Official Title: A Phase IIIb Parallel Group, Open Label Study of Pegylated Interferon alfa-2a Monotherapy (PEG-IFN, Ro 25-8310) Compared to Untreated Control in Children with HBeAg Positive Chronic Hepatitis B in the Immune Active Phase

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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE IIIB PARALLEL GROUP, OPEN LABEL STUDY OF PEGYLATED INTEFERON ALFA-2A MONOTHERAPY (PEG-IFN, RO 25-8310) COMPARED TO UNTREATED CONTROL IN CHILDREN WITH HBeAg POSITIVE CHRONIC HEPATITIS B IN THE IMMUNE ACTIVE PHASE**

PROTOCOL NUMBER: **YV25718**

STUDY DRUG: **Pegylated Interferon alfa-2a**

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STATISTICAL ANALYSIS PLAN APPROVAL

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GLOSSARY OF ABBREVIATIONS

ACTG	AIDS Clinical Trials Group
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
anti-HBe	Hepatitis B envelope antibody
anti-HBs	Hepatitis B surface antibody
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
CHB	Chronic hepatitis B
CL/F	Clearance
C_{max}	Maximum concentration
CSR	Clinical Study Report
DAIDS	Division of AIDS
DAP	Data analysis plan
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
FPE	First patient enrollment
FT3	Free triiodothyronine
FT4	Free thyroxin

GGT	Gamma glutamyl transpeptidase
HBeAg	Hepatitis B envelope antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV-DNA	Hepatitis B DNA
ITT	Intent-to-treat
IxRS	Interactive voice or web response system
LLN	Lower limit of normal
LOCF	Last observation carried forward
LSM	Liver Stiffness Measure
LTFU	Long term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PEG-IFN	Pegylated-interferon alfa-2a
PK	Pharmacokinetic
PT	Preferred Term
RNA	ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SI units	International System of Units

SOC	System Organ Class
TBG	Thyroxine-binding globulin
TPO	Thyroid peroxidase
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
V/F	Volume of distribution/bioavailability

1. BACKGROUND

This randomized, controlled, parallel-group, open-label, multicenter study in children with hepatitis B envelope antigen (HBeAg) positive chronic hepatitis B (CHB) in the immune active phase will compare efficacy and safety between a group treated with pegylated interferon alfa-2a (PEG-IFN) monotherapy and an untreated control group, and evaluate pharmacokinetics (PK) of PEG-IFN following administration of a new body surface area (BSA)-based dosing regimen.

The rationale for conducting a randomized controlled study in pediatric patients with CHB is to establish the efficacy and safety of PEG-IFN treatment in this pediatric immunoactive population.

This statistical analysis plan (SAP, which is also known as Data Analysis Plan [DAP] Module 1) describes the data handling rules and statistical analysis methods to be used for the analysis of the clinical data from the phase IIIb study YV25718. The layout of tables, listings and figures will be provided in DAP Module 2; the data specification will be addressed in DAP Module 3.

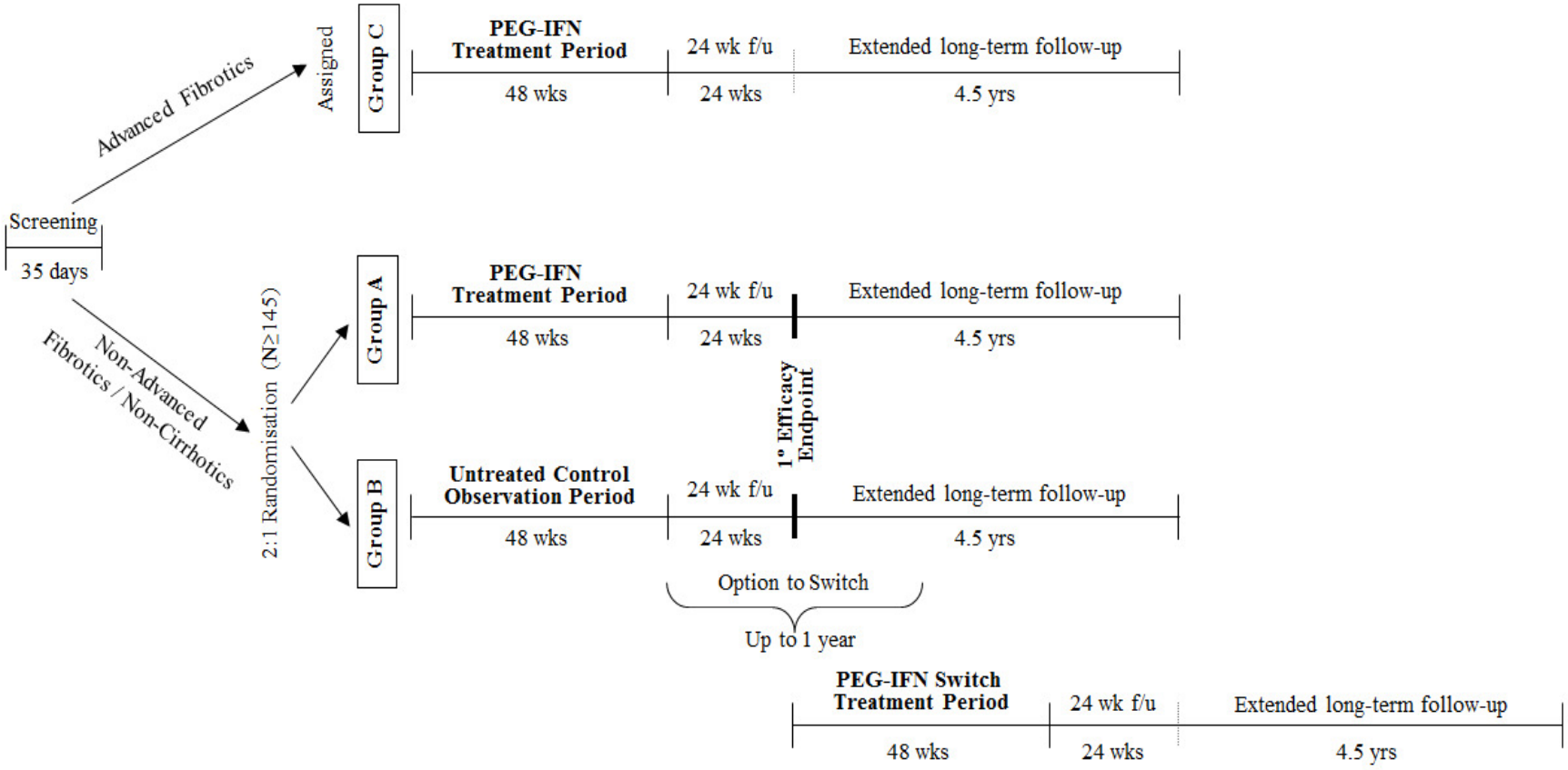
2. STUDY DESIGN

This is a 2:1 randomized, controlled, parallel-group, open-label, multicenter study of PEG-IFN treatment compared to an untreated control (Figure 1). Patients without advanced fibrosis/cirrhosis will be randomized 2:1 to PEG-IFN treatment (Group A) or untreated control (Group B), respectively. Patients with advanced fibrosis will be assigned to PEG-IFN treatment (Group C). Patients in Groups A and C will receive PEG-IFN for 48 weeks. The first 48 weeks from randomization will be referred to as the treatment period for Groups A and C and the principal observation period (this is also the untreated control observation period in Figure 1) for Group B. The primary endpoint will be assessed 24 weeks after the end of treatment/principal observation period.

Forty-eight weeks after randomization, PEG-IFN will be offered to patients in the Group B untreated control group who have not experienced HBeAg seroconversion. This offer will be available for up to 1 year following Week 48. If eligible, these patients will enter the Switch arm, where they will receive PEG-IFN for 48 weeks.

The screening period will be up to 35 days. All patients will be followed up for 5 years after the end of treatment/principal observation period. For Group A, Group B non-switch, and Group C patients the study length is approximately 6 years (1-year treatment/principal observation period and 5 years of follow-up). For Group B switch patients the study length is up to approximately 8 years (1-year principal observation period, up to 1 year follow-up whilst deciding whether to switch, 1-year switch treatment period, and 5-year follow-up period).

Figure 1 Schematic of Study Design[1]



[1] The untreated control observation period is the same as the principal observation period.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 STUDY OUTCOME MEASURES

This study will compare efficacy and safety between a group treated with PEG-IFN monotherapy and an untreated control group, and evaluate pharmacokinetics (PK) of PEG-IFN following administration of a new BSA-based dosing regimen.

Details of the study objectives could be found in the Protocol Synopsis as in Appendix 1.

2.3 DETERMINATION OF SAMPLE SIZE

Sample size is based on the χ^2 test statistic. Assuming a 32% HBeAg seroconversion rate for Group A (PEG-IFN) and 10% for Group B (untreated control), a total sample size of 145 patients provides at least 80% power at the 0.05 level of significance with a two-sided χ^2 test[2]. The sample size shall be increased by 10% and rounded to 160 patients to allow for advanced fibrotics (Group C).

2.4 ANALYSIS TIMING

The clinical data cut for the primary analysis is determined based on the comparison of primary efficacy endpoint between Group A and Group B, i.e. 24 weeks after the end of treatment/principal observation period.

The primary CSR will present the study results of efficacy, safety and pharmacokinetics on data up to the initial 24 weeks follow up after the end of treatment/principle observation period from Group A and B. Results from Group C from enrollment to 24 weeks after the end of treatment will be summarized separately in the primary CSR. Data from the Switch arm will not be mature for reporting and interpreting, thus only a summary of patient disposition, patient listings for deaths, SAEs and AEs leading to discontinuation of study treatment as of the cutoff date when all patients in Group A and Group B had their visits at 24 weeks after the end of treatment/principal observation periodwill be provided in the primary CSR.

The final analysis will be performed at the end of the extended long-term follow-up (LTFU) period of the study, i.e. 5 years after the end of treatment/principal observation period for all patients (including patients who switched to PEG-IFN treatment from Group B). Long term efficacy and safety data from Group A, B, C, along with all data from the Switch arm will be summarized in the final CSR.

[2] At least 130 patients must be evaluable for the primary endpoint, as required by Pediatric Investigational Plan.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

After signing informed consent/assent and meeting screening parameters, patients without advanced fibrosis or cirrhosis (assessed by liver biopsy performed within 2 years prior to baseline) will be randomized 2:1 into the PEG-IFN treatment (Group A) or untreated control (Group B) respectively. Stratification will be performed by genotype (A versus non-A) and ALT (<5xULN versus ≥5xULN). Patients with advanced fibrosis (assessed by liver biopsy performed within 9 months prior to baseline) will be assigned to PEG-IFN treatment (Group C). Patients in Group A and Group C will receive PEG-IFN for 48 weeks. Group and dose, if applicable, will be assigned by an interactive voice or web response system (IxRS).

The randomization list for the study was created by the IxRS vendor using their internal validated process. The study statistician reviewed a dummy randomization list that was created using the same validated process.

3.2 DATA MONITORING

Starting from 8-10 months after first patient enrollment (FPE) and then approximately every 6 months thereafter, an external Data Safety Monitoring Board (DSMB) will review individual and aggregate safety data on a routine basis (see DSMB charter). Enrollment will be suspended and/or the study will be halted if serious concerns about safety are raised pending further analysis and review. Enrollment and/or study re-start will resume only if the DSMB and the Sponsor are satisfied with the safety of treatment.

4. STATISTICAL METHODS

All analyses for comparing the PEG-IFN treatment (Group A) with untreated control (Group B) are presented in Section 4.3 to Section 4.6. Analyses for Group C and the Switch arm will be presented in Section 4.7 and Section 4.8 respectively.

4.1 ANALYSIS POPULATIONS

All patient populations will be defined and determined prior to the database lock for the primary CSR. All analyses below are planned for the primary CSR unless otherwise specified. Analyses for data in LTFU period will be summarized in final CSR.

Analysis populations described in Section 4.1.1 to Section 4.1.3 are defined for Group A and Group B. Analysis of all efficacy endpoints will be based primarily on the Intent-to-treat (ITT) population. In addition Per Protocol (PP) population will be used for the primary endpoint. Safety analyses will be performed based on the Safety population.

Patients who have advanced fibrosis (diagnosed on liver biopsy) will receive PEG-INF treatment in an advanced fibrotic arm (Group C). Efficacy analyses and safety analyses will be reported from all patients in Group C who receive at least one dose of study

medication.

The Switch arm includes patients randomized to Group B who opt to switch to initiating treatment with PEG-IFN after Week 48. Efficacy and safety data will be reported from all patients entering the switch arm if at least one dose of study medication was taken.

4.1.1 Intent-to-treat (ITT) Population

For Group A, the ITT population shall include all patients who receive at least one dose of study medication. For the untreated Group B, the ITT population shall include all randomized patients. Patients will be assigned to the group to which they were randomized.

4.1.2 Per Protocol (PP) Population

The per protocol population will include all patients randomized in Group A and Group B, who received at least one dose of study medication if in Group A, and who had none of the major protocol violations or deviations listed below. Patients will be assigned to the treatment group as per actual treatment they received.

The criteria for exclusion from the PP populations are defined as:

1. those in Group A who meet any of the criteria below, including:
    - received less than 39 doses of PEG-IFN or took $\leq$ 80% of treatment duration of PEG-IFN (i.e., less than 39 weeks of PEG-IFN treatment)
2. those in Group A and Group B who meet the criteria below:
    - HBeAg negative at screening
3. those in Group A and Group B who meet the criteria below:
    - ALT $\leq$ 1xULN or ALT > 10xULN at both screening and baseline
4. those in Group A and Group B who meet the criteria below:
    - Who have had any of the treatment within 6 months prior to baseline or during study (Group A: up to 24 weeks after the end of treatment; Group B up to 24 weeks after the end of principle observation period or prior to switch if switch occurs) as: interferons, lamivudine, tenofovir,emtricitabine, adefovir, entecavir, telbivudine
5. those in Group A and Group B who meet the criteria below:
    - Neutrophil count < 1.5 x 10^9 cells/L at screening

6. those in Group A and Group B who meet the criteria below:

    - Platelet count < 90 x 10^9 cells/L at screening

7. those in Group A and Group B who meet the criteria below:

    - Hemoglobin < lower limit of normal (LLN) at screening

4.1.3 Safety Population

For Group A, the Safety population included all patients who received at least one dose of study medication and had at least one post-baseline safety assessment; for Group B, the safety population included all patients who had at least one post-baseline safety assessment. Patients will be assigned to treatment groups as treated.

4.1.4 Pharmacokinetic (PK) Population

The pharmacokinetic evaluable population consists of all patients who are consented to PK sub-study and received PEG-IFN treatment, who have adequate PK collection over the first 24 weeks.

4.2 ANALYSIS OF STUDY CONDUCT

Reasons for exclusion from study populations will be summarized by groups. Patients excluded from study populations will be listed.

All major protocol violations will be listed and summarized by group.

Number and percentage of patients completed 12, 24, 36 and 48 weeks of treatment/principal observation period, and 12, 24 weeks of follow-up will be summarized for Group A and Group B.

The number of patients randomized to Group A who withdraw from treatment period, and the number of patients randomized to Group A and Group B who withdraw from study, will be separately summarized and presented; further the reasons for withdrawal will be included. Listing of withdrawal from study medication and withdrawal from study for all patients in Group A and Group B will be produced.

Time windows will be defined in DAP Module 2.

4.3 BASELINE CHARACTERISTICS

4.3.1 Demographics and Baseline Characteristics

Summary statistics will be presented for ITT population for the following demographics, including categorical variables:

Sex, Age group (<5, 5 ~ 12, ≥12), Race, Ethnicity, Body surface area group, Country

and continuous variables:

age, weight at baseline, height at baseline, Body Mass Index (BMI), body surface area, weight for age percentile, height for age percentile, weight for age z-score, height for age z-score.

Summary statistics will be presented by ITT population for the baseline characteristics, including categorical factors:

- ALT at Baseline (<1xULN, ≥1xULN ~ <2xULN, ≥2xULN ~ <5xULN, ≥5xULN ~ <10xULN, ≥10xULN)
- HBV genotype
- Family history of HBV
- Mode of HBV acquisition
- Histological diagnosis for fibrosis
- Scale or method used for fibrosis score
- Fibrosis score

and continuous factors:

- HBV-DNA at Baseline
- HBeAg at Baseline
- HBsAg at Baseline
- ALT at Baseline.

4.3.2 Previous and Concomitant Diseases

All previous diseases and concomitant diseases will be summarized for ITT population.

4.3.3 Previous and Concomitant Medications

All previous medications and concomitant medications will be summarized for ITT population.

4.4 EFFICACY ANALYSIS

Analysis of all efficacy endpoints will be based primarily on the ITT population. In addition, the PP population will be used for the primary endpoint.

Unless otherwise stated, all statistical tests will be two-sided and performed at the 5% of significance level.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is HBeAg seroconversion at 24 weeks after the end of treatment/ principal observation period for Group A and Group B. HBeAg seroconversion

is defined as absence of HBeAg (that is, a negative result for HBeAg) and presence of anti-HBe (that is, a positive result for anti-HBe).

The response rate of HBeAg seroconversion for a particular analysis population will be determined by:

$$\frac{\text{The number of patients with Negative HBeAg and Positive HBeAb at each visit}}{\text{The number of patients in each group for that analysis population}} \times 100\%.$$

Patients without either HBeAg or anti-HBe at 24 weeks after the end of treatment/principal observation period will be counted as non-responders. Patients in Group B who switched to receive PEG-IFN after Week 48 and prior to 24 weeks post-observation period will also be counted as non-responders.

4.4.1.2 Hypothesis Testing and Analysis Methods

The following hypotheses will be tested using the Cochran-Mantel-Haenszel (CMH) test[3] stratified by genotype (A vs. non-A) and ALT (< 5xULN and ≥ 5xULN) at screening:

H_0: odds ratio of {probability to achieve HBeAg seroconversion in group A} versus {probability to achieve HBeAg seroconversion in group B} = 1

against the alternative

H_a: odds ratio of {probability to achieve HBeAg seroconversion in group A} versus {probability to achieve HBeAg seroconversion in group B} ≠ 1.

The Cochran-Mantel-Haenszel estimates of the common odds ratio, adjusted by stratification factors (genotype (A vs. non-A) and ALT (< 5xULN and ≥ 5xULN)) , will be reported, accompanied by the associated 95% confidence intervals. Breslow-Day test will be used to assess the homogeneity of the odds ratios across the strata. The CMH test stratified by genotype (A vs. non-A) and ALT (< 5xULN and ≥ 5xULN) at screening will also be performed based on the PP population.

4.4.1.3 Sensitivity Analysis for Primary Endpoints

In addition to the stratified statistical tests, unstratified tests such as Pearson chi-square test and Fisher's exact test will be performed.

In the primary efficacy analysis, patients with missing values of primary endpoint will be considered as non-responders. In order to evaluate the robustness, sensitivity analysis will be carried out using CMH test, where missing values will be imputed with the approach of last observation carried forward (LOCF).

[3] which is a superiority test.

4.4.2 Secondary Efficacy Endpoints

The secondary efficacy analyses will be performed in the ITT population. No hierarchical or sequential testing will be used for secondary efficacy endpoints.

Several secondary parameters will be assessed at the end of treatment/principal observation period, 24 weeks after the end of treatment/principal observation period in primary CSR; in addition, during the extended LTFU period, i.e. at 1, 2, 3, 4 and 5 years after the end of treatment/principal observation period in final CSR.

Secondary efficacy endpoints include two types of endpoints:

- Binary endpoints:
    - HBeAg seroconversion (except HBeAg seroconversion at the time point of 24 weeks at the end of treatment/principal observation period)
    - Loss of HBeAg
    - HBsAg seroconversion
    - Loss of HBsAg
    - Normal ALT (defined as ALT $\leq$ ULN, where each ULN is given by each laboratory)
    - Suppression of HBV-DNA:
        - <20,000 IU/mL
        - <2,000 IU/mL
        - Undetectable (defined as <29 IU/mL as per TAQMAN-HBV QUANT polymerase chain reaction (PCR) assay)
    - Combined endpoints:
        - HBeAg seroconversion and HBV-DNA <20,000 IU/ml
        - HBeAg seroconversion and HBV-DNA <2,000 IU/mL
- Continuous endpoints:
    - Quantitative serum ALT value, and its change from baseline
    - Quantitative HBV-DNA value, and its change from baseline
    - Quantitative HBeAg value, and its change from baseline
    - Quantitative HBsAg value, and its change from baseline

For all binary endpoints, missing values would be considered as non-responders. For all continuous endpoints, no imputation approach will be implemented to missing values.

Descriptive statistics of the secondary efficacy binary endpoints will be summarized by treatment group. P-values of these binary endpoints will be presented using Fisher's exact test.

Continuous endpoints will be descriptively summarized over time by treatment group. Graphs of continuous secondary endpoints and their corresponding 95% confidence intervals over time will be displayed by treatment group.

4.4.3 Subgroup Analyses

Subgroup analyses will be conducted for the primary endpoint, i.e. HBeAg seroconversion at 24 weeks after the end of treatment/principal observation period in ITT population. The follow baseline factors will be included in the subgroup analyses:

- Age groups (<12, ≥12)
- Age groups (<5, ≥5)
- Baseline BSA groups
- Race (Asian, Caucasian, Other)
- Sex
- BMI (<18.5, 18.5 ~ 24.9, >25.0)
- HBV genotype (A, B, C, D, Other)
- Baseline ALT (<5xULN, ≥5xULN)
- Baseline $\log_{10}$(HBV-DNA) (≤median, >median)
- Baseline $\log_{10}$(HBeAg) (≤median, >median)
- Baseline $\log_{10}$(HBsAg) (≤median, >median).

4.4.4 Exploratory Analysis

Exploratory logistic regression analyses will be performed to examine the demographics and baseline disease characteristics on the response rate of HBeAg seroconversion at 24 weeks after the end of treatment/principal observation period. Baseline factors including age, sex, race, BSA, BMI, HBV genotype, treatment group and ALT will be examined. Stepwise, backward and multiple logistic regression models will be explored.

4.4.5 Liver Elasticity Sub-study

Liver elasticity analysis in this section will be performed on those patients enrolled in liver elasticity sub-study[4]. Liver elasticity analysis results will be separately displayed for those patients enrolled in liver elasticity sub-study.

Liver stiffness measure (LSM) and its change from baseline over time will be summarized by treatment group. Graphs of change from baselines of LSM and their corresponding 95% confidence intervals over time will be displayed by treatment group.

Baseline LSM will be summarized by baseline characteristics subgroups, including fibrosis stages, age groups (<12, ≥12) and BMI (<18.5, 18.5 ~ 24.9, >25.0). Box plots of baseline LSM will be displayed by various baseline characteristics subgroups above.

Baseline liver elasticity will also be explored for association with the screening liver biopsy result in these sub-study patients using liver biopsy fibrosis score, using Spearman's correlation coefficients. Confidence intervals of correlation coefficients will be provided as needed.

4.5 PHARMACOKINETIC ANALYSES

PK parameters (e.g., clearance [CL/F], volume of distribution [V/F], area under the curve [AUC], maximum concentration [C_{max}], etc.) of PEG-IFN will be estimated using a population PK modeling approach.

All PK parameters will be presented descriptively including arithmetic means, standard deviations, geometric means, coefficients of variation, medians, and ranges.

The relationship between clinical endpoints and PEG-IFN serum exposure may be explored.

The relationship between PK and pharmacodynamics (PD) parameters (e.g., AUC vs. neutropenia) may be explored.

Detailed PK and PK/PD results will be separately planned and presented in a separate population PK analysis report.

4.6 SAFETY ANALYSES

Safety analyses will be performed based on the Safety population.

4.6.1 Exposure of Study Medication

The duration of study drug administration, actual cumulative dose and percentage of actual cumulative dose in planned cumulative dose will be summarized for Group A. A patient listing of study drug administration by center/patient number for Safety Population of Group A will be provided.

[4] At least 50 consenting/assenting patients at specific sites will take part in the liver elasticity sub-study.

4.6.2 Adverse Events

All adverse events (AEs) will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version during the study and will be classified by Preferred Term (PT) and System Organ Class (SOC). In primary CSR, AEs from study beginning to 24 weeks after the end of treatment/principal observation period will be reported.

AE summaries will be generated as what follows:

- All AEs by SOC and PT;
- All AEs by intensity[5];
- AEs by relation to treatment;
- Most frequent AEs with an incidence rate of at least 5% in decreasing order;
- Serious adverse events (SAEs);
- Non-serious AEs of special interests, including: ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN; ALT or AST > 3 x baseline value in combination with clinical jaundice; Suspected transmission of an infectious agent by the study drug
- AEs and lab abnormalities leading to dose modification (Group A);
- AEs and lab abnormalities leading to withdrawal from the study treatment.

Listings of all reported AEs, SAEs, non-serious AEs of special interests, death, AEs and lab abnormalities leading to dose modification, and AEs and lab abnormalities leading to withdrawal from the study treatment, will be provided.

All AEs by SOC and PT will be summarized for age subgroups (<12, ≥12), and age subgroups (<5, ≥5),

4.6.3 Laboratory Data

If more than one visit occurred during a single visit window, then the laboratory data closest to the scheduled visit day will be used. If the two laboratory assessments were equidistant from the scheduled visit day then the later assessment will be used; if there was more than one 'later assessment', that is recorded on the same date and time, then the 'worst' case will be used. The exception is the data within the Baseline visit; in this case, if two or more samples were collected on the day that was closest to the Baseline

[5] The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events should be used to assist in the assessment of intensity

target day, then the earliest sample was selected; if the sample collection time was the same then the worst value was selected.

Laboratory data not reported in International System of Units (SI units) will be converted to SI units before further processing. The reference ranges of each investigator/local laboratory will be used for all parameters.

Listings of laboratory parameters at each visit will be provided by treatment group for Safety population. Summary tables of mean change from baseline of laboratory parameters will be provided (some laboratory parameters will be summarised as multiples of ULN instead of raw values: ALT, AST, alkaline phosphatase (ALP), total bilirubin, gamma glutamyl transpeptidase (GGT)).

Lowest and/or highest values of laboratory data post-baseline will be summarized by treatment group using the DAIDS grading system (except for those laboratory parameters with project-specific grandings provided in Figure 2). Shift table of the lowest and/or highest post-baseline DAIDS grade for laboratory parameters will be provided (except for those laboratory parameters with project-specific grandings provided). Patients with one or more thyroid function values outside the normal range and with change from baseline meeting pre-specified cutoffs (for free triiodothyronine [FT3] and free thyroxin [FT4], it is increase >=20% or decrease >=20%; for thyroid-stimulating hormone [TSH], it is increase >=30%) will be summarized and listed by treatment group in Safety Population.

Figure 2 Potentially Clinically Relevant Laboratory Abnormalities for Neutrophil, Lymphocyte, Platelet Counts, Hemoglobin, Triglyceride Concentration and ALT

Parameter	Project Specific Normal					
Neutrophil Count	≥2.0 x 10^9/L	1.5 - <2.0 x 10^9/L	1.0 - <1.5 x 10^9/L	0.75 - <1.0 x 10^9/L	0.5 - <0.75 x 10^9/L	<0.5 x 10^9/L
Lymphocyte Count	≥1.5 x 10^9/L	1.0 - <1.5 x 10^9/L	0.5 - <1.0 x 10^9/L	<0.5 x 10^9/L		
Platelet Count	≥100 x 10^9/L	75 - <100 x 10^9/L	50 - <75 x 10^9/L	20 - <50 x 10^9/L	<20 x 10^9/L	
Hemoglobin Concentration	≥10.0 g/dL	8.5 - <10.0 g/dL	<8.5 g/dL			
Triglyceride Concentration	< 1.13 mmol/L (<100 mg/dL)	1.13 - <2.26 mmol/L (100 – < 200 mg/dL)	2.26 - <3.39 mmol/L (200 – < 300 mg/dL)	3.39-<4.52 mmol/L (300 - <400 mg/dL)	≥ 4.52 mmol/L (≥ 400 mg/dL)	
Serum ALT Activity	<1.25 x ULN	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	

Note: ULN = upper limit of normal

Patients with ALT flares (including ALT elevations over 10xULN, ALT elevations larger than 5xULN and less than 10xULN) will be summarized by treatment group based on Safety population.

ALT and neutropenia will be summarized respectively by age subgroups (<12, ≥12), and age subgroups (<5, ≥5).

AEs under infections and infestations for patients with ACTG grade 3-4 lymphopenia or neutropenia will be listed.

4.6.4 Vital Signs

A summary table and a patient listing of the following vital signs parameters will be provided for Safety Population:

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Heart rate
- Temperature.

A summary table of vital sign abnormalities will be provided by treatment group in Safety Population.

4.6.5 Growth

The continuous growth will be analyzed through the analyses of weight and height for patients in Safety Population. Growth (height) velocity will be explored. In primary CSR, growths from study beginning to 24 weeks after the end of treatment/principal observation period will be reported.

4.6.5.1 Definitions

The primary endpoints for assessing treatment effects on growth are actual values at visit and their changes from baseline in (1) height (weight, BMI) for age percentile; (2) height (weight, BMI) for age z-score.

For the current analysis, the gender-specific Centers for Disease Control and Prevention (CDC) Growth Charts for 2000 (Kuczmarski et al. 2000) will be used as reference to calculate the height (weight, BMI) for age percentile and height (weight, BMI) for age z-score.

4.6.5.2 Summary of Growth Measurements

All growth variables will be listed by treatment group and center/patient number in Safety Population, including raw height (weight, BMI) measurements at each visit, height (weight, BMI) for age z-scores and height (weight, BMI) for age percentiles (actual value and change from baseline).

Descriptive summaries of the z-scores and percentiles for height, weight and BMI for age (actual value and change from baseline) for patients in Safety Population will be presented by visit.

Patients with height (weight, BMI) for age percentile drop (≥15%) from baseline will be summarized and listed by treatment group in Safety Population.

Plots of the mean (and 95% CI) of z-score and percentile for height, weight and BMI for age by treatment group in Safety Population will be depicted from the study baseline to 24 weeks after the end of treatment/principal observation period.

Plots of the mean change from the baseline (and 95% CI) of z-score and percentile for height, weight and BMI for age by treatment group in Safety Population will be depicted from the study baseline to 24 weeks after the end of treatment/principal observation period.

Individual change from baseline plots of z-score and percentile for height, weight and BMI for age by group will be depicted.

4.6.6 Child Depression Inventory (CDI)

Child Depression Inventory (CDI) is a questionnaire that has been validated for children ages 7-17 years old to assess a range of depressive symptoms (Kovacs 1992). In primary CSR, CDI scores from study beginning to 24 weeks after the end of treatment/principal observation period will be reported.

A list of patients, with a CDI raw score >19 (with or without an AE of depression) will be provided for Safety Population.

The total T-scores are standardized scores with a mean of 50 and a standard deviation of 10 derived from a normative samples of 1226 Florida public school students (see CDI manual in [Kovacs 1992] for more details).

The total T-score at each visit, and its change from baseline to week 12, 24, 36, 48 during treatment/principal observation period and at week 4 of initial follow-up, will be summarized for Safety Population.

4.7 ANALYSES OF GROUP C

Efficacy analyses and safety analyses from enrollment to 24 weeks after the end of treatment will be reported from all patients in Group C who receive at least one dose of study medication.

The patient major PVs, patient disposition, and patient discontinuation for Group C will be summarized.

Demographics and baseline characteristics, previous and concurrent disease, previous and concomitant Hepatitis B treatment for Group C will be summarized.

The primary efficacy endpoint and all secondary efficacy endpoints will be descriptively summarized for Group C. Continuous secondary efficacy endpoints will be summarized over time. Graphs of continuous secondary endpoints and their corresponding 95% confidence intervals over time will be displayed.

All the safety analyses for Group C will be conducted similarly as the safety analyses performed as described in Section 4.6.

4.8 ANALYSES OF SWITCH ARM

By the clinical cutoff for the primary CSR (24 weeks after the end of treatment period (Group A) or principal observation period (Group B)), very few patients in Switch arm would have completed their 24 week follow-up period after completion of treatment. Hence, only listings of deaths, SAEs, and AEs leading to discontinuation of study treatment will be presented in the primary CSR. All the other efficacy and safety data for Switch arm will be summarized and reported in the final CSR.

4.9 INTERIM ANALYSES

No interim efficacy analyses are planned.

5. REFERENCES

Kovacs M. Children's Depression Inventory Manual. North Tonawanda NY: Multi-Health Systems; 1992.

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Advance data from vital and health statistics; No. 314. Hyattsville, Maryland: National Center for Health Statistics; 2000.

Appendix 1
Protocol Synopsis

SYNOPSIS OF PROTOCOL YV25718, VERSION E

TITLE	A Phase IIIb Parallel Group, Open Label Study of Pegylated Interferon alfa-2a Monotherapy (PEG-IFN, Ro 25-8310) Compared to Untreated Control in Children with HBeAg Positive Chronic Hepatitis B in the Immune Active Phase		
SPONSOR	Hoffmann-La Roche	CLINICAL PHASE	IIIb
INDICATION	Treatment of HBeAg positive chronic hepatitis B (CHB) in children.		
OBJECTIVES	• To compare efficacy and safety between a group treated with Pegylated-Interferon Alfa-2a (PEG-IFN) monotherapy and an untreated control group in HBeAg positive children with CHB virus infection in the immune active phase. • To evaluate the pharmacokinetics of PEG-IFN following administration of a new BSA-based dosing regimen in HBeAg positive PEG-IFN treated children with CHB virus infection.		
TRIAL DESIGN	• A 2:1 randomized, controlled, parallel group, open label, multicenter study of PEG-IFN treatment (Group A) compared to an untreated control (Group B). • Subjects without advanced fibrosis and without cirrhosis (assessed by liver biopsy) will be randomized 2:1 to PEG-IFN treatment (Group A) or untreated control (Group B) respectively. That is for every 2 subjects randomized to PEG-IFN only 1 will be randomized to the untreated control. Subjects in Group A will receive PEG-IFN for 48 weeks. • Subjects with advanced fibrosis (assessed by liver biopsy) will be assigned to PEG-IFN treatment (Group C: Advanced Fibrotic arm). Subjects in Group C will receive PEG-IFN for 48 weeks. • The first 48 weeks from randomization will be referred to as the treatment period for Group A and Group C and the principal observation period for Group B. • Forty-eight weeks after randomization, PEG-IFN will be offered to subjects in the Group B untreated control group who have not experienced HBeAg seroconversion. This offer will be available for up to one year following Week 48. If eligible, these subjects will enter the Switch arm and receive PEG-IFN for 48 weeks. • All subjects will be followed up for 5 years after the end of treatment/principal observation period. • Liver elastography will be performed in at least 50 subjects as a site specific sub-study.		
NUMBER OF SUBJECTS	N = 160		

TARGET POPULATION	• Children aged 3 to < 18 years of age with CHB, HBeAg+ve, HBsAg+ve, detectable HBV DNA (> 10,000 copies/mL [> 2,000 IU/mL]) by PCR and ALT >ULN but ≤ 10 × ULN (using the reference range of the testing laboratory). • Liver biopsy needs to have been performed within 2 years prior to baseline, or within 9 months prior to baseline for subjects with advanced fibrosis. Subjects with advanced fibrosis will be assigned to PEG-IFN treatment (Group C), and those without advanced fibrosis or cirrhosis will be randomized. Cirrhotic subjects will be excluded from the study. • Subjects co-infected with HCV, HDV, HIV or who have received therapy for hepatitis B in the prior 6 months or who have de-compensated liver disease will be excluded.
LOCATION (Regions)	Americas, Europe, Asia-Pacific.
LENGTH OF STUDY	• For Group A, Group B non-switch and Group C subjects the study length is 6 years (1 year treatment/principal observation period, 5 years follow-up). • For Group B switch subjects the study length is up to 8 years (1 year principal observation period, up to 1 year follow-up whilst deciding whether to switch, 1 year treatment period, 5-year follow-up period).
END OF STUDY	• Primary endpoint is assessed 24 weeks after the end of treatment/principal observation period, with a further 4.5 years of follow- up. • End of study is last subject last visit.
INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	PEG-IFN for 48 weeks subcutaneously once weekly with dosing based on the following 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
NON-INVESTIGATIONAL MEDICAL PRODUCT(S)	N/A
COMPARATOR "DRUG" (or STANDARD OF CARE) DOSE/ ROUTE/ REGIMEN	N/A (Untreated control)
ASSESSMENTS OF:	
- EFFICACY	Primary: HBeAg seroconversion (loss of HBeAg and presence of anti-HBe) at 24 weeks post-end of treatment/principal observation period. Secondary: • Loss of HBeAg, HBsAg seroconversion (loss of HBsAg and presence of anti-HBs), loss of HBsAg, quantitative serum ALT, proportion of normal ALT, quantitative HBV DNA, suppression of HBV DNA < 100,000 copies/mL (< 20,000 IU/mL),< 10,000 copies/mL (< 2,000 IU/mL), undetectable and change from baseline, combined endpoint of HBeAg seroconversion and HBV DNA < 100,000 copies/mL (< 20,000 IU/mL), and combined endpoint of HBeAg seroconversion and HBV DNA < 10,000 copies/mL (< 2,000 IU/mL) at the end of treatment/principal observation period, at 24 weeks after end of treatment/principal observation period, and at 1, 2, 3, 4 and 5 years after end of treatment/principal observation period.

	• Persistence of HBeAg seroconversion (loss of HBeAg and presence of anti-HBe) at the end of treatment/principal observation period, and at 1, 2, 3, 4 and 5 years after end of treatment/principal observation period. • Descriptive change from baseline in liver elasticity (in liver elasticity site specific sub-study subjects) at end of treatment/principle observation period, and at 24 weeks and 2 years after end of treatment/principal observation period.
- SAFETY	<u>Safety during the treatment/principal observation period and initial 24 weeks of follow-up:</u> • Serious and non-serious AEs (including neurological and psychiatric events, and non-serious AEs of special interest, and monitoring with neuro-psychiatric questionnaire for PEG-IFN treated subjects). • Laboratory test results (including thyroid function). • Vital signs. • Growth: weight and height. <u>Safety during the 4.5 year extended, long-term follow up period:</u> • All persisting AEs initially reported prior to follow-up Week 24 (including neuro-psychiatric events). • New-onset serious AEs (including neuro-psychiatric events) and non-serious AEs of special interest related to PEG-IFN. • Deaths • Thyroid function. • Growth: weight and height.
- PHARMACOKINETICS/ PHARMACODYNAMICS	• Site-specific sub-study • Blood samples will be collected in PEG-IFN treated subjects to evaluate the pharmacokinetics of PEG-IFN following administration of a new BSA-based dosing regimen. • Samples should be collected during weeks 1 and 24 at pre-dose (0 hour) and 24-48, 72-96, and 168 hours post-dose. Additional pre-dose samples should be collected at weeks 4, 8 and 12 within 6 hours prior to administration.
- EXPLORATORY BIOMARKERS	Optional Roche Clinical Repository (RCR) samples, including plasma and whole blood RNA and whole blood DNA (baseline only), will be taken from consenting/assenting subjects at Baseline, Weeks 12, 24 and 48, 24 weeks after end of treatment/principal observation period, and at 1, 2, 3, 4 and 5 years after end of treatment/principal observation period. These specimens will be used for research purposes, for example to help to better understand the pharmacogenetics, pathogenesis, course and outcome of CHB and related diseases, and identify dynamic biomarkers that are predictive of response to PEG-IFN treatment (in terms of dose, safety and tolerability). These specimen(s) may be stored for up to 15 years after the end of Study YV25718.
INTERIM ANALYSES AND STOPPING RULES	Individual subject treatment with PEG-IFN 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 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 A DSMB will review safety data on a routine basis (as per DSMB charter). Enrollment will be suspended and/or the study will be halted if serious concerns about safety are raised pending further analysis and review. Enrollment and/or study re-start will resume only if the DSMB and the sponsor are satisfied with the safety of treatment.

PROCEDURES (Summary):

After signing informed consent/assent and meeting screening parameters, subjects without advanced fibrosis and without cirrhosis (assessed by liver biopsy performed within 2 years prior to baseline) will be randomized 2:1 into the PEG-IFN treatment (Group A) or untreated control (Group B) respectively. Stratification will be performed by genotype (A versus non-A) and ALT (< and $\geq 5 \times$ ULN). Subjects with advanced fibrosis (assessed by liver biopsy performed within 9 months prior to baseline) will be assigned to PEG-IFN treatment (Group C). Subjects in Group A and Group C will receive PEG-IFN for 48 weeks.

Subjects treated with PEG-IFN (Group A and Group C) will be seen for evaluation at Weeks 1, 2, 4, 8, 12 and then every 6 weeks during the treatment period, and during the initial 24 weeks of follow-up at follow-up Weeks 4, 12, and 24.

Subjects in the untreated arm (Group B) will be seen for evaluation at 12 weekly intervals during the principal 48-week observation period and during the initial 24 weeks of the follow-up period.

For consenting/assenting subjects in the site specific liver elasticity sub-study, liver elastography will be performed at baseline, end of treatment/principal observation period, follow-up Week 24, and follow-up Year 2.

Forty-eight weeks after randomization, PEG-IFN will be offered to subjects in the Group B untreated control group who have not experienced HBeAg seroconversion. This offer will be available for up to 1 year following 48 weeks from randomization. If eligible, these subjects will enter the Switch arm, where they will start the Switch schedule of assessments and receive PEG-IFN for 48 weeks.

For consenting/assenting subjects in the site specific PK sub-study, additional visits will also be required for PK blood sampling. When adequate PK data have been collected over the first 24 weeks for at least 15 PEG-IFN-treated subjects, ideally with representation from all BSA categories, exposure will be analyzed and if necessary an adjustment will be made to the dosing regimen. Once PK data up to Week 24/switch Week 24 are available for at least 5 to 10 subjects in each BSA category, subject PK sampling will be stopped. However, the sub-study may be stopped even if data from a minimum of 5 subjects in each BSA category are not obtained in the case of excessively long recruitment times.

Those subjects that do not complete the treatment period should still return for all follow-up visits. As well as evaluation during the initial 24 weeks post-end of treatment/principal observation period, all subjects will be followed up annually for 5 years after the end of treatment/principal observation period. Safety assessments at these extended long-term follow-up visits will include evaluation of persisting AEs which were initially reported prior to follow-up Week 24, assessment of new-onset SAEs (including neuro-psychiatric events) and non-serious AEs of special interest related to PEG-IFN, deaths, thyroid function, and growth (weight and height).

Standard measures will be taken in this study to minimize the pediatric subjects' possible pain and distress.

STATISTICAL ANALYSES

Sample Size

Sample size is based on the χ^2 test statistic. Assuming a 32% HBeAg seroconversion rate for Group A (PEG-IFN) and 10% for Group B (untreated control), a total sample size of 145 subjects provides at least 80% power at the 0.05 level of significance with a two-sided χ^2 test. The sample size shall be increased by 10% and rounded to 160 subjects to allow for advanced fibrotics (Group C) and withdrawals.

Populations

ITT population: For Group A, the ITT population shall include all subjects who receive at least one dose of study drug. For the untreated Group B the ITT population shall include all subjects with at least the baseline efficacy or safety data. For the ITT population subjects will be analyzed according to the groups to which they were randomized.

Subjects in Group B who switched to receive PEG-IFN after Week 48 and prior to 24 weeks post-observation period will be counted as non-responders.

Switch Population: The switch population shall be those subjects randomized to Group B who opt to switch to initiating treatment with PEG-IFN after Week 48.

Group C: Subjects who have advanced fibrosis (diagnosed on liver biopsy) will receive PEG-IFN in an advanced fibrotic arm (Group C).

Efficacy

- The primary efficacy analysis will compare efficacy in Group A with Group B. Subjects with missing values will be considered as non-responders. The efficacy data of Group A and Group B will be qualitatively evaluated alongside subjects in Group C and the Switch arm.
- The primary analysis of the response rate variables will be with the Cochran-Mantel-Haenszel test (χ^2) stratified by genotype (A versus non-A) and ALT (< and $\geq 5 \times$ ULN). Fisher's exact test will be used as a secondary analysis. The response rates for HBeAg seroconversion will be analyzed at the end of the initial 24-week follow-up period.
- Several secondary analyses are planned, including descriptive statistics of secondary endpoints, and exploratory p-values between Group A and Group B.

Safety

- The primary safety analysis will compare safety in Group A with Group B. The safety data of Group A and Group B will be qualitatively evaluated alongside subjects in Group C and the Switch arm.
- Adverse events: AEs will be assigned preferred terms and categorized into body systems according to the Medical Dictionary for Regulatory Activities (MedDRA) classification of the World Health Organization (WHO) terminology. Descriptive statistics will be used to summarize safety parameters by group. Neurological and psychiatric AEs will be assessed in further detail, including persistence and duration, as well as new onset of SAEs and non-serious AEs of special interest related to PEG-IFN reported during the extended long-term follow-up period of this study.
- Laboratory Safety Data: The laboratory data will be analyzed according to Roche's "International Guideline for the Handling and Reporting of Laboratory Data".
- Growth (weight and height): The continuous growth will be analyzed with residual maximum likelihood, or analysis of covariance. The assumptions of the analysis such as normally distributed residuals will be assessed. If necessary rectifying transformations shall be applied. Growth (height) velocity will be explored.

Pharmacokinetic

- PK parameters (e.g., CL/F V/F, AUC, C_{max}, etc,) of PEG-IFN will be estimated using non-compartmental analysis and/or a population PK modeling approach. All PK parameters will be presented descriptively including arithmetic means, standard deviations, geometric means, coefficient of variation, medians, and ranges.
- The relationship between clinical endpoints and PEG-IFN serum exposure may be explored.

The relationship between pharmacokinetic and pharmacodynamic parameters may be explored.

Appendix 2
Schedule of Assessments

Table 1 Schedule of Assessments and Procedures—Group A (PEG-IFN) and Group C (Advanced Fibrotic PEG-IFN)

Assessment/Procedure	Screen (days)	BL (days)	Treatment Period (weeks)											Initial 24 Weeks of Follow-Up (Weeks Post-End of Treatment)			Extended Long-Term Follow-Up Period (Years Post-End of Treatment Period)					
	−35 to −1	1	1	2	4	8	12	18	24	30	36	42	48 [a]	4 [a]	12 [a]	24 [a]	1 [a]	1.5 [a, b]	2 [a]	3 [a]	4 [a]	5 [a]
Informed Consent/Assent [c]	x																					
Complete medical history, including family history of HBV	x																					
Physical examination	x															x						
Symptom-directed physical examination		x	x	x	x	x	x	x	x	x	x	x	x	x	x							
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Weight [d]	x	x [f]	x	x	x	x	x [f]	x	x [f]	x	x [f]	x	x	x	x	x	x		x	x	x	x
Height [d, e]	x	x [f]					x [f]		x [f]		x [f]		x		x	x	x		x	x	x	x
Parental height [g]		x																				
Ultrasound [h, j]	x																					
Ophthalmology exam [i, j]	x								x				x			x						

[a] Or upon and following study treatment withdrawal.

[b] By telephone.

[c] Informed Consent obtained from legal guardian, and assent obtained from child if appropriate.

[d] Measurements must be taken using the same instruments in the same individual.

[e] Using stadiometer and taking the mean of three readings.

[f] Weight and height to be provided to IXRS.

[g] From consenting biological parents.

[h] To rule out hepatocellular carcinoma. Further liver imaging assessment may be performed if necessary.

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

[j] Within 6 months prior to baseline; repeat only if any change in the subject's medical condition.

Table 1 Schedule of Assessments and Procedures—Group A (PEG-IFN) and Group C (Advanced Fibrotic PEG-IFN) (cont.)

Assessment/Procedure	Screen (days)	BL (days)	Treatment Period (weeks)											Initial 24 Weeks of Follow-Up (Week Post-End of Treatment)			Extended Long-Term Follow-Up Period (Year Post-End of Treatment Period)					
	−35 to −1	1	1	2	4	8	12	18	24	30	36	42	48 [a]	4 [a]	12 [a]	24 [a]	1 [a]	1.5 [a, b]	2 [a]	3 [a]	4 [a]	5 [a]
Urine or serum HCG pregnancy test (selected subjects) [c, d]	x				x	x	x	x	x	x	x	x	x	x		x						
Alfa-fetoprotein [e, h]	x																					
Anti-HAV IgM, anti-HCV, anti-HIV, anti-HDV [h]	x																					
HBV genotype [h]	x																					
Ceruloplasmin, A1AT, AMA, ASMA, ALKM1 [h]	x																					
Anti-nuclear antibody (ANA) [h]	x								x				x									
Hematology [f, i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x						
Chemistry [f, i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x						
Urinalysis [d, f, g]	x	x			x	x	x	x	x	x	x	x	x	x		x						

[a] Or upon and following study treatment withdrawal.
[b] By telephone.
[c] For females of childbearing potential, a pregnancy test will be performed within 24 hours prior to baseline, and at any time secondary amenorrhea of more than 1 week occurs. Result of baseline pregnancy test must be available prior to randomization and commencement of treatment.
[d] To be performed by local laboratory.
[e] Subjects need to have serum alfa-fetoprotein assessed during the screening period to rule out hepatocellular carcinoma.
[f] If there are clinically significant laboratory abnormalities, repeat no less frequently than every 2 weeks or as clinically indicated, with appropriate toxicity management, until they return to normal or baseline values.
[g] Urinalysis to be performed via dipstick, with subsequent microscopic evaluation if positive for blood at the discretion of the investigator.
[h] Parameter does not need to be repeated at re-screening if performed within 6 months prior to baseline, unless dictated by a change in the subject's medical condition or the parameter accounted for the original screen failure.
[i] To be performed by a local laboratory in countries activated prior to April 2013, and by a central laboratory in countries activated after April 2013.

Table 1 Schedule of Assessments and Procedures—Group A (PEG-IFN) and Group C (Advanced Fibrotic PEG-IFN) (cont.)

	Screen (days)	BL (days)	Treatment Period (weeks)											Initial 24 Weeks of Follow-Up (Week Post-End of Treatment)			Extended Long-Term Follow-Up Period Year Post-End of Treatment Period)					
Assessment/Procedure	−35 to −1	1	1	2	4	8	12	18	24	30	36	42	48 [a]	4 [a]	12 [a]	24 [a]	1 [a]	1.5 [a,b]	2 [a]	3 [a]	4 [a]	5 [a]
FT3, FT4, TSH [c]	x[l]						x		x		x		x		x	x	x		x	x	x	x
TBG	x[l]																					
TPO antibodies	x[l]								x				x									
Population PK [d]		x	x		x	x	x		x													
HBeAg, anti-HBe [e]	x[l]	x					x		x		x		x		x	x	x		x	x	x	x
HBV DNA [e]	x[l]	x					x		x		x		x	x	x	x	x		x	x	x	x
HBsAg, anti-HBs [e]	x[l]	x					x		x		x		x		x	x	x		x	x	x	x
Quantitative HBsAg and HBeAg [e]		x					x		x		x		x			x						
Serum bank [f]		x					x		x		x		x		x	x	x		x	x	x	x
RCR plasma & RNA specimen		x					x		x				x			x	x		x	x	x	x
RCR DNA specimen		x																				
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]
Concomitant medications (including for CHB [h])	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Concomitant medications for CHB only [h]																	x	x	x	x	x	x
Subject study drug diary			x	x	x	x	x	x	x	x	x	x	x									
Dispense study drug		x			x	x	x	x	x	x	x	x										
Compliance			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Neuro-Psychiatric Questionnaire [i]	x	x					x		x		x		x	x								
Liver biopsy	x[j]																					
Liver elastography [k]		x											x			x			x			

[a] Or upon and following study treatment withdrawal.
[b] By telephone.
[c] If there are clinically significant laboratory abnormalities, repeat no less frequently than every 2 weeks or as clinically indicated, with appropriate toxicity management, until they return to normal or baseline values.

Table 1 Schedule of Assessments and Procedures—Group A (PEG-IFN) and Group C (Advanced Fibrotic PEG-IFN) (cont.)

[d] Specific sites. Blood samples should be collected for PK analysis during Weeks 1 and 24 at pre-dose (0 hour) and 24–48, 72–96, and 168 hours post-dose. Additional pre-dose samples should be collected at Weeks 4, 8, and 12 within 6 hours prior to PEG-IFN administration. The time of PEG-IFN administration on PK sampling days must be recorded on the eCRF.

[e] Frozen for central processing.

[f] Sample to be retained frozen at site in the event that any tests need to be repeated. From RCR-consenting subjects, they also may be used for exploratory HBV biomarker analyses (DNA and/or non-DNA). Sample to be retained frozen at site in the event that any tests need to be repeated.

[g] During the 5-year follow-up period, only persistent AEs initially reported prior to follow-up Week 24, new-onset SAEs, non-serious AEs of special interest related to PEG-IFN, and deaths will be collected.

[h] Concomitant medications for CHB include licensed or investigational immunomodulatory or antiviral therapy, and herbal, botanical and other agents (e.g., ursodeoxycholic acid) that are traditionally used for chronic HBV disease.

[i] Not required for children < 7 years of age.

[j] Within 2 years prior to baseline **or** within 9 months prior to baseline for subjects with advanced fibrosis.

[k] Subjects in site-specific liver elasticity sub-study only.

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

Table 2 Schedule of Assessments and Procedures—Group B (Untreated Control)

Assessment/Procedure	Screen (days)	BL (days)	Principal Observation Period (weeks)				Initial 24 Weeks of Follow-up (Week Post-End of Principal Observation Period)		Extended Long-Term Follow-Up Period (Year Post-End of Principal Observation Period)					
	−35 to −1	1	12	24	36	48 [a]	12[a]	24 [a]	1 [a]	1.5 [b]	2	3	4	5
Informed Consent/Assent [c]	x													
Complete medical history, including family history of HBV	x													
Physical examination	x							x						
Symptom-directed physical examination		x	x	x	x	x	x							
Vital signs	x	x	x	x	x	x	x	x						
Weight [d]	x	x [f]	x	x	x	x	x	x			x	x	x	x
Height [d, e]	x	x [f]	x	x	x	x	x	x			x	x	x	x
Parental height [g]		x												
Ultrasound [h, i]	x													
Ophthalmology exam [i, j]	x													

[a] Eligible subjects may switch at any time between Week 48 and 1 year following Week 48 at which time subjects will continue on the Switch Schedule of Assessments and Procedures.
[b] By telephone.
[c] Informed Consent obtained from legal guardian, and assent obtained from child if appropriate.
[d] Measurements must be taken using the same instruments in the same individual.
[e] Using stadiometer and taking the mean of three readings.
[f] Weight and height to be provided to IXRS.
[g] From consenting biological parents.
[h] To rule out hepatocellular carcinoma. Further liver imaging assessment may be performed if necessary.
[i] Within 6 months prior to baseline; repeat only if any change in medical condition.
[j] By ophthalmologist and including fundoscopic examination, visual acuity assessment, visual field testing, and color visual testing. Any subject who develops ocular symptoms should receive a prompt eye examination by an ophthalmologist and additional examinations as necessary.

Table 2 Schedule of Assessments and Procedures—Group B (Untreated Control) (cont.)

Assessment/Procedure	Screen (days)	BL (days)	Principal Observation Period (weeks)				Initial 24 Weeks of Follow-up (Week Post-End of Principal Observation Period)		Extended Long-Term Follow-Up Period (Year Post-End of Principal Observation Period)					
	−35 to −1	1	12	24	36	48 [a]	12[a]	24 [a]	1 [a]	1.5 [b]	2	3	4	5
Urine or serum HCG pregnancy test (selected subjects) [c, d]	x													
Alfa-fetoprotein [e, h]	x													
Anti-HAV IgM, anti-HCV, anti-HIV, and anti-HDV [h]	x													
HBV genotype [h]	x													
Ceruloplasmin, A1AT, AMA, ANA, ASMA, ALKM1 [h]	x													
Hematology [f, i]	x	x	x	x	x	x		x						
Chemistry [f, i]	x	x	x	x	x	x		x						
Urinalysis [d, f, g]	x	x				x		x						
FT3, FT4, TSH [f, h]	x					x		x	x		x	x	x	x
TPO antibodies, TBG [h]	x													

[a] Eligible subjects may switch at any time between Week 48 and 1 year following Week 48 at which time subjects will continue on the Switch Schedule of Assessments and Procedures.

[b] By telephone.

[c] For females of childbearing potential, a pregnancy test will be performed within 24 hours prior to baseline, and at any time secondary amenorrhea of more than 1 week occurs. Result of baseline pregnancy test must be available prior to randomization and commencement of treatment.

[d] To be performed by local laboratory.

[e] Subjects need to have serum alfa-fetoprotein assessed during the screening period to rule out hepatocellular carcinoma.

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

[g] Urinalysis to be performed via dipstick, with subsequent microscopic evaluation if positive for blood at the discretion of the investigator.

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

[i] To be performed by a local laboratory in countries activated prior to April 2013, and by a central laboratory in countries activated after April 2013.

Table 2 Schedule of Assessments and Procedures—Group B (Untreated Control) (cont.)

Assessment/Procedure	Screen (days)	BL (days)	Principal Observation Period (weeks)				Initial 24 Weeks of Follow-Up (Week Post-End of Principal Observation Period)		Extended Long-Term Follow-Up Period (Year Post-End of Principal Observation Period)					
	–35 to –1	1	12	24	36	48 [a]	12 [a]	24 [a]	1 [a]	1.5 [b]	2	3	4	5
HBeAg, anti-HBe [c]	x *j*	x	x	x	x	x	x	x	x		x	x	x	x
HBV-DNA [c]	x *j*	x	x	x	x	x	x	x	x		x	x	x	x
HBsAg, anti-HBs [c]	x *j*	x	x	x	x	x	x	x	x		x	x	x	x
Quantitative HBsAg and HBeAg [c, j]		x	x	x	x	x		x						
Serum bank [d]		x	x	x	x	x	x	x	x		x	x	x	x
RCR plasma and RNA specimen		x	x	x		x		x	x		x	x	x	x
RCR-DNA specimen		x												
Adverse events		x	x	x	x	x	x	x	x [e]	x [e]	x [e]	x [e]	x [e]	x [e]
Concomitant medications (including for CHB [f])	x	x	x	x	x	x	x	x						
Concomitant medications for CHB only [f]									x	x	x	x	x	x
Compliance			x	x	x	x	x	x	x	x	x	x	x	x
Neuro-Psychiatric Questionnaire [g]	x	x												
Liver biopsy	x [h]													
Liver elastography [i]		x				x		x			x			

[a] Eligible subjects may switch at any time between Week 48 and 1 year following Week 48 at which time subjects will continue on the Switch Schedule of Assessments and Procedures.

[b] By telephone.

[c] Frozen for central processing.

[d] Sample to be retained frozen at site in the event that any tests need to be repeated. From RCR-consenting subjects, they also may be used for exploratory HBV biomarker analyses (DNA and/or non-DNA).

[e] During the 5-year follow-up period, only persistent AEs initially reported prior to follow-up Week 24 and deaths.

[f] Concomitant medications for CHB include licensed or investigational immunomodulatory or antiviral therapy, and herbal, botanical and other agents (e.g., ursodeoxycholic acid) that are traditionally used for chronic HBV disease.

Table 2 Schedule of Assessments and Procedures—Group B (Untreated Control) (cont.)

[g] Not required for children < 7 years of age.
[h] Within 2 years prior to baseline or within 9 months prior to baseline for subjects with advanced fibrosis.
[i] Subjects in site-specific liver elasticity sub-study only.
[j] Parameter does not need to be repeated at re-screening if performed within 6 months prior to baseline, unless dictated by a change in the subject's medical condition or the parameter accounted for the original screen failure.

Table 3 Schedule of Assessments and Procedures—Switch (PEG-IFN)

Assessment/Procedure	Switch BL [a]	Treatment Period (weeks)											Initial 24 Weeks of Follow-Up (Week Post-End of Treatment Period)			Extended Long-Term Follow-Up Period (Year Post-End of Treatment Period)					
		SW 1	SW 2	SW 4	SW 8	SW 12	SW 18	SW 24	SW 30	SW 36	SW 42	SW 48 [b]	SW 4 [b]	SW 12 [b]	SW 24 [b]	SW 1 [b]	SW 1.5 [b, c]	SW 2 [b]	SW 3 [b]	SW 4 [b]	SW 5 [b]
Physical examination	x														x						
Symptom-directed physical examination		x	x	x	x	x	x	x	x	x	x	x	x	x							
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Weight [d]	x [f]	x	x	x	x	x [f]	x	x [f]	x	x [f]	x	x	x	x	x	x		x	x	x	x
Height [d, e]	x [f]					x [f]		x [f]		x [f]		x		x	x	x		x	x	x	x
Ophthalmology exam [g]	x [j]							x				x			x						
Urine or serum HCG pregnancy test (selected subjects) [h, i]	x			x	x	x	x	x	x	x	x	x	x	x	x						
Anti-HAV IgM, anti-HCV, anti-HIV, and anti-HDV [j]	x																				
ANA	x [j]							x				x									

[a] Switch baseline will take place at the time of the final visit of the pre-switch schedule. Results from all switch baseline assessments must be available and subjects must meet all switch criteria prior to commencing PEG-IFN.

[b] Or upon and following study treatment withdrawal.

[c] By telephone.

[d] Measurements must be taken using the same instruments in the same individual.

[e] Using stadiometer and taking the mean of three readings.

[f] Weight and height to be provided to IXRS.

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

[h] For females of childbearing potential, a pregnancy test will be performed within 24 hours prior to switch baseline, and at any time secondary amenorrhea of more than 1 week occurs. Result of baseline pregnancy test must be available prior to randomization and commencement of treatment.

[i] To be performed by local laboratory.

[j] Parameter does not need to be repeated at switch baseline if performed within 6 months prior to switch baseline, unless dictated by a change in the subject's medical condition.

Table 3 Schedule of Assessments and Procedures—Switch (PEG-IFN) (cont.)

Assessment/Procedure	Switch BL [a]	Treatment Period (weeks)											Initial 24 Weeks of Follow-Up (Week Post-End of Treatment Period)			Extended Long-Term Follow-up Period (Year Post-End of Treatment Period)					
		SW 1	SW 2	SW 4	SW 8	SW 12	SW 18	SW 24	SW 30	SW 36	SW 42	SW 48 [b]	SW 4 [b]	SW 12 [b]	SW 24 [b]	SW 1 [b]	SW 1.5 [b,c]	SW 2 [b]	SW 3 [b]	SW 4 [b]	SW 5 [b]
Hematology [d,j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Chemistry [d,j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Urinalysis [d, e, f]	x			x	x	x	x	x	x	x	x	x	x	x	x						
FT3, FT4, TSH [d]	x[i]					x		x		x		x		x	x	x			x	x	x
TPO antibodies	x[i]							x				x									
TBG	x[i]																				
Population PK [g]	x	x		x	x	x		x													
HBeAg, anti-HBe [h]	x[i]					x		x		x		x		x	x	x			x	x	x
HBV-DNA [h]	x[i]					x		x		x		x	x	x	x	x			x	x	x
HBsAg, anti-HBs [h]	x[i]					x		x		x		x		x	x	x			x	x	x

[a] Switch baseline will take place at the time of the final visit of the pre-switch schedule. Results from all switch baseline assessments must be available and subjects must meet all switch criteria prior to commencing PEG-IFN.

[b] Or upon and following study treatment withdrawal.

[c] By telephone.

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

[e] Urinalysis to be performed via dipstick, with subsequent microscopic evaluation if positive for blood at the discretion of the investigator.

[f] To be performed by local laboratory.

[g] Specific sites. Blood samples should be collected for PK analysis during switch Weeks 1 and 24 at pre-dose (0 hour) and 24—48, 72—96, and 168 hours post-dose. Additional pre-dose samples should be collected at switch Weeks 4, 8 and 12 within 6 hours prior to PEG-IFN administration. The time of PEG-IFN administration on PK sampling days must be recorded on the eCRF.

[h] Frozen for central processing.

[i] Parameter does not need to be repeated at switch baseline if performed within 6 months prior to switch baseline, unless dictated by a change in the subject's medical condition.

[j] To be performed by a local laboratory in countries activated prior to April 2013, and by a central laboratory in countries activated after April 2013.

Table 3 Schedule of Assessments and Procedures—Switch (PEG-IFN) (cont.)

Assessment/Procedure	Switch BL[a]	Treatment Period (weeks)											Initial 24 Weeks of Follow-Up (Weeks Post-End of Treatment Period)			Extended Long-Term Follow-up Period (Year Post-End of Treatment Period)					
		SW 1	SW 2	SW 4	SW 8	SW 12	SW 18	SW 24	SW 30	SW 36	SW 42	SW 48[b]	SW 4[b]	SW 12[b]	SW 24[b]	SW 1[b]	SW 1.5[b,c]	SW 2[b]	SW 3[b]	SW 4[b]	SW 5[b]
Quantitative HBsAg and HBeAg[d]	x[k]					x		x		x		x			x						
Serum bank[e]	x					x		x		x		x		x	x			x	x	x	x
RCR plasma and RNA specimen	x					x		x				x			x			x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]
Concomitant medications (including for CHB[g])	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Concomitant medications for CHB only[g]																	x	x	x	x	x
Subject study drug diary		x	x	x	x	x	x	x	x	x	x	x									
Dispense study drug	x			x	x	x	x	x	x	x	x										
Compliance	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Neuro-Psychiatric Questionnaire[h]	x					x		x		x		x	x								
Liver biopsy[i]	x																				
Ultrasound[i]	x																				
Liver elastography[j]												x			x			x			

[a] Switch baseline will take place at the time of the final visit of the pre-switch schedule. Results from all switch baseline assessments must be available and subjects must meet all switch criteria prior to commencing PEG-IFN.

[b] Or upon and following study treatment withdrawal.

[c] By telephone.

[d] Frozen for central processing.

[e] Sample to be retained frozen at site in the event that any tests need to be repeated. From RCR-consenting subjects, they also may be used for exploratory HBV biomarker analyses (DNA and/or non-DNA).

[f] During the 5-year follow-up period, only persistent AEs initially reported prior to follow-up Week 24, new-onset SAEs, non-serious AEs of special interest related to PEG-IFN, and deaths will be collected.

Table 3 Schedule of Assessments and Procedures—Switch (PEG-IFN) (cont.)

[g] Concomitant medications for CHB include licensed or investigational immunomodulatory or antiviral therapy, ursodeoxycholic acid, and herbal, botanical and other agents (e.g., ursodeoxycholic acid) that are traditionally used for chronic HBV disease.

[h] Not required for children < 7 years of age.

[i] Either a liver biopsy performed within 2 years prior to switch baseline to exclude cirrhosis, OR clinical, laboratory, and ultrasound data within 6 months prior to switch baseline which together exclude cirrhosis.

[j] Subjects in site-specific liver elasticity sub-study only.

[k] Parameter does not need to be repeated at switch baseline if performed within 6 months prior to switch baseline, unless dictated by a change in the subject's medical condition.