *year* post-treatment are as follows:

- Seroconversion to anti-HBs (loss of HBsAg and presence of anti-HBs)
- Seroconversion to anti-HBe (loss of HBeAg and presence of anti-HBe)
- Loss of HBsAg
- Loss of HBeAg
- HBV DNA $<$20,000 IU/mL, $<$2000 IU/mL, undetectable and change from baseline (by PCR or hybridization)
- Combined endpoints: HBeAg seroconversion and HBV DNA $<$20,000 IU/mL
- Combined endpoints: HBeAg seroconversion and HBV DNA $<$2000 IU/mL

These secondary efficacy endpoints will be summarized descriptively at 1 *year* post-treatment for the Pegasys®+lamivudine or entecavir treatment group.

6.5 SAFETY ANALYSES

The following safety outcome measures will be compared between groups using descriptive statistics at 24 weeks post-treatment/end of untreated observation:

- Incidence, nature, and severity of serious and non-serious AEs (including neuropsychiatric assessment)
- Reasons for the discontinuation of any study medication
- Dose modifications for laboratory abnormalities and clinical AEs
- Changes in vital signs and laboratory tests from screening/baseline, including thyroid function
- Effect on growth (height, weight, and sexual maturity)

The following safety outcome measures will be assessed using descriptive statistics at *1 year* post-treatment:

- Incidence, nature, and severity of persisting AEs, new-onset related SAEs/ non-serious AEs of special interest
- Changes in thyroid function from screening/baseline
- Effect on growth (height, weight, and sexual maturity)

AEs will be assigned preferred terms and categorized into body systems according to the Medical Dictionary for Regulatory Activities classification of the World Health Organization terminology. AEs will be summarized by body system and preferred term

for each group. AE summaries will be presented for events with an onset date during up to 24 weeks post treatment (follow-up Week 24)/end of untreated observation (Week 80) by group and for events with an onset at any time up to the end of the *1*-year safety follow-up for the Pegasys®+lamivudine or entecavir treatment group only.

Neurological and psychiatric AEs will be assessed in further detail, including persistence and duration, as well as new onset of related SAEs reported during the follow-up period of this study for the Pegasys®+lamivudine or entecavir treatment group.

Laboratory Safety Data: Laboratory data will be descriptively summarized by treatment group over time. The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.0, Nov 2014, or more recent) will be used to assess the severity of laboratory abnormalities.

Growth (weight, height and sexual maturity): Descriptive summaries of weight and height will be presented by group over time. Sexual maturity data will be summarized as appropriate.

The number of patients who discontinued study medication and reason for discontinuation will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum Pegasys® concentration versus time data will be tabulated.

Additional PK analyses will be conducted as appropriate.

6.7 EXPLORATORY ANALYSES

The exploratory outcome measures for this study are as follows:

- Quantitative HBsAg and quantitative HBeAg
- Presence of lamivudine or entecavir resistance mutations
- Incidence of ADAs from all patients treated with Pegasys®+lamivudine or Pegasys®+entecavir

Exploratory analyses may not be reported in the Clinical Study Report.

6.8 INTERIM ANALYSES

No interim analysis is planned for the primary efficacy endpoint.

The primary efficacy analysis *was planned* when the last patient reaches the end of the 24-week after the end of treatment (follow-up Week 24)/end of untreated observation (Week 80).

Due to the early termination of recruitment and consequent reduction in both sample size and statistical power, the study data will be summarized using descriptive

statistics and reported in a clinical study report after the last patient has completed the last study visit at 1-year post end of treatment.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data from paper CDI questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes,

evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of study treatments, including eCRFs, Informed Consent/Assent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU)/European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent/Assent Forms or any alternate consent/assent forms proposed by the site (collectively, the "consent forms") before IRB/EC submission. The final IRB/EC-approved consent forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's parent/legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. Patients within the specified age range who are legally considered to be adults according to national legislation must consent in their own right. Patients enrolled as minors who attain legal adulthood during the course of the study must consent in their own right at that time and if required by national legislation.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient

to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's parent/legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent/Assent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of the FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, informed consent/assent forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 *PROTOCOL DEVIATIONS*

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

This study will be sponsored and managed by F. Hoffman-La Roche. Approximately 55 centers worldwide may participate in the study and will enroll approximately 114 patients.

A system will be in place to confirm patients intended dose of Pegasys®, based on patient's weight and height provided by the investigator, at the time points indicated in Appendix 1.

Central laboratories will be used for study assessments, including PK samples (see Table 4). If local laboratories are used for hematology and biochemistry assessments, local laboratory ranges will be collected. The RCR will receive all RCR samples at the end of the study.

Data for this study will be recorded via an EDC system using eCRFs. Except where specified (see Section 4.5.1), in no case will the eCRF be considered source data for this trial.

The study will be overseen by the Study Management Team (SMT). During the study the SMT will review study data according to the Data Quality Plan.

A DSMB and IMC will be utilized (see Sections 3.1.3 and 3.1.4). Information regarding the structure and role of the DSMB and IMC will be provided in a separate DSMB Charter and IMC Agreement.

9.5 *DISSEMINATION* OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific meetings. *For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.*

The investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1A
Schedule of Assessments: Pegasys® Monotherapy for Previous IST Patients Only

Assessment/Procedure	Screen Week -6 to -1	Pegasys® Treatment Week										Initial Follow-up Week		Long-term Follow-up Year [a]				
		BL	1	2	4	6	8	12	24	36	48	4	26	1	2	3	4	5 [b]
Informed consent/assent [c]	x																	
Medical history [d]	x	x																
Demography	x																	
Concomitant medications [e]	x	x			x		x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x													x				
Symptom-directed PE		x			x		x	x	x	x	x	x	x		x	x	x	x
ECG	x																	
Vital signs [f]	x	x			x		x	x	x	x	x	x	x	x	x	x [n]	x [n]	x [n]
Height (cm) [g]	x	x			x		x	x	x	x	x	x	x	x	x	x	x	x
Weight (kg) [g]	x	x			x		x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmology [h]	x											x						
Liver biopsy [m]	x																	
AEs [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dispense study drug		x			x		x	x	x	x								
Hematology [j, l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [n]	x [n]	x [n]
Chemistry [k, l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [n]	x [n]	x [n]
FT3, FT4, TSH [l,]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [n]	x [n]	x [n]
ASMA, ALKM1, ANA, A1AT	x	x			x		x	x	x	x	x	x	x	x	x	x [n]	x [n]	x [n]

Appendix 1A
Schedule of Assessments: Pegasys® Monotherapy for Previous IST Patients Only (cont.)

Assessment/Procedure	Screen Week -6 to -1	Pegasys® Treatment Week										Initial Follow-up Week		Long-term Follow-up Year [a]				
		BL	1	2	4	6	8	12	24	36	48	4	26	1	2	3	4	5 [b]
AFP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [n]	x [n]	x [n]
Pregnancy test	x	x			x		x	x	x	x	x	x	x	x				
Anti-HCV, anti-HIV, and anti-HDV	x																	
HBV genotype	x																	
HBsAg, HBeAg, (anti-HBe, anti-HBs)	x	x			x		x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA	x	x			x		x	x	x	x	x	x	x	x	x	x	x	x
Lamivudine or entecavir viral resistance	x											x						

A1AT = α-1-antitrypsin; AFP = α-fetoprotein; ALKM1 = anti-liver-kidney microsome-1 antibody; ANA = antinuclear antibody; ASMA = anti–smooth muscle antibody; BL = baseline; FT3 = free triiodothyronine; FT4 = free thyroxin; f/u = follow-up; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; PE = physical examination; TSH = thyroid-stimulating hormone; YMDD = tyrosine-methionine-aspartate-aspartate.

Notes: For description of Pegasys® Monotherapy group see Section 3.1.5.

On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

a. For visits after follow-up Week 26, the visit window is ± 28 days.
b. For patients withdrawing after follow-up Week 26, the assessments as per follow-up year 5 visit should be completed.
c. Informed consent signed by the patient's parent/legal guardian and informed consent or assent (if applicable) signed by the patient.
d. Clinically significant diseases within the previous 2 years and HBV history. After baseline, new or worsening abnormalities should be recorded on the AE eCRF.

Appendix 1A
Schedule of Assessments: Pegasys® Monotherapy for Previous IST Patients Only (cont.)

e. Including any significant concomitant medications taken within 2 years prior to baseline. During long term follow-up only concomitant medications (including herbal agents) for HBV need to be recorded. Including any significant surgeries/procedures prior to baseline. During long-term follow-up, only surgeries/procedures associated with reportable adverse events need to be recorded (see Section 5.3.1).

f. Blood pressure, heart rate, temperature.

g. Measurements to be taken using the same instruments in the same individual. A stadiometer with mean of three readings should be used for height measurement.

h. By ophthalmologist and including fundoscopic examination, visual acuity assessment, visual field testing, and color visual testing. Any patient who develops ocular symptoms should receive a prompt eye examination by an ophthalmologist and additional examinations as necessary.

i. After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol mandated intervention should be reported. Beyond follow-up Week 26 investigators should report persisting AEs, new-onset SAEs, including AEs of concern, that are believed to be

j. Complete blood count (hemoglobin, hematocrit, reticulocytes, total WBC count, differential WBC count [neutrophils, lymphocytes, monocytes, eosinophils, basophils], platelet count), INR.

k. ALT, AST, GGT, bilirubin (total, direct and indirect), alkaline phosphatase, total protein, albumin, BUN/urea, creatinine, uric acid, total calcium, phosphorus, cholesterol, triglycerides, random glucose, sodium, chloride, potassium. Estimated creatinine clearance to be calculated internally by Roche at baseline and Week 48.

l. If there are clinically significant laboratory abnormalities, repeat no less frequently than every 2 weeks or as clinically indicated, with appropriate toxicity management, until values return to normal or baseline.

m. If applicable (see Section 4.1.1). Where available the biopsy score should be reported in the CRF.

n. Assessment does not need to be performed by any previous IST patients who are continuing into follow-up as part of the Roche-sponsored study.

Appendix 1B
Schedule of Assessments: Pegasys® + Lamivudine or Entecavir

Assessment/Procedure	Screen Week	Lamivudine or Entecavir Treatment Week [a]			Pegasys® + Lamivudine or Entecavir Treatment Week [a]													Initial Follow-up Week [b]		Follow-up (*Year* Post *End of T*reatment) [c]
	-6 to -1	**BL**	**1[d]**	**4[d]**	**8**	**9[d]**	**10[d]**	**12[d]**	**14[d]**	**16[d]**	**20**	**26[d]**	**32**	**38[d]**	**44**	**50[d]**	**56[e]**	**4**	**24[f]**	**1** *[g]*
Informed consent/assent *[h]*	x																			
Medical history *[i]*	x	x																		
Demography	x																			
Concomitant medications *[j]*	x	x		x	x			x		x	x	x	x	x	x	x	x	x	x	x
Surgeries/procedures *[k]*	x	x		x	x			x		x	x	x	x	x	x	x	x	x	x	x
Physical examination	x	x			x														x	
Symptom-directed PE				x				x		x	x	x	x	x	x	x	x	x		x
ECG *[l]*	x																			
Vital signs *[m]*	x	x			x			x		x	x	x	x	x	x	x	x	x	x	
Height (cm) *[n]*	x	x *[o]*			x *[o]*						x *[o]*		x *[o]*		x *[o]*		x		x	x
Weight (kg) *[n]*	x	x *[o]*		x	x *[o]*			x		x	x *[o]*	x	x *[o]*	x	x *[o]*	x	x	x	x	x
Parental height *[p]*		x																		
Date of menarche for females *[q]*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tanner Stage *[r]*		x															x			x
Ophthalmology *[l, s]*	x												x				x		x	
Liver abdominal ultrasound *[l, t]*	x																			
Liver biopsy *[u]*	x																			
CDI *[v]*	x	x			x						x		x		x		x	x		
AEs *[w]*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Patient medication diary		x		x	x			x		x	x	x	x	x	x	x	x			
Dispense study drug		x		x	x			x		x	x	x	x	x	x	x				
Urinalysis *[x, aa]*	x	x						x		x	x	x	x	x	x	x	x	x	x	
Hematology, coagulation *[y, aa]*	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Chemistry *[z, aa]*	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1B
Schedule of Assessments – Pegasys + Lamivudine/Entecavir (cont.)

Assessment/Procedure	Screen Week	Lamivudine or Entecavir Treatment Week [a]			Pegasys® + Lamivudine or Entecavir Treatment Week [a]													Initial Follow-up Week [b]		Follow-up (*Year* Post *End of T*reatment) [c]
	-6 to -1	**BL**	**1[d]**	**4[d]**	**8**	**9[d]**	**10[d]**	**12[d]**	**14[d]**	**16[d]**	**20**	**26[d]**	**32**	**38[d]**	**44**	**50[d]**	**56[e]**	**4**	**24[f]**	**1** *[g]*
Lactate		x			x						x		x		x		x			
FT3, FT4, TSH *[l, aa]*	x				x						x		x		x		x		x	x
TBG *[l]*	x																			
TPO antibodies *[l]*	x												x				x			
ASMA, ALKM1, ANA *[l]*	x	x			x						x		x		x		x		x	
AFP, A1AT *[l]*	x																			
Pregnancy test *[bb]*	x	x		x	x			x		x	x	x	x	x	x	x	x	x	x	
Anti-HAV IgM, anti-HCV, anti-HIV, and anti-HDV *[l]*	x																			
HBV genotype *[l]*	x																			
HBsAg, HBeAg, (anti-HBe, anti-HBs) *[l]*	x	x			x						x		x		x		x	x	x	x
Quantitative HBsAg/HBeAg *[l]*		x			x						x		x		x		x		x	
HBV DNA *[l]*	x	x			x						x		x		x		x	x	x	x
Serum bank sample *[cc]*		x			x						x		x				x		x	x
Lamivudine or entecavir viral resistance		x			x													x	x *[dd]*	x *[dd]*
RCR samples (optional) [ee]		x			x			x			x		x				x		x	x

A1AT = α-1-antitrypsin; Ab = antibody; AFP = α-fetoprotein; ALKM1 = anti-liver-kidney microsome-1 antibody; ANA = antinuclear antibody; ASMA = anti–smooth muscle antibody; BL = baseline (Day 1); BSA = body surface area; CDI = Children's Depression Inventory; eCRF = electronic Case Report Form; FT3 = free triiodothyronine; FT4 = free thyroxin; f/u = follow-up; HAV = hepatitis A virus; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDV = hepatitis D virus; IgM = immunoglobulin M; PE = physical examination; RCR = Roche Clinical Repository; SAE = serious adverse event; TBG = Thyroxine-binding globulin; TPO = Thyroid peroxidase; TSH = thyroid-

stimulating hormone.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] For visits during the treatment period the visit window is ±3 days.

[b] For visits during the initial f/u period (24 week period post-treatment), up to and including follow-up Week 24, the visit window is ±7 days.

[c] For visits after f/u Week 24, the visit window is ±28 days.

[d] Visit may be undertaken at the patient's primary physician clinic/local hospital (Visit 1, 9, 10, or 14 only) or patient's home (e.g., by mobile nurse), if this is feasible and more convenient for the patient, and upon agreement with the investigator. The primary physician/local hospital laboratory must be accredited and local laboratory ranges must be provided. If the visit occurs at the primary physician clinic/local hospital, AEs will then be recorded via a telephone call from investigator site to patient's parent/legal guardian.

[e] Week 56 assessments should be completed for patient's prematurely discontinuing treatment. Patient's remaining in the study should then continue onto the follow-up visit schedule.

[f] For patients withdrawing after the end of treatment but prior to follow-up 24, the assessments as per the follow-up Week 24 visit should be completed.

[g] For patients withdrawing after follow-up Week 24, the assessments as per follow-up Year 1 visit should be completed.

[h] Informed consent signed by the patient's parent/legal guardian and informed consent or assent (if applicable) signed by the patient.

[i] Clinically significant diseases within the previous 2 years and HBV history. After baseline, new or worsening abnormalities should be recorded on the adverse events eCRF

[j] Including any significant concomitant medications taken within 2 years prior to baseline. During follow-up only concomitant medications (including herbal agents) for HBV need to be recorded.

[k] Including any significant surgeries/procedures prior to baseline. During follow-up, only surgeries/procedures associated with reportable adverse events need to be recorded (see Section 5.3.1).

[l] Within 6 months prior to baseline; repeat at screening only if any change in the medical condition. Parameters do not need to be repeated at rescreening if performed within 6 months prior to baseline, unless dictated by a change in the patient's medical condition or the parameter accounted for the original screen failure

[m] Blood pressure, heart rate, temperature.

[n] Measurements to be taken using the same instruments in the same individual. A stadiometer with mean of three readings should be used for height measurement. Exception to using the same instruments in the same individual is if patients are measured at home by a mobile nurse, in which case the same brand of scales must be used by both the site and the mobile nurse for weight, and a stadiometer must still be used for height.

[o] A system will be in place to confirm the patient's BSA and intended dose of Pegasys® based on the patient's weight and height.

[p] From consenting biological parents. May be collected at any point during the study.

[q] *Date of menarche should be assessed at each visit as appropriate.*

[r] *If the patient/guardian agrees, Tanner Stage for all patients will be determined at baseline. Once a patient is deemed to have reached Tanner Stage 5, no further assessments are required.*

[s] By ophthalmologist and including fundoscopic examination with dilation, visual acuity assessment, visual field testing and color visual testing. Eye examination by a pediatric ophthalmologist is recommended. Visual field testing by confrontation is recommended for younger patients. Any patient who develops ocular symptoms should receive a prompt eye examination by an ophthalmologist and additional examinations as necessary.

[t] Must show no signs of HCC, and for patients without study entry liver biopsy must also show no signs of cirrhosis or splenomegaly.

[u] If applicable (see Section 4.1.1). Where available, the liver biopsy score should be reported on the CRF

[v] Children ≥7 years of age only. Should be performed prior to the completion of other study assessments.

[w] After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol mandated intervention should be reported. Beyond follow-up Week 24 investigators should report persisting AEs, new-onset SAEs or, non-serious AEs of special interest that are believed to be related to prior treatment with study drugs and any deaths.

[x] Dipstick with subsequent microscopic evaluation if positive for blood. To be performed by site/local laboratory.

[y] Complete blood count (hemoglobin, hematocrit, reticulocytes, total WBC count, differential WBC count [neutrophils, lymphocytes, monocytes, eosinophils, basophils], platelet count), INR.

[z] ALT, AST, GGT, bilirubin (total, direct and indirect), alkaline phosphatase, total protein, albumin, BUN/urea, creatinine, uric acid, total calcium, phosphorus, cholesterol, triglycerides, random glucose, sodium, chloride, potassium. Estimated creatinine clearance to be calculated by sites during lamivudine or entecavir treatment any time creatinine is abnormal (see formula in Appendix 5), and internally by Roche at baseline and Week 56.

[aa] If there are clinically significant laboratory abnormalities, repeat no less frequently than every 2 weeks or as clinically indicated, with appropriate toxicity management, until values return to normal or baseline.

[bb] Females of child bearing potential only (Tanner stage ≥2, where available, or onset of menarche). Test as per schedule and any time secondary amenorrhea of more than 1 week occurs. Serum pregnancy test at screening. Urine pregnancy tests may be performed at subsequent visits. Result of baseline pregnancy test must be available prior to randomization and commencement of treatment. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test. Urine pregnancy test to be performed by site.

[cc] Sample will be retained frozen at the central laboratory in the event that repeat testing is required. If patient provides consent/assent to RCR

samples, residual serum bank samples will be converted into additional RCR serum samples at the end of the study.

[dd] If lamivudine or entecavir viral resistance is detected at follow-up Week 4 or the test is unsuccessful, a blood sample to assess for lamivudine or entecavir viral resistance should be collected at follow-up Week 24; if lamivudine or entecavir viral resistance is detected at follow-up Week 24, then testing should continue *up to the last* time point *of* the follow-up period. If HBV DNA measurement was negative at follow-up Week 4 but becomes positive at follow-up Week 24, an unscheduled blood sample may be requested for lamivudine or entecavir viral resistance testing, preferably within 2–4 weeks; if lamivudine or entecavir viral resistance is detected, lamivudine or entecavir viral resistance testing should *be performed* at *the last* time point *of* the follow-up period.

[ee] Not applicable for a site that has not been granted approval for RCR sampling. RCR sample for DNA extraction at baseline only.

Appendix 1C
Schedule of Assessments: Untreated Control

Assessment/Procedure	Screen Week	Untreated Observation Week [a]			
	-6 to -1	BL	32[w]	56[w]	80[b]
Informed consent/assent [c]	x				
Medical history [d]	x	x			
Demography	x				
Concomitant medications [e]	x	x	x	x	x
Surgeries/procedures [f]	x	x	x	x	x
Physical examination	x	x			x
Symptom-directed PE			x	x	
ECG [g]	x				
Vital signs [h]	x	x	x	x	x
Height (cm) [i]	x	x	x	x	x
Weight (kg) [i]	x	x	x	x	x
Parental height [j]		x			
Date of menarche for females	x	x	x	x	x
Tanner Stage [x]		x		x	
Ophthalmology [k, g]	x				
Liver abdominal ultrasound [l, g]	x				
Liver biopsy [m]	x				
CDI [n]	x	x			
AEs [o]	x	x	x	x	x
Urinalysis [p, s]	x	x	x	x	x
Hematology, coagulation [s, q]	x	x	x	x	x
Chemistry [r, s]	x	x	x	x	x
Lactate		x			
FT3, FT4, TSH [s, g]	x		x	x	x
TPO antibodies, TBG [g]	x				
ASMA, ALKM1, ANA [g]	x	x	x	x	x
AFP, A1AT [g]	x				
Pregnancy test [t]	x	x			
Anti-HAV IgM, anti-HCV, anti-HIV, and anti-HDV [g]	x				
HBV genotype [g]	x				
HBsAg, HBeAg, (anti-HBe, anti-HBs) [g]	x	x	x	x	x
Quantitative HBsAg/HBeAg [g]		x	x	x	x
HBV DNA [g]	x	x	x	x	x
Serum bank sample [u]		x	x	x	x
Lamivudine or entecavir viral resistance		x			
RCR samples (optional) [v]		x	x	x	x

AE = adverse event, A1AT = α-1-antitrypsin; Ab = antibody; AFP = α-fetoprotein; ALKM1 = anti-liver-kidney microsome-1 antibodies; ANA = antinuclear antibody; ASMA = anti–smooth muscle antibody; anti-HBe = hepatitis B envelope antibody; anti-HBs = hepatitis B surface antibody; BL = baseline (Day 1); BSA = body surface area; CDI = Children's Depression Inventory; eCRF = electronic Case Report Form; FT3 = free triiodothyronine; FT4 = free thyroxin; f/u = follow-up; HAV = hepatitis A virus; HBeAg = hepatitis B envelope antigen; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDV = hepatitis D virus; IgM = immunoglobulin M, PE = physical examination; PK = pharmacokinetic; RCR = Roche Clinical Repository;

Appendix 1C
Schedule of Assessments – Untreated Control (cont.)

SAE = serious adverse event; TBG = Thyroxine-binding globulin; TPO = Thyroid peroxidase; TSH = thyroid stimulating hormone.

a. For visits up to and including Week 80, the visit window is ±7 days.
b. For patients withdrawing prior Week 80, the assessments as per the Week 80 visit should be completed.
c. Informed consent signed by the patient's parent/legal guardian and informed consent or assent (if applicable) signed by the patient.
d. Clinically significant diseases within the previous 2 years and HBV history. After baseline, new or worsening abnormalities should be recorded on the AE eCRF
e. Including any significant concomitant medications taken within 2 years prior to baseline.
f. Including any significant surgeries/procedures prior to baseline.
g. Within 6 months prior to baseline; repeat at screening only if any change in the medical condition. Parameters do not need to be repeated at rescreening if performed within 6 months prior to baseline, unless dictated by a change in the patient's medical condition or the parameter accounted for the original screen failure
h. Blood pressure, heart rate, temperature.
i. Measurements to be taken using the same instruments in the same individual. A stadiometer with mean of three readings should be used for height measurement. Exception to using the same instruments in the same individual is if patients are measured at home by a mobile nurse, in which case the same brand of scales must be used by both the site and the mobile nurse for weight, and a stadiometer must still be used for height.
j. From consenting biological parents. May be collected at any point during the study.
k. By ophthalmologist and including fundoscopic examination with dilation, visual acuity assessment, visual field testing, and color visual testing. Eye examination by a pediatric ophthalmologist is recommended. Visual field testing by confrontation is recommended for younger patients. Any patient who develops ocular symptoms should receive a prompt eye examination by an ophthalmologist and additional examinations as necessary.
l. Must show no signs of HCC, and for patients without study entry liver biopsy must also show no signs of cirrhosis or splenomegaly.
m. If applicable (Section 4.1.1). Where available, the liver biopsy score should be reported on the CRF.
n. Children ≥7 years of age only.
o. After informed consent has been obtained but prior to baseline, only SAEs caused by a protocol mandated intervention should be reported.
p. Dipstick with subsequent microscopic evaluation if positive for blood. To be performed by site/local laboratory.
q. Complete blood count (hemoglobin, hematocrit, reticulocytes, total WBC count, differential WBC count [neutrophils, lymphocytes, monocytes, eosinophils, basophils], platelet count), INR.
r. ALT, AST, GGT, bilirubin (total, direct and indirect), alkaline phosphatase, total protein, albumin, BUN/urea, creatinine, uric acid, total calcium, phosphorus, cholesterol, triglycerides, random glucose, sodium, chloride, potassium. Estimated creatinine clearance to be calculated internally by Roche at baseline and Week 56.
s. If there are clinically significant laboratory abnormalities, repeat no less frequently than every 2 weeks or as clinically indicated, with appropriate toxicity management, until values return to normal or baseline.
t. Females of child bearing potential only. Test any time secondary amenorrhea of more than 1 week occurs. Serum pregnancy test at screening. Urine pregnancy tests may be performed at subsequent visits. Result of baseline pregnancy test must be available prior to randomization and commencement of treatment. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test. Urine pregnancy test to be performed by local laboratory.

Appendix 1C
Schedule of Assessments – Untreated Control (cont.)

u. Sample will be retained frozen at the central laboratory in the event that repeat testing is required. If patient provides consent/assent to additional RCR samples, residual serum bank samples will be converted into RCR serum samples at the end of the study. Not applicable for a site that has not been granted approval for RCR sampling.

v. Not applicable for a site that has not been granted approval for RCR sampling. RCR sample for DNA extraction at baseline only.

w. Visit may be conducted at the patient's home (e.g., by a mobile nurse), if this is feasible and more convenient for the patient, and upon agreement with the investigator.

x. Depending on IRB/EC and HA approval, and if the patient/guardian agrees, Tanner stage for all patients will be determined at baseline. Once a patient is deemed to have reached Tanner stage 5, no further assessments are required.

Appendix 2
Child Pugh Classification of Severity of Liver Disease

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality		
	1	2	3
Encephalopathy (grade) [a]	None	1 or 2	3 or 4
Ascites [b]	Absent	Slight	Moderate
Bilirubin (μmol/L)	< 34	34–50	> 50
Albumin (g/L)	> 35	28–35	< 28
Prothrombin time prolongation (seconds prolonged) **OR**	< 4	4–6	> 6
Prothrombin time (International Normalized Ratio)	< 1.7	1.7–2.3	> 2.3

[a] According to grading of Trey et al.1966.

[b] As determined by physical examination alone.

1, 2, or 3 points are scored for increasing abnormality of each of the 5 parameters measured.

Class A: 5 or 6

Class B: 7 to 9

Class C: 10 to 15

Appendix 3 Liver Biopsy Scores

Various liver biopsy classification systems may be used for entry into this study. Some examples are included below.

Scores considered as minimal or mild fibrosis will be Metavir Fibrosis Score 0 – 2; Knodell Fibrosis Score 0 – 1; Modified Ishak Fibrosis Score 0 – 3; Batts & Ludwig Fibrosis Score 0 – 2; or Scheuer Fibrosis Score 0 – 2.

Scores considered as advanced fibrosis and cirrhosis will be Metavir Fibrosis Score 3 – 4; Knodell Fibrosis Score 3 – 4; Modified Ishak Fibrosis Score 4 – 6; Batts & Ludwig Fibrosis Score 3 – 4; or Scheuer Fibrosis Score 3 – 4. Patients with these scores are excluded from the study.

METAVIR FIBROSIS SCORE

0. No fibrosis
1. Stellate enlargement of portal tract but without septa formation
2. Enlargement of portal tract with rare septa formation
3. Numerous septa without cirrhosis
4. Cirrhosis

KNODELL FIBROSIS SCORE

5. No fibrosis
6. Fibrous portal expansion
7. Bridging fibrosis (portal-portal or portal-central linkage)
8. Cirrhosis

MODIFIED ISHAK FIBROSIS SCORE

9. No fibrosis
10. Fibrous expansion of some portal areas, with or without short fibrous septa
11. Fibrous expansion of most portal areas, with or without short fibrous septa
12. Fibrous expansion of most portal areas, with occasional portal to portal (P-P) bridging
13. Fibrous expansion of portal areas, with marked bridging (P-P) as well as portal-central (P-C)
14. Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)
15. Cirrhosis, probable or definite

Appendix 3 Liver Biopsy Scores (cont.)

BATTS & LUDWIG FIBROSIS SCORE

0. No fibrosis; normal connective tissue

1. Portal fibrosis; fibrous portal expansion

2. Periportal fibrosis; periportal or rare portal-portal septa

3. Septal fibrosis; fibrous septa with architectural distortion; no obvious cirrhosis

4. Cirrhosis

SCHEUER FIBROSIS SCORE

0. None

1. Enlarged by fibrosis

2. Portal-portal linkage

3. Distortion, not cirrhotic

4. Cirrhosis (or probable)

Appendix 4
Pegasys® Dose Modification Guidance

The intention of the protocol is that patients remain on study treatment until the completion of the allocated treatment period. However, it is possible that some patients will encounter transient or prolonged adverse effects at some juncture during their participation in the study leading to adjustment of study drug dosage. To minimize the effects of these modifications on the eventual evaluation of the safety, tolerability, and efficacy of test drug regimens, dose adjustment guidance is provided in this Appendix, including guidance for management of specific effects. It should be kept in mind that, whereas this guidance should be generally followed to promote consistency across centers, other responses by an investigator may be more appropriate in some circumstances.

Moderate or severe adverse reactions (clinical and/or laboratory) may require dose reduction. Decremental adjustments should be uniform across centers and patients. When practicable, abnormal laboratory results should be confirmed as soon as possible following notification of the investigator. For laboratory and vital signs abnormalities, "severe" may be considered as any value requiring intervention, further work up, or more frequent follow-up (Section 5.3.3).

If consistent with patient safety, doses should not be held or eliminated. This recommendation stems from concerns that extended periods of lowered drug concentrations in the blood may be associated with the replication of the more resistant clones of the virus, resulting in a lack of sustained response at the conclusion of therapy. Investigators should consider if adjusting the dose, either transiently or permanently, might be appropriate rather than holding a dose.

The investigator will record the patient's recommended dose of study medication on the medication diary.

Missing Consecutive Doses

If four or more consecutive doses of Pegasys® are held or otherwise not administered (i.e., the patient has not received test medication for more than 28 days), the patient will be considered intolerant of the test medication or non-compliant, whichever is more appropriate to the clinical situation. No additional test drug may be administered to such patients, without explicit permission from the sponsor.

Appendix 4
Pegasys® Dose Modification Guidance (cont.)

Dose Delay

If a Pegasys® dose is delayed but eventually administered, the following guidelines should be utilized for the next scheduled dose(s):

- Dose delayed 1 or 2 days: administer on usual dosing day of the week (e.g., if Monday is the usual dosing day and the dose is delayed until Wednesday, the next dose may be administered as usual on Monday).
- Dose delayed 3 to 5 days: administer subsequent doses every fifth or sixth day until the patient is back to his or her original schedule (e.g., if Monday is the usual dosing day and the dose is delayed until Saturday, the next dose should be administered on Thursday, the following dose on Tuesday, then the dose after that as usual on Monday).
- Dose delayed 6 days: hold the dose for that week then continue on the usual schedule the following week (e.g., if Monday is the usual dosing day but the patient is not ready to be dosed until the following Sunday, the dose is considered to have been held and the next injection should be for the following week's dose on Monday).
- Dose delayed ≥7 days: the investigator may reintroduce test drug at any time and, if necessary, dose the patient every fifth or sixth day until the patient resumes weekly dosing on their usual scheduled day.

Dose Reduction Levels

The downward adjustments in Table 1 below should be utilized. If appropriate, downward adjustments in one level decrements should be considered.

Table 1 Pegasys® Dose Reduction Levels

Starting Dose		One-Level Reduction		Two-Level Reduction		Three-Level Reduction	
(μg)	(mL)	(μg)	(mL)	(μg)	(mL)	(μg)	(mL)
45	0.25	30	0.17	20	0.11	10	0.06
65	0.36	45	0.25	30	0.17	20	0.11
90	0.50	65	0.36	45	0.25	20	0.11
135	0.75	90	0.50	65	0.36	30	0.17
180	1.00	135	0.75	90	0.50	45	0.25

Appendix 4
Pegasys® Dose Modification Guidance (cont.)

Once the patient's unit dose has been decreased, the investigator may attempt to increase the dose back to or toward that which was originally assigned only if the following conditions are satisfied:

- The event or circumstance responsible for the dosage adjustment has resolved or improved
- Patients who have received more than four consecutive or six total doses at the lower dose level should not generally have their dosage regimen readjusted upward.

Specific Dose Reduction Guidance

Neutropenia, Thrombocytopenia and Elevated Serum ALT

Table 2 Neutropenia

ANC ($\times 10^9$ cells/L)	Response
≥0.75	None
0.5–0.749	Immediate one-level adjustment and monitor
0.25–0.499	Delay or hold dose until ≥1.0 then resume dose with two-level adjustment and monitor
<0.25 or febrile neutropenia	PERMANENTLY DISCONTINUE STUDY TREATMENT

Table 3 Thrombocytopenia

Platelets ($\times 10^9$ cells/L)	Response
<50	Two-level dose reduction
<25	PERMANENTLY DISCONTINUE STUDY TREATMENT

Table 4 Elevated Serum ALT

ALT	Response
Persistent or increasing elevations ≥ 5 but < 10 × ULN	Reduce dose with a 1 level adjustment and monitor weekly ALT level to ensure it is stable or decreasing
Persistent ALT values ≥ 10 × ULN	PERMANENTLY DISCONTINUE STUDY TREATMENT

Appendix 4
Pegasys® Dose Modification Guidance (cont.)

Severe Mood or Psychiatric Disorder

In cases of severe mood or psychiatric disorder, study treatment must be permanently discontinued and the patient referred for psychiatric intervention.

Table 5 Recommended PEGASYS® Dosage Modifications and Psychiatric Visits Due to Depression

Depression Severity	Initial Depression Management 4-8 Weeks		Depression Management after 8 Weeks		
	Dosage Modification	Visit Schedule	Depression Severity Remains Stable	Depression Severity Improves	Depression Severity Worsens
Mild	No change	Evaluate once weekly by visit and/or phone	Continue weekly visit schedule	Resume normal visit schedule	Consider psychiatric consultation. Discontinue Pegasys® or one or two level dose reduction
Moderate	One or two level dose reduction	Evaluate once weekly (office visit at least every other week)	Consider psychiatric consultation. Continue reduced dosing	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosage or return to normal dosage	Obtain immediate psychiatric consultation Discontinue Pegasys® permanently.

Appendix 4
Pegasys® Dose Modification Guidance (cont.)

Depression Severity	Initial Depression Management 4-8 Weeks		Depression Management after 8 Weeks		
	Dosage Modification	Visit Schedule	Depression Severity Remains Stable	Depression Severity Improves	Depression Severity Worsens
Severe	Discontinue Pegasys® Permanently	Obtain immediate psychiatric consultation	Psychiatric therapy necessary		

Change of Body Surface Area Category

Investigators will adjust the dose of Pegasys® upward or downward to reflect the most current Body Surface Area (BSA) category. A system will be in place to confirm BSA and dose based on the patient's weight and height at the time points indicated in the Schedule of Assessments (see Appendix 1). Investigators may also assess the patient's BSA (using the Mosteller formula) at other interim time points if they are concerned that the BSA and therefore Pegasys® dosing category may have changed. It is recommended that an online calculator is utilized for the BSA calculation.

Mosteller Formula:

$$BSA\ (m^2) = \sqrt{[Height(cm) \times Weight(kg)] / 3600}$$

If BSA falls below <0.51m^2 during treatment, any dose adjustments should be made only after consultation between the Investigator and Medical Monitor. The recommended dose will be recorded on the medication diary.

Appendix 5
Estimated Creatinine Clearance
Schwartz Formula 2009

$$\text{Estimated creatinine clearance (mL/min/1.73 m}^2\text{)} = \frac{0.413 \times \text{Height (cm)}}{\text{Serum Creatinine (mg/dL)}}$$

(Formula reproduced from Schwartz et al 2009)

Appendix 6
Tanner Stages

Sexual Maturity Stages in Boys and Girls

Stage	Male Genitalia	Pubic Hair	Female Breasts
1	Pre-adolescent—testes, scrotum, and penis are child-like in size	None; may be vellus hair, as over abdomen	Pre-adolescent—elevation of papilla only
2	Slight enlargement of scrotum with reddening of skin; little or no enlargement of penis	Sparse growth of long, slightly pigmented, downy hair, straight or slightly curled, primarily at base of penis or along labia	Breast bud stage; breast and papilla form a small mound; areolar diameter enlarges
3	Further enlargement of scrotum; penis enlarges, mainly in length	Hair considerably darker, coarser, and more curled; spreads sparsely over junction of pubes	Further enlargement of breast and areola with no separation of their contours
4	Further enlargement and darkening of scrotum; penis enlarges, especially in breadth; glans develops	Adult-type hair that does not extend onto thighs, covering a smaller area than in adult	Areola and papilla project to form a secondary mound above the contour of the breast; stage 4 development of the areolar mound does not occur in 10% of girls and is slight in 20%; when present, it may persist well into adulthood
5	Adult in size and shape	Adult in quantity and type with extension onto thighs but not up linea alba	Mature female; papilla projects and areola recesses to general contour of breast

Data from Tanner JM: Normal growth and techniques of growth assessment. Clin Endocrinol Metab 15:436, 1986.

In boys, if different scores are obtained for pubic hair and genitalia, the score for genitalia should be used.

In girls, if different scores are obtained for pubic hair and breast development, the score for breast development should be used.