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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CLINICAL STUDY PROTOCOL
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PROTOCOL APPROVAL

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Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	28-May-2014 15:03:27

Confidentiality Statement

PROTOCOL AMENDMENT, VERSION *E*: RATIONALE

Protocol YV25718 has been amended as follows:

- Negative hepatitis B surface antibody (anti-HBs) and hepatitis B envelope antibody (anti-HBe) results at screening has been removed as an inclusion critierion. This is to avoid inappropriately excluding potential patients who have low level of anti-HBs or anti-HBe in the context of fulfilling all other eligibility criteria. With the increasing sensitivity of laboratory assays, there have been several reports described with the coexistance of hepatitis B surface antigen (HBsAg) and anti-HBs antibodies in 10% to 25% of chronic hepatitis B (CHB) patients. Some patients screened for this study have shown this. In addition, current clinical guidelines (European Association for the Study of the Liver 2012, American Association for the Study of Liver Diseases 2009, Asian Pacific Association for the Study of the Liver 2012) do not require negative results for anti-HBs and anti-HBe for the diagnosis of CHB.
- For clarity and consistency, the exclusion criteria, switch exclusion criteria, and the stopping rule concerning hepatic decompensation have been updated.
- The normal range of hemoglobin varies with age in pediatric patients; therefore the exclusion criterion and switch exclusion criterion for hemoglobin have been amended to below the lower limit of normal ($<$LLN) as opposed to using fixed cut-off values of $<$11 g/dL for females and $<$12 g/dL for males. This may prevent unnecessary exclusion of some eligible patients.
- The renal exclusion criterion has been amended to exclude patients with evidence of renal impairment.
- Serum alanine aminotransferase (ALT) $>10\times$ upper limit of normal (ULN) at switch baseline has been added into the switch exclusion criteria as treatment of Pegylated-Interferon Alfa-2a should normally not be initiated if ALT is $>10\times$ ULN.
- Changes have been made to the stopping rules to align with the current approved prescribing information, including removal of certain stopping rules, and separation of stopping rules into those where treatment must be discontinued and those where treatment discontinuation should be considered.
- Scheuer Scoring system has been added in Appendix 1 (Liver Biopsy Scores) to help sites using this scoring system to classify the degree of liver fibrosis.

Additional changes to the protocol are as follows:

- The Medical Monitors' details have been updated.
- For clarity and consistency of occurrences of "post-treatment" have been changed to "post-end of treatment"
- Additional rationale for the untreated control arm has been included, including procedures for minimizing the risk of bias in this open-label study.
- Given the different schedule of assessments for the treatment group compared with the untreated group, it is practically not possible to blind the assessor within this

study. Therefore, the blinding of central laboratory to the treatment assignment has been removed.

- Additional clarity has been included regarding administration of the Children's Depression Inventory and assessment of patients with symptoms of major depression.
- Additional clarity regarding the timepoint and contents of the primary safety analysis has been added. In addition, following safety outcome measures until 1, 2, 3, 4, and 5 years post-end of treatment have been added.
- The schedule of assessments has been updated to clarify that the result of baseline pregnancy test must be available prior to randomization and commencement of treatment.
- Additional text has been included regarding extensions of screening period, retesting of screening parameters, and circumstances for re-screening.
- To fully evaluate the fundus of the eye and accurately detect any retinopathy, fundoscopic examination has been updated to specify that it should be with dilation. To facilitate a successful eye examination and minimize distress in this pediatric population, a Pediatric Ophthalmologist has been recommended. To facilitate successful visual field testing in younger patients, confrontation has been recommended, as it is simpler than visual field test performed in automated machine and requires less collaboration of the child

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION *E*:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 3.1: OVERVIEW OF STUDY DESIGN AND DOSING REGIMEN

The screening period will be up to 35 days.~~*All subjects 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 subjects the study length is approximately 6 years (1-year treatment/principal observation period and 5 years of follow-up). For Group B switch subjects 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).

SECTION 3.1.1.1: Use of Untreated Control Arm and Compassionate Switch

An untreated control arm has been selected for this study as the use of a placebo control arm is not considered appropriate for several reasons. Firstly, the use of placebo injections would not effectively blind treatment as the known adverse effects of IFN therapy, particularly influenza-like illness, would not occur. It would therefore be likely that subjects/parents would become aware that the subject was not receiving IFN resulting in a potential risk of noncompliance. Secondly, it would be unethical to administer weekly placebo injections for 48 weeks as administration requires an invasive procedure with an associated risk of injection-site infections and no associated benefit. A further benefit of using an untreated control arm is that the study burden for the untreated subjects is reduced as their visit schedule is less frequent compared with that of the treated subjects, 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 central randomization, use of a central laboratory and standardized assays, and the choice of the intent-to-treat (ITT) population for the primary analysis.

SECTION 3.1.3: <u>End of Study</u>

The primary endpoint will be assessed 24 weeks after the end of treatment/principal observation period, with a further 4.5 years of extended long-term follow-up. The end of study is *defined as* last subject last visit *(LSLV)*.

SECTION 4.1: OVERVIEW

The study population will be children aged 3 to < 18 years of age with CHB, who are HBeAg positive (+ve), HBsAg+ve, ~~*anti HBs negative (ve), anti HBe ve,*~~ with detectable HBV-DNA (> 10,000 copies/mL [> 2,000 IU/mL]) by polymerase chain reaction (PCR)

and ALT > ULN but ≤ 10 × the ULN (using the reference range of the testing laboratory). Liver biopsy needs to have been performed within 2 years prior to baseline to confirm or exclude the presence of advanced fibrosis or cirrhosis (see Appendix 1). For subjects with advanced fibrosis, a liver biopsy needs to have been performed within 9 months prior to baseline to ensure that the subject has not progressed to cirrhosis. Subjects co-infected with HCV, hepatitis D virus (HDV), human immunodeficiency virus (HIV) or who have received therapy for hepatitis B in the prior 6 months or who have de-compensated liver disease will be excluded.

SECTION 4.2: INCLUSION CRITERIA

A subject may be included if the answer to all of the following statements is "yes":

- Male or female subjects aged 3 to < 18 years old at baseline
- Positive HBsAg for more than 6 months
- Positive HBeAg and detectable HBV-DNA at screening (subjects must have > 10,000 copies/mL [> 2,000 IU/mL] as measured by PCR)
- ~~*Negative anti-HBs and anti-HBe at screening. (Exception: subjects with positive antibodies based on central laboratory result but negative antibodies based on local laboratory result and who meet the other CHB inclusion criteria of positive HBsAg, positive HBeAg, detectable HBV-DNA, and elevated ALT may be included.)*~~
- A liver biopsy performed within 2 years prior to baseline to confirm the presence of advanced fibrosis or exclude cirrhosis (see Appendix 1). For subjects with advanced fibrosis, a liver biopsy needs to be performed within 9 months prior to baseline
- Compensated liver disease (Child-Pugh Class A clinical classification; see Appendix 2)
- Elevated serum ALT > ULN but ≤ 10 × the ULN as determined by two abnormal values taken ≥ 14 days apart during the 6 months before the first dose of study drug with at least one of the determinations obtained ≤ 35 days prior to the first dose. Reference range of the testing laboratory should be used
- Signed informed consent from *parent/*legal guardian and willingness of *parent/*legal guardian to abide by the requirements of the study, and signed assent from child if appropriate. *Patients <18 years of age at baseline who are legally adults according to national legislation must consent in their own right.*

SECTION 4.3: EXCLUSION CRITERIA

A subject will be excluded if the answer to any of the following statements is "yes":

- Subjects with cirrhosis (see Appendix 1)

- Subjects who have received investigational drugs or licensed treatments with anti-HBV activity within 6 months prior to baseline (e.g., IFNs, systemic corticosteroids, lamivudine, tenofovir, emtricitabine, adefovir, entecavir, telbivudine, systemic acyclovir, systemic famciclovir) (Exception: Subjects 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.)
- Known hypersensitivity to PEG-IFN
- Positive test results at screening for hepatitis A virus immunoglobulin M antibody (HAV IgM Ab), anti-HCV antibody (Ab), anti-HDV Ab, or anti-HIV Ab
- History or other evidence of a medical condition associated with chronic liver disease other than CHB
- History or other evidence of bleeding from esophageal varices
- Decompensated liver disease (e.g., ~~*ascites, varices,*~~ Child-Pugh Class B or C clinical classification [see Appendix 2] *or clinical evidence such as ascites or varices*)
- History or other evidence of metabolic liver disease
- Suspicion of HCC on ultrasound or other liver imaging (all subjects to have ultrasound within 6 months prior to baseline)
- Screening alfa-fetoprotein (AFP) ≥ 100 ng/mL
- Screening neutrophil count $< 1.5 \times 10^9$ cells/L, platelet count $< 90 \times 10^9$ cells/L, or hemoglobin < ~~*11 g/dL for females and < 12 g/dL for males*~~*lower limit of normal (LLN)*
- Screening albumin < lower limit of normal or total bilirubin > ULN

  Exception: Subjects with non–hepatitis-related factors which may elevate bilirubin such as Gilbert's disease
- ~~*Screening serum creatinine concentration > 1.5 × the ULN for age or severe*~~ *Evidence of* renal impairment ~~*disease, e.g., glomerulonephritis*~~
- Autoimmune hepatitis
- History of immunologically mediated disease to include, but not limited to: 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
- History or other evidence of chronic pulmonary or cardiac disease associated with clinically significant functional limitation
- History of thyroid disease 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/or thyroxine-binding globulin [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 (international normalized ratio > 1.5), hemoglobinopathy, hemophilia, or history of severe illness or other blood disorders that would make subject unsuitable for the study
- History of seizure disorder requiring treatment with anticonvulsant medication (excluding febrile seizures)
- History or other evidence of severe retinopathy (all subjects to have ophthalmological examination within 6 months prior to baseline)
- History or other evidence of severe illness or any other conditions that would make the subject, in the opinion of the investigator, unsuitable for the study
- Active substance abuse within the last 6 months before the study
- Sexually active females of childbearing potential and sexually active males who are not willing to utilize reliable contraception during the treatment/principal observation period and during the initial 24-week follow-up period
- Females of childbearing potential who have a positive urine or serum pregnancy test result within 24 hours of baseline, or who are breast-feeding

SECTION 4.6.1: Withdrawal of Subjects from Study Treatment

In the case that the subject decides to prematurely discontinue study treatment ("refuses treatment"), all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible preferably by returning to site to complete assessments as per the Week 48/Switch Week 48 visit (see Table 2 and Table 4) and the Treatment Completion eCRF. The subject should then enter the post-*end of* treatment follow-up period.

SECTION 4.8.2: Switch Exclusion Criteria

Subjects in Group B may not switch to treatment with PEG-IFN if the answer to any of the following statements is "yes".

- Cirrhosis (see Appendix 1)
- Subjects who have received any anti-HBV treatment within 6 months prior to switch baseline
- Positive test results within 6 months prior to switch baseline for HAV IgM Ab, anti-HCV Ab, anti-HDV Ab, or anti-HIV Ab

- Evidence of decompensated liver disease (e.g., ~~*ascites, varices,*~~ Child–Pugh Class B or C clinical classification, see Appendix 2 *or clinical evidence such as ascites or varices*) *at switch baseline*
- *Serum ALT >10 ×the ULN at switch baseline. Reference range of the testing laboratory should be used*
- International normalized ratio >1.5 at switch baseline
- Neutrophil count $<1.5\times10^9$ cells/L, platelet count <90 $\times 10^9$ cells/L, or hemoglobin *<~~11 g/dL for females and <12 g/dL for males~~ lower limit of normal (LLN)* at switch baseline
- *Evidence of ~~Serum creatinine concentration >1.5 ×the ULN for age or severe~~* renal *impairement ~~disease, e.g., glomerulonephritis, at switch baseline~~*
- Evidence of severe illness or any other conditions or contraindications that would make the subject, in the opinion of the investigator, unsuitable for commencing PEG-IFN
- Clinically relevant abnormal thyroid function tests (TSH, FT3, FT4, TPO antibodies, and/or TBG) within 6 months prior to switch baseline
- Sexually active females of childbearing potential and sexually active males who are not willing to use reliable contraception during the switch treatment period and initial 24-week switch follow-up period
- Females of childbearing potential who have a positive urine or serum pregnancy test result within 24 hours of switch baseline

SECTION 5.1: SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM

The assessments in Table 5 ~~*must*~~*should* be obtained within a period of no more than 35 days before the subject is randomized, except as noted. *Extensions to the screening period of up to 7 days may be permitted under exceptional circumstances if certain results concerning eligibility are not available within the 35 days and only upon approval from the Medical Monitor.* Subjects must fulfill all the entry criteria for participation in the study (see Sections 4.2 to 4.4). An Eligibility Screening Form documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator. A screen failure log must be maintained by the investigator.

If a subject 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 below. If the subject 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.

Subjects who fail to meet the entry criteria may be re-screened on one more occasion provided that enrollment remains open *and upon approval from the Medical Monitor*. ~~*If re-*~~

~~*screening occurs within the 35-day screening window for the original screening, then only the parameter that failed will need to be repeated. If re-screening will take the screening period beyond 35 days, then*~~*If re-screening is required, then the complete screening module should be repeated* (except for those parameters indicated in Table 5). *Re-screening is required if a subject has not met all of the eligibility criteria within 35 days from the original screening visit. It will not be considered a re-screening if blood samples have to be redrawn because of sample handling problems, breakage, or sample integrity.*

SECTION 5.2: PROCEDURES FOR ENROLLMENT OF ELIGIBLE SUBJECTS

The enrollment of subjects in the rest of world will remain unchanged; patients aged 3 to <18 years old at baseline will be enrolled. During study conduct, the Sponsor may postpone or stop the enrollment of subjects in certain age ranges in order to *ensure that a broad* ~~*maintain the*~~ age distribution ~~*balance in the study population*~~*and representative dosing categories have been adequately studied*.

SECTION 5.3: CLINICAL ASSESSMENTS AND PROCEDURES

A baseline visit will be performed, and for subjects in Group A and Group C all baseline assessments and procedures must occur prior to administration of the first dose of PEG-IFN. *The first dose of PEG-IFN should be administered at the baseline visit.* Subjects will subsequently be seen for evaluation at the following timepoints:

Group A and Group C

- During treatment period: Weeks 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48
- During initial 24 weeks of follow-up: follow-up Weeks 4, 12, and 24 post-*end of* treatment
- During extended long-term follow-up: Years 1, 1.5, 2, 3, 4, and 5 post-*end of* treatment

Group B—Switch

- During principal observation period: Weeks 12, 24, 36, and 48*
- During initial 24 weeks of follow-up: follow-up Weeks 12* and 24* post-principal observation period
- During extended long-term follow-up: Year 1* post–principal observation period
- During switch treatment period: Weeks 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48
- During initial 24 weeks of switch follow-up: switch follow-up Weeks 4, 12, and 24 post~~–*principal observation*~~*end of treatment* period
- During extended long-term switch follow-up: Years 1, 1.5, 2, 3, 4, and 5 post-~~*principal observation*~~*end of treatment* period

Any subject who discontinues study treatment should return to complete assessments as per the Week 48/Switch Week 48 visit and enter the post-*end of* treatment follow-up period (see Section 4.6.1).

SECTION 5.3.2: Safety

All subjects need to have an ophthalmological examination (~~*including*~~ *consisting of* fundoscopic examination *with dilation*, visual acuity assessment, visual field testing *(confrontation test is recommended for younger children)*, and color visual testing) by an ophthalmologist *(pediatric ophthalmologist is recommended)* within 6 months prior to baseline. *During the study,* ~~*Thereafter,*~~ subjects treated with PEG-IFN will receive *additional* ophthalmological examination as per the schedules in Table 2 and Table 4. Any subject who develops ocular symptoms should receive a prompt eye examination by an ophthalmologist and additional examinations as necessary.

SECTION 5.3.2.1: Neuro-psychiatric Questionnaire

As part of the overall assessment of subjects and their mental state, and collation of neurological and psychiatric AEs, the CDI [50] will be used in subjects ≥7 ~~*to 17*~~ 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 subject'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 subjects and then post-baseline for treated subjects as per the schedules in Table 2 to Table 4. CDI should be performed prior to the completion of other study assessments. *Note: If a subject 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 17-year-old subjects who turn 18 years old during the study, the CDI should continue to be administered.*

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

Once the subject 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. *Note: 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.

~~Pathway of Referral for~~ Follow up of* Subjects *~~Who Have~~ with Symptoms of Major Depression or Potential* CDI *~~Scores >19~~Indicators

Whether the CDI is administered or not, investigators should still assess the mental state of their subjects per their standard clinical practice. If any subject exhibits symptoms of major depression *and/*or if CDI total score is >19 *and/or the subject 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 subject will be referred to a mental health professional (e.g., counsellor). If this is at screening or baseline, then the subject will be excluded from the study. *While in the study, the investigator will determine whether AE criteria have been met and report as an AE on the eCRF, if appropriate (see Section 7.1).* If whilst on study the subject is found to have severe depression, PEG-IFN ~~*should*~~ *must* be permanently discontinued and the subject referred for psychiatric intervention (as per Section 6.2.1 and Section 6.2.5.5).

SECTION 5.4: LABORATORY ASSESSMENTS

All virological and serological efficacy parameters will be assessed by the central laboratory. ~~*The central laboratory will not have access to clinical data or randomization information, and therefore is blinded to treatment assignment for the duration of the study.*~~

SECTION 6.2.1: Stopping Rules

Individual subject treatment with PEG-IFN ~~*will*~~ *must*be stopped in the event of any of the following:

- Severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchoconstriction)
- ~~*Evidence of hepatic decompensation, e.g., significant deterioration in hepatic function including those requiring alternative therapies (see also Section 6.2.5.3)*~~
- Severe depression (see also Section 6.2.5.5)
- ~~*Convulsions*~~
- ~~*Thyroid abnormalities that cannot be adequately treated*~~
- ~~*Hypoglycemia, hyperglycemia, or diabetes mellitus that cannot be effectively controlled by medication*~~
- ~~*New or worsening visual disorders such as field deficits, decreased or loss of vision*~~
- ~~*Persistent or unexplained pulmonary infiltrates or pulmonary function impairment*~~
- ~~*Worsening of psoriatic lesion*~~
- ~~*Development of autoimmunity, including autoimmune hepatitis*~~
- ~~*Renal failure, including creatinine >100 µmol/L*~~
- ~~*Severe symptoms e.g., rigors (see Sections 6.2.4 and 7.1.1)*~~

- Absolute neutrophil count $< 0.25 \times 10^9$ cells/L or febrile neutropenia (see also Section 6.2.5.1)
- Platelets $< 25 \times 10^9$ cells/L (see also Section 6.2.5.2)
- ~~*Pregnancy (see also Section 7.2.4)*~~

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) (see also Section 6.2.5.3)*
- *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 (see also Section 7.2.4)*

SECTION 6.2.4: Dose Reduction Levels

Moderate or severe adverse reactions (clinical and/or laboratory) may require dose reduction of PEG-IFN. Decremental adjustments should be uniform across centers and subjects. Toward this end, the following downward adjustments should be utilized:

~~*Starting Dose (µg)*~~	~~*One Level Reduction (µg)*~~	~~*Two Level Reduction (µg)*~~	~~*Three Level Reduction (µg)*~~
~~*45*~~	~~*30*~~	~~*20*~~	~~*10*~~
~~*65*~~	~~*45*~~	~~*30*~~	~~*20*~~
~~*90*~~	~~*65*~~	~~*45*~~	~~*20*~~
~~*135*~~	~~*90*~~	~~*65*~~	~~*30*~~
~~*180*~~	~~*135*~~	~~*90*~~	~~*45*~~

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*

SECTION 6.2.5.4: Dosage Adjustments for BSA Decrease/Increase

Investigators will adjust the dose of PEG-IFN upward or downward to reflect the most current BSA. BSA and dose will be provided by IXRS at Weeks 12, 24, and 36. *Investigators may also assess the patient's BSA (using the Mosteller formula) at other interim timepoints 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 a subject's BSA falls below $< 0.51\ m^2$ during treatment, any dose adjustments should be made only after consultation between the investigator and ~~*Roche Clinical Science study personnel*~~ *the Medical Monitor (*Appendix 3 *) or delegate*. The recommended dose will be recorded in the SMD.

SECTION 7.2.1: Reporting of Adverse Events

All AEs (related and unrelated) occurring during the treatment/principal observation period and initial 24 weeks of follow-up must be reported. During the extended long-term follow-up period, only persisting AEs, new-onset SAEs *and*~~,~~ non-serious AEs of special interest related to PEG-IFN, and deaths will be reported.

SECTION 7.2.2: Reporting of Serious Adverse Events (immediately reportable)

Related SAEs **must** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. *Every effort should be made to follow all SAEs considered to be related to the study drug or study-related procedures until a final outcome can be reported.*

SECTION 8.1.1: Primary Endpoints

- HBeAg seroconversion (loss of HBeAg and presence of anti-HBe) at the 24-week post-*end of* treatment/principal observation period follow-up visit

SECTION 8.2.5.3: Safety Data Analysis

The primary safety analysis will compare safety in Group A with Group B *at 24 weeks post-end of treatment/end of untreated observation*. The safety data of Group A and Group B will be qualitatively evaluated alongside subjects in Group C and the switch arm.

- *Incidence, nature, and severity of serious and non-serious AEs (including neurological and psychiatric events)*
- *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 and weight)*

The following safety outcome measures will be assessed using descriptive statistics at 1, 2, 3, 4, and 5 years post-end of 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 and weight)*

SECTION 10: STUDY COMMITTEES

A DSMB will review safety data on a routine basis (*as per~~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~~is~~* satisfied with the safety of treatment.

SECTION 12.2.1: Main Study Informed Consent

If children are old enough to understand the risks and benefits of the study, they should also be informed and should also provide their written assent. *Patients within the specified age range who are legally 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, if required by national legislation.* With regard to the donation of a specimen(s) by the minor that will be stored in the RCR this same principle will apply. If the minor is not old enough to form an opinion or assess this information, the legal representative/guardian will replace the minor in recognizing his/her rights and responsibilities until he/she reaches legal age.

TABLE 5: Screening assessments

Table 5 has been revised to reflect changes to medical history recording and ophthalmological examination:

Medical history and physical examination	Includes family history of HBV, concomitant medication (including for CHB), *surgeries/procedures,* and vital signs (blood pressure, heart rate, temperature).
Ophthalmological examination[a]	Within 6 months prior to baseline; repeat at screening only if any change in medical condition. By ophthalmologist *(pediatric ophthalmologist is recommended)* and including fundoscopic examination *with dilation*, visual acuity assessment, visual field testing *(confrontation test is recommended for younger children)*, 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 6: Laboratory assessments

Table 6 has been revised to reflect the required availability of pregnancy test results:

HCG pregnancy test[b]	Urine or serum pregnancy test for females of childbearing potential at any time secondary amenorrhea of more than 1 week occurs. *The result of the baseline pregnancy test must be available prior to randomization and commencement of treatment.*

Schedule of Assessments

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 1: Liver Biopsy Scores

Appendix 1 has been revised to include Scheuer Fibrosis scores:

Scores considered as advanced fibrosis will be Metavir fibrosis 3, Knodell fibrosis score 3, Modified Ishak fibrosis score 4, ~~*or*~~ Batts & Ludwig score 3, *or Scheuer score 3*. Subjects with these scores will be assigned to Group C.

Scores considered as cirrhosis will be Metavir fibrosis 4, Knodell fibrosis score 4, Modified Ishak fibrosis score 5 and 6, ~~*or*~~ Batts & Ludwig score 4, *or Scheuer score 4*. Subjects with these scores are excluded from the study.

SCHEUER FIBROSIS SCORE

0. None

1. Enlarged fibrotic portal tracts

2. Periportal or portal -portal septa but intact architecture

3. Fibrosis with architecture distortion but no cirrhosis

4. Probable or definite cirrhosis

APPENDIX 3: ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

Appendix 3 has been revised to reflect changes to the medical monitor:

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor:

See provided forms for details of *study* administrative and contact information*, including the Local Monitor*.

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

ROCHE HEADQUARTERS CONTACT for ~~*SAEs and Other*~~ Medical Emergencies:
~~*Clinical Operations/Clinical Science:*~~

Medical Monitor Contact Information

Primary Contact

Medical Monitor: [redacted], MD

Telephone No.: [redacted]

Mobile Telephone No.:

Secondary Contact

Medical Monitor: [redacted]~~*, MD, PhD*~~ [redacted], *MBChB Dip Pharm. Med*

Telephone No.: [redacted]

Mobile Telephone No.:

~~*24 HOUR MEDICAL COVERAGE:*~~

~~*Identification of a contact for 24-hour medical coverage is mandatory to be compliant with worldwide regulatory agencies and to ensure the safety of study subjects.*~~

~~*An Emergency Medical Call Center Help Desk will access the Roche Medical Emergency Contact List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with the Roche medical contact for this study and track all calls. The Emergency Medical Call Center Help Desk will be manned 24 hours a day, 7 days a week, 52 weeks a year. Toll free numbers will be distributed to all investigators. The Help Desk will be used for medical emergencies outside regular business hours, or when the regular Clinical Science or Clinical Pharmacology contact cannot be reached.*~~

~~*Protocol Contact Information and Emergency Medical Call Center Help Desk toll-free numbers will be provided.*~~

SAMPLE INFORMED CONSENT FORMS

The sample Informed Consent Forms have been revised to reflect the changes to the protocol.

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 hepatitis B envelope antigen (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 body surface area (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, hepatitis B surface antigen (HBsAg)+ve, detectable hepatitis B virus (HBV) DNA (> 10,000 copies/mL [> 2,000 IU/mL]) by polymerase chain reaction and alanine aminotransferase (ALT) > upper limit of normal (ULN) but $\leq 10 \times$ 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 hepatitis C virus, hepatitis D virus, human immunodeficiency virus 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 *to decide* whether to *receive treatment*, 1 year treatment, 5-year follow-up).
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 *defined as* 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 hepatitis B envelope antibody [anti-HBe]) at 24 weeks post-*end of* treatment/principal observation period. Secondary: • Loss of HBeAg, HBsAg seroconversion (loss of HBsAg and presence of hepatitis B surface antibody), 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/principal observation period, and at 24 weeks and 2 years after end of treatment/principal observation period.
- SAFETY	Safety during the treatment/principal observation period and initial 24 weeks of follow-up: • Serious and non-serious adverse events (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. Safety during the 4.5 year extended, long-term follow up period: • 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 data safety monitoring board (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 pharmacokinetic (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 serious adverse events (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

Intent to treat (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 *at 24 weeks post-end of treatment/end of untreated observation*. 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.

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GLOSSARY OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
Ab	Antibody
AE	Adverse event
AFP	Alpha-fetoprotein
A1AT	Alpha-1 antitrypsin
ALKM1	Anti–liver-kidney microsome-1 antibody
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibody
ANA	Anti-nuclear antibody
Anti-HBe	Hepatitis B envelope antibody
Anti-HBs	Hepatitis B surface antibody
ASMA	Anti-smooth muscle antibody
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\tau}$	Area under the curve from 0 hours to a given time point
BSA	Body surface area
BUN	Blood urea nitrogen
CA	Competent Authority
CDI	Children's Depression Inventory
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CL/F	Clearance/bioavailability
C_{max}	Maximum concentration
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
EASL	European Association for the Study of the Liver

GLOSSARY OF ABBREVIATIONS

ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
EEG	Electroencephalogram
eform	Electronic form (page)
ELISA	Enzyme-linked immunosorbent assay
EMEA	European Medicines Agency
EU	European Union
FT3	Free triiodothyronine
FT4	Free thyroxin
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
HAV IgM Ab	Hepatitis A virus Immunoglobulin M antibody
HBeAb	Hepatitis B envelope antibody
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B DNA
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon

GLOSSARY OF ABBREVIATIONS

IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IXRS	Interactive voice or web response system
LLN	lower limit of normal
LSM	Liver Stiffness Measure
MedDRA	Medical Dictionary for Regulatory Activities
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PEG	polyethylene glycol
PEG-IFN	Pegylated-interferon α-2a
PK	Pharmacokinetic
RCR	Roche Clinical Repository
REVEAL	Risk Evaluation of Viral Load Elevation and Associated Liver Disease
RNA	ribonucleic acid
SAE	Serious adverse event
SMD	Subject Medication Diary
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
SW	switch week
TBG	Thyroxine-binding globulin
TPO	Thyroid peroxidase
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

GLOSSARY OF ABBREVIATIONS

US	United States
+ve	Positive
-ve	Negative
V/F	Volume of distribution/bioavailability
WBC	White blood cell
WHO	World Health Organization

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

1.1.1 Disease

Despite the availability of effective vaccination in the western world, hepatitis B is one of the most common infectious diseases in the world. Of the 2 billion individuals infected by the hepatitis B virus (HBV), more than 350 million are chronically infected [1]. Over a million individuals die annually of HBV-related chronic liver disease [2].

The prevalence of chronic hepatitis B (CHB) varies widely in different parts of the world. In areas of low prevalence such as Northern Europe, infection is typically acquired during adulthood via intravenous drug abuse or sexual transmission. In the United States, although prevalence of CHB is low, around 1.25 million people are infected. Moreover, in certain areas and populations in the United States, such as in Alaskan natives, Pacific Islanders, and infants of first-generation immigrant mothers from highly endemic areas, prevalence of HBV infection is high. The majority of individuals in areas with a high prevalence of CHB infection, where $>$5% of the population are HBV-infected carriers, are infected either at the time of birth by vertical transmission from mother to child or during early childhood [3].

The natural history of CHB is highly variable with respect to the course, outcome, and complications. This is partly attributable to the timing of infection e.g., whether acquired in childhood, as occurs in Asia and developing countries, or in adulthood, as occurs in western countries. Viral strain and genotype as well as sex, age, racial/ethnic background, and other host factors also influence the natural history of CHB infection. The onset of CHB is characterized by the persistence of hepatitis B virus DNA (HBV-DNA), hepatitis B surface antigen (HBsAg), and hepatitis B envelope antigen (HBeAg) in serum for more than 6 months after acute infection. During the early phase of CHB, the underlying disease is generally subclinical and often mild. In some cases, the virus can further evolve variants that either do not show or show markedly reduced expression of HBeAg, thereby evading the immune control and a further late phase of reactivated, HBeAg-negative disease can occur. Both HBeAg-positive and HBeAg-negative CHB can lead to cirrhosis and end-stage liver disease. CHB is generally milder in children compared with adults and is almost always asymptomatic. Despite effective vaccination being available in some countries of the world, perinatal infection still occurs, and about 1% of children of those who are infected around the time of birth will spontaneously clear the infection in the first decade of life [4].

The natural history of CHB infection in children differs from that of adults, particularly in those infected vertically. The key differences between children and adults are the high rate of chronic infection that develops with infection in childhood and the long immunotolerant phase. After exposure to HBV, the probability of becoming chronically

infected is inversely proportional to the age at infection: 90% to 95% of neonates, 80% of children, and 30% of adolescents become persistently infected. Rates of spontaneous seroconversion are variable, depending on age at onset of infection, genotype, lower viral load at onset of infection, mode of acquisition, elevated alanine aminotransferase (ALT) level and higher histological inflammatory score on liver biopsy [4, 5, 6].

Chronic disease in children is typically characterized by three phases: the immunotolerant phase, the immunoactive phase, and the inactive carrier state. A large majority of pediatric subjects with perinatally acquired HBV infection with HBeAg-positive disease are considered to be immunotolerant. This phase is associated with minimal or no evidence of clinical symptoms, normal ALT levels, and high serum HBV-DNA. This phase can persist throughout childhood, with disease only becoming active with consequent liver damage in a proportion of subjects later in life. Therefore, severe disease with significant fibrosis is very rarely found in children and adolescents, although instances of hepatocellular carcinoma (HCC) and decompensated cirrhosis have been reported [4, 7].

The immunoactive phase normally follows the immunotolerant phase. Early in this phase, there may be high HBV-DNA levels, but then during this phase, the HBV-DNA levels may decrease to $<$10,000 copies/mL. It is characterized by varying degrees of liver inflammation and fibrosis and increased levels of aspartate aminotransferase (AST) and ALT. Seroconversion of HBeAg to hepatitis B envelope antibody (HBeAb) occurs 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.

Rates of spontaneous HBeAg seroconversion are much higher in the immunoactive phase than in the immunotolerant phase varying between 8% and 12%. As in adults, a further late phase of reactivated, HBeAg-negative disease can occur. Such patients tend to be older and have more advanced liver disease, however, as this represents a later stage in the natural history of CHB infection.

In adults, the risk with CHB is of progression to advanced liver disease, and histologic progression to cirrhosis has a cumulative incidence of 5%–20% of chronically infected individuals over 5 years. This carries the further risk of HCC, which has an annual incidence of 2%–5% when cirrhosis is established [8]. CHB is thought to be responsible for 75% of the cases of HCC on a global level. In adults who acquired CHB infection as an infant or as a child, approximately 15%–25% will die from liver-related causes [9, 10, 11, 12]. It is now established that the risk factors for cirrhosis and HCC include a longer immunoactive phase of infection, earlier age of infection (particularly perinatal acquisition is associated with the highest risk of HCC), prolonged elevation of HBV-DNA, elevated ALT, presence of HBeAg, family history of HCC, genotype C in Asia (although HCC in

younger patients is more often genotype B), co-infection with hepatitis C and D virus, and male sex [13, 14, 15, 16, 17, 18, 19].

Furthermore, the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer Hepatitis B Virus (REVEAL-HBV) study suggested that during the immunoactive phase, high HBV-DNA and elevated ALT levels were associated with greater risk of cirrhosis and HCC [16, 17, 18]. These findings have prompted a new and more aggressive approach to treatment of adults during the immunoactive phase and heightened awareness amongst some pediatric liver specialists that treatment during a prolonged immunoactive phase is important for decreasing an infected child's risk of developing cirrhosis and/or cancer later in life.

Therefore, given the medium- to long-term risk of chronic infection and liver disease with perinatal infection, treatment of children with CHB represents an opportunity to minimize and avoid the risk of long-term complications such as cirrhosis and HCC in later life.

1.1.2 Study Drug

A development program exploring the use of pegylated interferon alfa-2a (PEG-IFN) in the treatment of CHB was initiated with a Phase II study using 90, 180, and 270-μg doses of PEG-IFN doses, which were compared against the licensed dose of conventional interferon (IFN) alfa for 24 weeks of therapy [20]. This pilot trial showed a two-fold improvement in efficacy of PEG-IFN over unpegylated 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 PEG-IFN was superior to lamivudine in both HBeAg-positive and -negative disease when assessed 24 weeks after stopping 48 weeks of therapy. Furthermore, both studies contained a third arm containing the combination of PEG-IFN with lamivudine, which while showing significantly greater HBV-DNA suppression on treatment than lamivudine monotherapy, did not show any improvement over PEG-IFN monotherapy at 24 weeks after the end of therapy [21, 22]. These HBV studies included more than 1500 subjects and led to regulatory approval of PEG-IFN use in CHB in the European Union (EU), United States (US), and many other countries with high incidence of HBV disease. The safety profile of 180 μg of PEG-IFN in subjects with CHB was no worse and possibly a little better tolerated than that in subjects with hepatitis C virus (HCV) treated with PEG-IFN, particularly with regards to the incidence of depression.

The NEPTUNE study was a Phase IV trial which examined two doses of PEG-IFN (90 and 180 μg/wk), and two durations (24 and 48 weeks) in adults with HBeAg-positive chronic HBV infection [23]. This trial incorporated a non-inferiority study design and showed that the highest response rate was achieved in the 180-μg/wk 48-week treatment group, confirming the registered dose and duration of 180 μg/wk 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/wk 48-week treatment group. The results confirmed that

the overall safety profile of PEG-IFN in subjects with HBeAg-positive CHB was consistent with the currently approved label, with no new signals identified.

The present study aims to evaluate the efficacy and safety of treating children with immunoactive CHB disease with PEG-IFN in a prospective, open-label, randomized study of PEG-IFN monotherapy compared with untreated control in children with HBeAg-positive CHB. The dose and duration of PEG-IFN are based on the results of the NEPTUNE study, which showed clearly that the best response rates were in those treated with the licensed dose of 180 μg of PEG-IFN for 48 weeks. This is discussed in Section 3.1.2.

1.2 RATIONALE FOR THE STUDY

The principal rationale for conducting a controlled study in pediatric subjects with CHB is to establish the risk–benefit balance of treatment in this immunoactive population, given that there is no consensus established among experts with regard to the most appropriate treatment and timing of therapy for pediatric HBV infection, or with regard to the appropriate pediatric HBV target population(s). Pediatric subjects with immunoactive disease may have no signs or symptoms of disease, other than raised transaminases (e.g., ALT). While some experts prefer not to treat and allow for natural resolution of the infection, spontaneous seroconversion, and viral clearance, others believe that promoting childhood treatment of HBV infection reduces the risk of transmission and progression to cirrhosis and HCC.

There are several arguments in favor of not delaying treatment in pediatric subjects with CHB. For example, children are more likely than adults to develop chronic HBV and therefore have higher risk of long-term complications. Earlier HBeAg seroconversion, and a higher chance of HBsAg seroconversion with IFN-based treatment, therefore may reduce the risk of long-term complications of liver disease, and also the risks of horizontal secondary infection. In addition, children above the age of 3 years old appear to tolerate IFN therapy better than adults, with few persisting serious adverse events (SAEs). Of note, safety concerns in treating children under the age of 3 years with IFN therapy exist, and therefore treatment of such infants is not recommended [24, 25, 26, 27, 28].

Although anti-HBV treatment using small molecules (nucleos[t]ide therapy) is available to suppress levels of HBV-DNA, IFN-based therapies have the advantage that a defined duration of treatment is required, rather than apparent life-long treatment, and also that interferons lack the development of drug resistance. PEG-IFN is a long-acting IFN alfa-2a that has been successfully used for treating CHB in adults and chronic hepatitis C (CHC). Its reduced frequency of injection (once per week) has an advantage over conventional IFN-alfa 2a particularly in children.

The available literature data suggest and support a positive benefit–risk balance for the treatment of pediatric subjects with IFN-based therapy. Treatment with 24 weeks of IFN

[29] showed similar or better response rates to adult studies with pegylated alfa interferon, with HBeAg loss and HBV-DNA negativity in 26% of treated patients versus 11% of controls ($p = 0.03$), loss of HBsAg in 10% of treated patients versus 1% of controls at 48 weeks. A publication reporting two combined IFN-treated cohorts and an untreated control group reported that 32% of IFN-treated pediatric subjects and 13.5% of control patients achieved HBeAg seroconversion ($p < 0.05$) 12 months after finishing therapy [30]. Data suggest that IFN appears to accelerate an early HBeAg seroconversion rate compared with controls, whereas untreated children may have similar overall rates of HBeAg seroconversion as treated children, but the seroconversion lags behind by 2–3 years in terms of timing [30, 31]. Shifting the time to seroconversion by 12–36 months could therefore be helpful in preventing long-term damage to the liver, although this has not been demonstrated in clinical studies to date. Of note, however, HBeAg seroconversion frequencies among treated children with raised ALT at baseline (ALT was $\geq 2\times$ the upper limit of normal [ULN]) were almost twice that of the untreated children or children with baseline of ALT $\leq 2\times$ the ULN, showing an enhanced response in those patients with a higher degree of hepatic injury at baseline. Pediatric subjects treated with IFN have higher rates of HBsAg seroconversion than untreated controls (10% vs. 1.2%, respectively; $p = 0.03$) [29], supporting the idea that treatment enhances cure rates in terms of loss of HBsAg and production of hepatitis B surface antibodies (anti-HBs).

A review in 2003 [32] identified factors predictive of IFN response in the pediatric CHB population, including higher baseline ALT levels, lower DNA levels, higher histological activity on biopsy in children [33] and younger age [34]. In addition, genotypes A and B appeared to respond better to IFN than types C and D with standard therapy [35, 36, 37]. PEG-IFN data have suggested that genotype C responded similarly to genotype B [37, 38].

Pawlowska et al. [37] reported on the treatment of 13 children (9 boys and 4 girls), aged 11–17 years with CHB, who were treated with PEG-IFN (100 μg/m^2/wk; doses ranged from 135 to 180 μg/wk) for 48 weeks. There were 5 HBeAg-positive and 8 HBeAg-negative children. Five children achieved sustained virological response (undetectable serum HBV-DNA 24 weeks after the end of treatment) and continued to sustain this response 48 weeks after the end of treatment; 2 children had HBsAg loss at the end of 48 weeks of treatment.

A study conducted in China evaluated the safety and efficacy of extended PEG-IFN therapy in children with HBeAg-positive CHB [39]. Forty-two children, aged 8–16 years, were treated with PEG-IFN 104 μg/m^2 body surface area (BSA) once weekly. Treatment duration was extended from 48 weeks to a maximum of 96 weeks with a subsequent follow-up of 24 weeks. All response rates were higher at Week 96 and at 24 weeks after end of treatment compared with responses at 48 weeks with HBeAg seroconversion rate at Week 96 being significantly higher than at Week 48 (83.8% vs. 19.1%, respectively; $p < 0.005$). These data indicate that extension of PEG-IFN may improve response rates

for those with poorer predictors of response, e.g., genotype C, and appears to be tolerated in children.

The major adverse events (AEs) seen in children treated with non-pegylated or pegylated alfa interferon were similar to those seen in adults and included fever, fatigue, headaches, muscle aches, dizziness, irritability, arthralgia, anorexia, nausea, abdominal discomfort, injection-site reactions, neutropenia, and thrombocytopenia. The AEs which seem to be more prominent in children than in adults were hair loss, personality changes, and transient growth suppression [29, 30, 37, 38, 39, 40]. Changes in height and growth percentiles over time were assessed at the end of treatment and at 2 years of follow-up in 114 subjects with CHC who were treated with PEG-IFN as part of the PEDS-C trial [41]. Although reductions in weight and height were observed compared to the normative population at the end of treatment, these had returned to baseline by Year 2 of follow-up.

Therefore, the available data involving treatment with both non-pegylated and pegylated interferon alfa suggest that the risk–benefit balance of not delaying treatment may be positive. While there may be an emerging consensus from pediatricians that the potential therapeutic benefit of treatment might outweigh the risks in most children to avoid the risk of long-term liver disease, opinion and practice still diverge, and there is a need to assess the benefit–risk balance of treatment against observed untreated controls.

2. OBJECTIVES

This controlled study in children with HBeAg positive CHB in the immune active phase 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.

2.1 PRIMARY OBJECTIVE

To compare HBeAg seroconversion (loss of HBeAg and presence of hepatitis B envelope antibody [anti-HBe]) between a group treated with PEG-IFN monotherapy and an untreated control group. The primary endpoint will be assessed 24 weeks after the end of treatment/principal observation period, with a further 4.5 years of follow-up (see Section 8.1.1).

2.2 SECONDARY OBJECTIVES

To examine the short and longer term effects on various efficacy and safety measures between a group treated with PEG-IFN monotherapy and an untreated control group, and to evaluate PK in PEG-IFN–treated subjects (see Section 8.1.2), as follows:

Efficacy

- 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)
- Persistence of HBeAg seroconversion (loss of HBeAg and presence of anti-HBe) over extended long-term follow-up
- Descriptive change from baseline in liver elasticity (in liver elasticity sub-study subjects—see Section 5.3.1.2)

Safety

- AEs (including neurological and psychiatric events), serious and non-serious, and non-serious AEs of special interest
- Laboratory test results (including thyroid function)
- Vital signs (blood pressure, heart rate, temperature)
- Growth: weight and height

Pharmacokinetic

- PK of PEG-IFN following administration of a new BSA-based dosing regimen in PEG-IFN–treated subjects

2.3 EXPLORATORY OBJECTIVES

The Roche Clinical Repository (RCR) is a centrally administered group of facilities for the long-term storage of human biological specimens including body fluids, solid tissues and derivatives thereof (e.g., DNA, RNA proteins/peptides; see Section 5.4.3). 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. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, AEs, or other effects associated with medicinal products
- 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

3. STUDY DESIGN

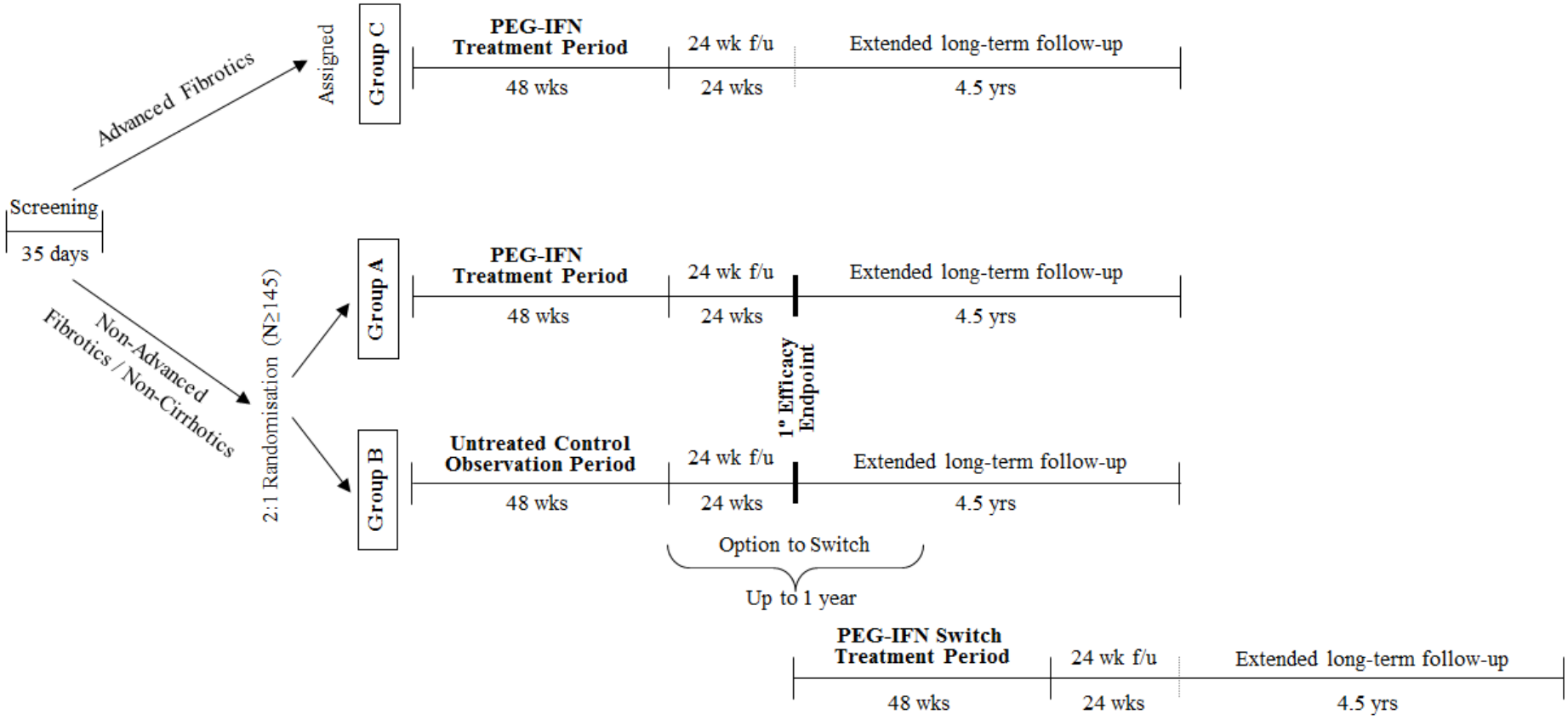
3.1 OVERVIEW OF STUDY DESIGN AND DOSING REGIMEN

This is a 2:1 randomized, controlled, parallel-group, open-label, multicenter study of PEG-IFN treatment compared to an untreated control (Figure 1). Subjects without advanced fibrosis/cirrhosis will be randomized 2:1 to PEG-IFN treatment (Group A) or untreated control (Group B), respectively. Subjects with advanced fibrosis will be assigned to PEG-IFN treatment (Group C). Subjects 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 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 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 Week 48. If eligible, these subjects will enter the switch arm, where they will receive PEG-IFN for 48 weeks.

The screening period will be up to 35 days. For Group A, Group B non-switch, and Group C subjects the study length is approximately 6 years (1-year treatment/principal observation period and 5 years of follow-up). For Group B switch subjects 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



3.1.1 Rationale for Study Design

3.1.1.1 Use of *Untreated* Control Arm and Compassionate Switch

Experts have debated whether a need exists for treatment during childhood, since the majority of children infected with HBV are in the immunotolerant phase [11], and only a minority of subjects might fulfill the criteria to be considered for antiviral therapy on grounds of absolute clinical need. The current European Association for the Study of the Liver (EASL) guidance recommends consideration of treatment in children with CHB in those with immunoactive disease i.e., those with persistently elevated ALT greater than the ULN for 6 months [42].

It is acknowledged that few children with immunoactive disease show any signs or symptoms of disease. Some experts take the view that treatment should be delayed in children with chronic HBV disease given the lack of clinical signs, the possible natural resolution of infection, the uncertainties around treatment effectiveness, the AEs reported during treatment, and the possible development of newer more effective, less toxic therapies [43]. This has led to a lack of consensus among experts with regard to the most appropriate treatment and timing of therapy for pediatric HBV infection, or with regard to the appropriate pediatric HBV target population(s). The inclusion of an untreated control arm for 48 weeks in the study design therefore takes account of this area of uncertainty by allowing a period of direct comparison of efficacy and safety with untreated subjects.

The study design also takes into account these management uncertainties by ensuring that all subjects randomized to the untreated control arm who request it and who have not seroconverted will be offered treatment with PEG-IFN at the end of the 48-week observation period and up to 1 year after this point.

An untreated control arm has been selected for this study as the use of a placebo control arm is not considered appropriate for several reasons. Firstly, the use of placebo injections would not effectively blind treatment as the known adverse effects of IFN therapy, particularly influenza-like illness, would not occur. It would therefore be likely that subjects/parents would become aware that the subject was not receiving IFN resulting in a potential risk of noncompliance. Secondly, it would be unethical to administer weekly placebo injections for 48 weeks as administration requires an invasive procedure with an associated risk of injection-site infections and no associated benefit. A further benefit of using an untreated control arm is that the study burden for the untreated subjects is reduced as their visit schedule is less frequent compared with that of the treated subjects, 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 central randomization, use of a central laboratory and standardized assays, and the choice of the intent-to-treat (ITT) population for the primary analysis.

The objective of this study would be therefore to establish the benefit–risk balance for treatment using PEG-IFN in this immunoactive pediatric population, by comparing the safety and efficacy of 48 weeks treatment with an untreated control group.

3.1.1.2 Use of Advanced Fibrotic Arm and Exclusion of Cirrhotic Subjects

This study will also evaluate the efficacy and safety of PEG-IFN–based treatment in a small subgroup of pediatric subjects with advanced fibrosis (see Appendix 1) and compensated liver disease. When these subjects are recruited they will be allocated to treatment arm (Group C; 48 weeks treatment with PEG-IFN), rather than being randomized to treatment or untreated control. This is because a majority of specialists surveyed on the clinical and ethical risk-benefit gave the opinion that it would be clinically and ethically unacceptable to them to delay treatment in subjects with advanced disease (advanced fibrosis/cirrhosis) by potentially randomizing them to an untreated control arm. Instead, subjects with advanced fibrosis will receive guaranteed immediate treatment.

The data from these subjects with more advanced fibrosis will therefore be analyzed descriptively and separately from the main comparison.

Subjects with cirrhosis will be excluded from this study. The current treatment guidance from the European and US experts (EASL and American Association for the Study of Liver Diseases [AASLD]) does not recommend interferon treatment for cirrhotic patients with CHB due to the risk of hepatic decompensation associated with IFN-related flares of hepatitis. Long-term treatment with nucleos(t)ides analogues are recommended for this patient population [42, 44].

3.1.1.3 Liver Elasticity Sub-study

Liver elasticity using liver elastography will also be assessed as a sub-study at specific sites in both treated and untreated subjects. Liver elastography is a non-invasive procedure used in some countries to assess liver fibrosis. It is a measure of liver elasticity as a Liver Stiffness Measure (LSM) that has been shown to correlate significantly with the degree of hepatic fibrosis [45, 46, 47]. Liver elastography is a potentially useful method of diagnosing degrees of fibrosis, and therefore will be utilized in this sub-study to assess progression and improvement in liver fibrosis. In addition, this sub-study will explore the association of baseline liver biopsy score with LSM in a proportion of subjects.

3.1.2 Rationale for Dose Selection

3.1.2.1 Establishment of Optimal Dose and Duration of PEG-IFN in CHB

The NEPTUNE study was a Phase IV trial that examined two doses of PEG-IFN (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 weeks 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 PEG-IFN in patients with HBeAg-positive CHB was consistent with the currently approved label, with no new signals identified.

The present study aims to evaluate the efficacy and safety of treating children with immunoactive CHB disease with PEG-IFN in an open-label, randomized study of PEG-IFN monotherapy compared with untreated control in children with HBeAg-positive CHB. The dose and duration of PEG-IFN are based on the results from the NEPTUNE study.

3.1.2.2 Pediatric Dosing of PEG-IFN

This study will use the dose and duration of PEG-IFN established in the NEPTUNE study but modified for pediatric use. Study NR16141 (Schwarz PK/pharmacodynamic [PD] 2006 study) [48] demonstrated 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 from 0 hours to a given time point [$AUC_{0-\tau}$]) to PEG-IFN in children was 25% to 70% higher than that observed in adults receiving a weekly dose of 180 μg of PEG-IFN (5667 ng • h/mL vs. a range of mean values from 3334 to 4348 ng • h/mL). There was a high 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 11125 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, indicating that dosing may be slightly reduced to improve exposure-related AEs 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 (NV17424 PEDS-C Study) [41] and in the PK/PD Study NR16141 (Schwarz PK/PD [2006] study) [48]. 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 (Table 1).

Table 1 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

This approach has been accepted by the European Medicines Agency (EMEA) for Pegasys pediatric dosing in HCV disease [49]. This also aligns with the approved Pegasys pediatric label in the United States, where the dose for children between the ages of 5 to 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 hepatitis B in adults, similarly 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 hepatitis C from adult to pediatric doses to 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 subjects 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).

Treated subjects will receive PEG-IFN subcutaneously once weekly for 48 weeks with dosing based on BSA categories.

3.1.3 End of Study

The primary endpoint will be assessed 24 weeks after the end of treatment/principal observation period, with a further 4.5 years of extended long-term follow-up. The end of study is *defined as* last subject last visit *(LSLV)*.

3.2 NUMBER OF SUBJECTS/ASSIGNMENT TO TREATMENT GROUPS

One-hundred-sixty subjects will be recruited. At least 145 subjects without advanced fibrosis or cirrhosis (assessed by liver biopsy performed within 2 years prior to baseline) will be randomized in a 2:1 ratio 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. Stratification will be performed by genotype (A

vs. non-A) and ALT ($<5\times$ the ULN vs. $\geq 5\times$ the 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: advanced fibrotic arm). Group and dose, if applicable, will be assigned by an interactive voice or web response system (IXRS [see Section 5.2]).

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 Week 48. If eligible, these subjects will enter the switch arm, where they will receive PEG-IFN for 48 weeks.

3.3 CENTERS

Subjects will be enrolled from approximately 40-70 centers globally. There will be a mean number of 2–4 subjects per center, with the majority of subjects being in Asia–Pacific regions.

4. STUDY POPULATION

Under no circumstances are subjects who enroll in this study permitted to be re-randomized to this study and enrolled for a second course of treatment.

4.1 OVERVIEW

The study population will be children aged 3 to <18 years of age with CHB, who are HBeAg positive (+ve), HBsAg+ve, with detectable HBV-DNA ($>10{,}000$ copies/mL [$>2{,}000$ IU/mL]) by polymerase chain reaction (PCR) and ALT $>$ ULN but $\leq 10\times$ the ULN (using the reference range of the testing laboratory). Liver biopsy needs to have been performed within 2 years prior to baseline to confirm or exclude the presence of advanced fibrosis or cirrhosis (see Appendix 1). For subjects with advanced fibrosis, a liver biopsy needs to have been performed within 9 months prior to baseline to ensure that the subject has not progressed to cirrhosis. Subjects co-infected with HCV, hepatitis D virus (HDV), human immunodeficiency virus (HIV) or who have received therapy for hepatitis B in the prior 6 months or who have de-compensated liver disease will be excluded.

4.1.1 Recruitment Procedures

Subjects will be identified for potential recruitment using pre-screening enrollment logs, Independent Ethics Committee (IEC)/Institutional Review Board (IRB)-approved newspaper/radio advertisements, and/or mailing lists prior to consenting/assenting to take place in this study.

4.2 INCLUSION CRITERIA

A subject may be included if the answer to all of the following statements is “yes”:

- Male or female subjects aged 3 to <18 years old at baseline

- Positive HBsAg for more than 6 months
- Positive HBeAg and detectable HBV-DNA at screening (subjects must have > 10,000 copies/mL [> 2,000 IU/mL] as measured by PCR)
- A liver biopsy performed within 2 years prior to baseline to confirm the presence of advanced fibrosis or exclude cirrhosis (see Appendix 1). For subjects with advanced fibrosis, a liver biopsy needs to be performed within 9 months prior to baseline
- Compensated liver disease (Child-Pugh Class A clinical classification; see Appendix 2)
- Elevated serum ALT > ULN but ≤ 10 × the ULN as determined by two abnormal values taken ≥ 14 days apart during the 6 months before the first dose of study drug with at least one of the determinations obtained ≤ 35 days prior to the first dose. Reference range of the testing laboratory should be used
- Signed informed consent from *parent*/legal guardian and willingness of *parent*/legal guardian to abide by the requirements of the study, and signed assent from child if appropriate. *Patients <18 years of age at baseline who are legally adults according to national legislation must consent in their own right.*

4.3 EXCLUSION CRITERIA

A subject will be excluded if the answer to any of the following statements is "yes":

- Subjects with cirrhosis (see Appendix 1)
- Subjects who have received investigational drugs or licensed treatments with anti-HBV activity within 6 months prior to baseline (e.g., IFNs, systemic corticosteroids, lamivudine, tenofovir, emtricitabine, adefovir, entecavir, telbivudine, systemic acyclovir, systemic famciclovir) (Exception: Subjects 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.)
- Known hypersensitivity to PEG-IFN
- Positive test results at screening for hepatitis A virus immunoglobulin M antibody (HAV IgM Ab), anti-HCV antibody (Ab), anti-HDV Ab, or anti-HIV Ab
- History or other evidence of a medical condition associated with chronic liver disease other than CHB
- 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*)
- History or other evidence of metabolic liver disease
- Suspicion of HCC on ultrasound or other liver imaging (all subjects to have ultrasound within 6 months prior to baseline)
- Screening alfa-fetoprotein (AFP) ≥ 100 ng/mL

- 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 < lower limit of normal or total bilirubin > ULN

  Exception: Subjects with non–hepatitis-related factors which may elevate bilirubin such as Gilbert's disease
- *Evidence of* renal impairment
- Autoimmune hepatitis
- History of immunologically mediated disease to include, but not limited to: 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
- History or other evidence of chronic pulmonary or cardiac disease associated with clinically significant functional limitation
- History of thyroid disease 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/or thyroxine-binding globulin [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 (international normalized ratio > 1.5), hemoglobinopathy, hemophilia, or history of severe illness or other blood disorders that would make subject unsuitable for the study
- History of seizure disorder requiring treatment with anticonvulsant medication (excluding febrile seizures)
- History or other evidence of severe retinopathy (all subjects to have ophthalmological examination within 6 months prior to baseline)
- History or other evidence of severe illness or any other conditions that would make the subject, in the opinion of the investigator, unsuitable for the study
- Active substance abuse within the last 6 months before the study

- Sexually active females of childbearing potential and sexually active males who are not willing to utilize reliable contraception during the treatment/principal observation period and during the initial 24-week follow-up period
- Females of childbearing potential who have a positive urine or serum pregnancy test result within 24 hours of baseline, or who are breast-feeding

4.4 CONCOMITANT MEDICATION AND TREATMENT

- Use of any investigational drugs as a result of participation in another clinical study is prohibited during the study including the extended long-term follow-up period.
- Concomitant use of any other investigational drugs (e.g., compassionate use), immunomodulatory treatments (e.g., interferons, systemic corticosteroids), growth factors (e.g., erythropoietin, granulocyte colony-stimulating factor) or antiviral treatments with anti-HBV activity (e.g., lamivudine, tenofovir, emtricitabine, adefovir, entecavir, telbivudine, systemic acyclovir, systemic famciclovir) other than those specifically allowed by this protocol are prohibited during either the treatment/principal observation period or initial 24 weeks of follow-up, in order to minimize the confounding effects of such treatments in determining treatment responses.

  Exceptions to this are as follows:

  Subjects with significant deterioration in hepatic function (e.g., decompensation) who permanently discontinue study drug and need to consider alternative therapies

  In Group C, treatments with anti-HBV activity will not be prohibited during the 24-week follow-up period.
- Commencing any anti-HBV treatment between follow-up Week 24 and follow-up Year 1 will make Group B subjects ineligible for entering the switch arm.
- 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.

All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF), including details of any previous anti-HBV treatment, as well as any other previous concomitant medications taken within 2 years prior to baseline.

During extended long-term follow-up, only concomitant medications for CHB will 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 chronic HBV disease.

4.5 MINIMIZING PAIN AND DISTRESS

As per the International Conference on Harmonisation (ICH) Guideline for Clinical Investigation of Medicinal Products in the Pediatric Population, Topic E11, measures will be taken in this study to minimize the pediatric subjects' possible pain and distress.

This study has been designed specifically for a pediatric population.

Considerations to ensure that subjects' experiences in the study are positive and to minimize discomfort and distress will include the following:

- Investigators will be experienced and skilled in the treatment of pediatric subjects and in dealing with the pediatric population and its age-appropriate needs, including skill in performing pediatric procedures.
- Investigator sites will provide a physical setting with furniture, play equipment, activities, and food appropriate for age.
- Investigator sites will be the hospitals or clinics where subjects normally receive their care and hence will provide a familiar environment.
- Approaches to minimize discomfort of procedures will be utilized, e.g., topical anesthesia to place IV catheters, indwelling catheters rather than repeated venepuncture for blood sampling.
- Blood draws will be kept to those absolutely necessary for the study, and volumes will be minimized.
- Subjects have the right to withdraw from the study at any time for any reason (see Section 4.6).

4.6 CRITERIA FOR PREMATURE WITHDRAWAL

4.6.1 Withdrawal of Subjects from Study Treatment

Subjects have the right to withdraw from study treatment at any time for any reason. Specific rules for stopping study treatment also apply (see Section 6.2.1).

In the case that the subject decides to prematurely discontinue study treatment ("refuses treatment"), all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible preferably by returning to site to complete assessments as per the Week 48/Switch Week 48 visit (see Table 2 and Table 4) and the Treatment Completion eCRF. The subject should then enter the post-*end of* treatment follow-up period.

4.6.2 Withdrawal of Subjects from the Study

Subjects have the right to withdraw from the study at any time for any reason.

In the case that the subject decides not to enter the follow-up period or prematurely discontinues from the follow-up period, he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be

documented in the medical records. If the subject is lost to follow-up, the investigator should contact the subject or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. In all cases, the Study Completion eCRF must be completed.

If possible, a complete final evaluation at the time of the subject's withdrawal from the study should be made with an explanation of why the subject is withdrawing from the study. For subjects withdrawing prior to Week 48, the assessments as per the Week 48 visit should be completed. For subjects withdrawing post–Week 48 but prior to follow-up Week 24, the assessments as per the follow-up Week 24 visit should be completed. For subjects withdrawing after follow-up Week 24, the assessments as per the follow-up Year 5 visit should be completed.

When applicable, subjects should be informed of circumstances under which their participation may be terminated by the investigator without the subject's consent/assent. The investigator may withdraw subjects from the study in the event of intercurrent illness, AEs, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits) or any reason where it is felt by the investigator that further follow-up of the subject is impossible or it is in the best interest of the subject to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the subject.

If the reason for removal of a subject from the study is an AE, the principal specific event will be recorded on the eCRF. The subject should be followed until the AE has resolved, if possible.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

See Section 7.2.4 for withdrawal due to pregnancy.

4.6.3 Withdrawal of Subjects from the Roche Clinical Repository (RCR)

Subjects 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 subject wishes to withdraw consent/assent to the testing of his or her specimens, the investigator must inform the Roche monitor in writing of the subject'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 eCRF. The subject will be provided with instructions on how to withdraw consent/assent after the trial is closed. A subject's withdrawal from Study YV25718 does not, by itself, constitute withdrawal

of specimens from the RCR. Similarly, a subject's withdrawal from the RCR does not constitute withdrawal from Study YV25718.

4.7 REPLACEMENT POLICY (ENSURING ADEQUATE NUMBERS OF EVALUABLE SUBJECTS)

4.7.1 For Subjects

No subject prematurely discontinued from the study for any reason will be replaced.

4.7.2 For Centers

A center may be replaced for the following administrative reasons:

- Excessively slow recruitment
- Poor protocol adherence

4.8 SWITCH CRITERIA

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 Week 48. Subjects must meet the following switch inclusion and exclusion criteria.

4.8.1 Switch Inclusion Criteria

Subjects in Group B may switch to treatment with PEG-IFN if the answer to all of the following statements is "yes."

- Positive HBeAg and positive HBsAg within 6 months prior to switch baseline
- Either

  A liver biopsy performed within 2 years prior to switch baseline to exclude cirrhosis (see Appendix 1) or

  Clinical, laboratory, and ultrasound data which together exclude cirrhosis

4.8.2 Switch Exclusion Criteria

Subjects in Group B may not switch to treatment with PEG-IFN if the answer to any of the following statements is "yes".

- Cirrhosis (see Appendix 1)
- Subjects who have received any anti-HBV treatment within 6 months prior to switch baseline
- Positive test results within 6 months prior to switch baseline for HAV IgM Ab, anti-HCV Ab, anti-HDV Ab, or anti-HIV Ab
- Evidence of decompensated liver disease (e.g., Child–Pugh Class B or C clinical classification, see Appendix 2 *or clinical evidence such as ascites or varices*) *at switch baseline*
- *Serum ALT >10 ×the ULN at switch baseline. Reference range of the testing laboratory should be used*

- International normalized ratio >1.5 at switch baseline
- Neutrophil count $<1.5\times10^{9}$ cells/L, platelet count <90 $\times10^{9}$ cells/L, or hemoglobin *< lower limit of normal (LLN)* at switch baseline
- *Evidence of* renal *impairement*
- Evidence of severe illness or any other conditions or contraindications that would make the subject, in the opinion of the investigator, unsuitable for commencing PEG-IFN
- Clinically relevant abnormal thyroid function tests (TSH, FT3, FT4, TPO antibodies, and/or TBG) within 6 months prior to switch baseline
- Sexually active females of childbearing potential and sexually active males who are not willing to use reliable contraception during the switch treatment period and initial 24-week switch follow-up period
- Females of childbearing potential who have a positive urine or serum pregnancy test result within 24 hours of switch baseline

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 2 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 Follow-Up (*w*eeks Post-End of Treatment)			Long-Term Follow-Up (*y*ears 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 *(pediatric ophthalmologist recommended)* and including fundoscopic examination *with dilation*, visual acuity assessment, visual field testing *(confrontation test is recommended for younger children)*, 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 2 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 Follow-Up (*w*eeks Post-End of Treatment)			Long-Term Follow-Up (*y*ears 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	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	x						
Chemistry [f, i]	x	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	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 2 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 Follow-Up (weeks Post-End of Treatment)			Long-Term Follow-Up (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]
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 2 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 *and* 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 3 Schedule of Assessments and Procedures—Group B (Untreated Control)

Assessment/Procedure	Screen (days)	BL (days)	Principal Observation Period (weeks)				Initial Follow-up (*weeks* Post-End of Principal Observation Period)		Long-Term Follow-Up (*years* 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	x
Height [d, e]	x	x [f]	x	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 *(pediatric ophthalmologist is recommended)* and including fundoscopic examination *with dilation*, visual acuity assessment, visual field testing *(confrontation test is recommended for younger children)*, 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 3 Schedule of Assessments and Procedures—Group B (Untreated Control) (cont.)

Assessment/Procedure	Screen (days)	BL (days)	Principal Observation Period (weeks)				Initial Follow-up (weeks Post-End of Principal Observation Period)		Long-Term Follow-Up (years 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 3 Schedule of Assessments and Procedures—Group B (Untreated Control) (cont.)

Assessment/Procedure	Screen (days)	BL (days)	Principal Observation Period (weeks)				Initial Follow-up (weeks Post-End of Principal Observation Period)		Long-Term Follow-Up (years 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 3 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 4 Schedule of Assessments and Procedures—Switch (PEG-IFN)

Assessment/Procedure	Switch BL [a]	Treatment Period (weeks)											Initial Follow-up (*w*eek*s* Post-End of Principal Observation Period)			Long-Term Follow-Up (*y*ears Post-End of Principal Observation 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 *(pediatric ophthalmologist is recommended)* and including fundoscopic examination *with dilation*, visual acuity assessment, visual field testing *(confrontation test is recommended for younger children)*, 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 4 Schedule of Assessments and Procedures—Switch (PEG-IFN) (cont.)

Assessment/Procedure	Switch BL [a]	Treatment Period (weeks)											Initial Follow-up (weeks Post-End of Principal Observation Period)			Long-Term Follow-Up (years Post-End of Principal Observation 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	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	x
HBV-DNA [h]	x[i]					x		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	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 4 Schedule of Assessments and Procedures—Switch (PEG-IFN) (cont.)

Assessment/Procedure	Switch BL[a]	Treatment Period (weeks)											Initial Follow-up (*w*eeks Post-End of Principal Observation Period)			Long-Term Follow-Up (*y*ears Post-End of Principal Observation 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	x
RCR plasma and RNA specimen	x					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	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	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 *and* non-serious AEs of special interest related to PEG-IFN, and deaths will be collected.

Table 4 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.

5.1 SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM

All legal guardians/subjects must sign and date the most current IRB/IEC-approved written informed consent/assent (where appropriate) before any study-specific assessments or procedures are performed.

The assessments in Table 5 *should* be obtained within a period of no more than 35 days before the subject is randomized, except as noted. *Extensions to the screening period of up to 7 days may be permitted under exceptional circumstances if certain results concerning eligibility are not available within the 35 days and only upon approval from the Medical Monitor.* Subjects must fulfill all the entry criteria for participation in the study (see Sections 4.2 to 4.4). An Eligibility Screening Form documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator. A screen failure log must be maintained by the investigator.

If a subject 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 below. If the subject 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.

Subjects who fail to meet the entry criteria may be re-screened on one more occasion provided that enrollment remains open *and upon approval from the Medical Monitor. If re-screening is required, then the complete screening module should be repeated* (except for those parameters indicated in Table 5). *Re-screening is required if a subject has not met all of the eligibility criteria within 35 days from the original screening visit. It will not be considered a re-screening if blood samples have to be redrawn because of sample handling problems, breakage, or sample integrity.*

Table 5 Screening Assessments

Medical history and physical examination	Includes family history of HBV, concomitant medication (including for CHB), *surgeries/procedures,* and vital signs (blood pressure, heart rate, temperature).
Ophthalmological examination[a]	Within 6 months prior to baseline; repeat at screening only if any change in medical condition. By ophthalmologist *(pediatric ophthalmologist is recommended)* and including fundoscopic examination *with dilation*, visual acuity assessment, visual field testing *(confrontation test is recommended for younger children)*, and color visual testing. Any subject who develops ocular symptoms should receive a prompt eye examination by an ophthalmologist and additional examinations as necessary.
Neuro-psychiatric Questionnaire	Children's Depression Inventory (CDI)
Growth	Weight and height

Ultrasound[a]	Within 6 months prior to baseline; repeat at screening only if any change in medical condition. To rule out hepatocellular carcinoma. Further liver imaging assessment may be performed if necessary.
Liver biopsy	Only if no previous histology available within 2 years prior to baseline or within 9 months prior to baseline for subjects with advanced fibrosis.
Liver elastography	For subjects taking part in site specific liver elasticity sub-study only
HCG pregnancy test[b]	For females of childbearing potential, a negative urine or serum HCG test needs to be documented within 24 hours prior to baseline. Note that the test may be performed at the baseline visit, provided that the result is available prior to randomization and commencement of treatment.
Hematology[c]	Complete blood count (hemoglobin, hematocrit, total white blood cell [WBC] count, differential WBC count [neutrophils, lymphocytes, monocytes, eosinophils, basophils]), platelet count, international normalized ratio (INR)
Clinical chemistry[c]	ALT, AST, GGT, total bilirubin, alkaline phosphatase, total protein, albumin, blood urea nitrogen (BUN)/urea, creatinine[e], uric acid, total calcium, phosphorus, cholesterol, triglycerides, random glucose, sodium, chloride, potassium
Urinalysis[b]	Dipstick with subsequent microscopic evaluation if positive for blood
Immunology and special chemistry [a,d]	Alfa-fetoprotein, ceruloplasmin, A1AT, anti-mitochondrial antibody (AMA), ANA, anti-smooth muscle antibody (ASMA), anti–liver-kidney microsome-1 antibody (ALKM1), anti-HAV IgM, anti-HCV, anti-HIV, anti-HDV
HBV serology and virology[a,d]	HBeAg, anti-HBe, HBsAg, anti-HBs, quantitative HBsAg and HBeAg, HBV-DNA, HBV genotype
Thyroid function tests[a,d]	FT3, FT4, TSH, TPO antibodies, TBG

[a] 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.

[b] To be performed by local laboratory.

[c] 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.

[d] To be performed by central laboratory.

[e] Estimated creatinine clearance will be calculated internally at baseline/switch baseline.

5.2 PROCEDURES FOR ENROLLMENT OF ELIGIBLE SUBJECTS

A subject will be enrolled in the study and assigned a screening number after the subject has given informed consent/assent. Once a subject has fulfilled the entry criteria they may be randomized or assigned, as applicable. Upon contacting IXRS, the investigator or designee must confirm/provide the following:

- Whether the subject has advanced fibrosis
- The subject's height and weight

- If the site is taking part in either the PK sub-study or the liver elastography sub-study, whether the subject will take part in these sub-studies

Advanced fibrotic subjects will be assigned to Group C. Non-advanced fibrotic/non-cirrhotic subjects will be randomized to Group A or Group B and stratified by genotype and ALT. Based on the height and weight provided, IXRS will confirm the dose for treated subjects.

In accordance with a request from the China Food and Drug Administration Clinical Trial Permit (CTP File No: 2013L00401), at sites in China only, this study will start with enrolling older pediatric patients first (aged 7 to <18 years old at baseline) in order to assess safety in this population before extending enrollment to younger patients. A Data Safety Monitoring Board (DSMB) will review the safety data from older pediatric patients enrolled in China together with all other available safety data from pediatric patients enrolled in rest of world, to support appropriate subsequent enrollment of the younger age group in China. The recruitment of younger patients at sites in China will only start if review of the data by the DSMB determines that there are no safety concerns.

The enrollment of subjects in the rest of world will remain unchanged; patients aged 3 to <18 years old at baseline will be enrolled. During study conduct, the Sponsor may postpone or stop the enrollment of subjects in certain age ranges in order to *ensure that a broad* age distribution *and representative dosing categories have been adequately studied*.

The subject randomization numbers will be generated by Roche or its designee and incorporated into a set of subject numbers and associated study group which will be given to the investigator over the telephone at the time of individual subject enrollment.

The investigator or designee will use the eCRF with the assigned subject number and enter the corresponding number for allocation to the study groups in the appropriate place on each subject's eCRF.

The subject randomization numbers are to be allocated sequentially in the order in which the subjects are enrolled according to the specification document agreed with the external randomization company/center. A subject Enrollment and Identification Code List must be maintained by the investigator.

5.3 CLINICAL ASSESSMENTS AND PROCEDURES

A baseline visit will be performed, and for subjects in Group A and Group C all baseline assessments and procedures must occur prior to administration of the first dose of PEG-IFN. *The first dose of PEG-IFN should be administered at the baseline visit.* Subjects will subsequently be seen for evaluation at the following timepoints:

Group A and Group C

- During treatment period: Weeks 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48

- During initial 24 weeks of follow-up: follow-up Weeks 4, 12, and 24 post-*end of* treatment
- During extended long-term follow-up: Years 1, 1.5, 2, 3, 4, and 5 post-*end of* treatment

Group B—Non-Switch

- During principal observation period: Weeks 12, 24, 36, and 48
- During initial 24 weeks of follow-up: follow-up Weeks 12 and 24 post-principal observation period
- During extended long-term follow-up: Years 1, 1.5, 2, 3, 4, and 5 post-principal observation period

Group B—Switch

- During principal observation period: Weeks 12, 24, 36, and 48*
- During initial 24 weeks of follow-up: follow-up Weeks 12* and 24* post-principal observation period
- During extended long-term follow-up: Year 1* post–principal observation period
- During switch treatment period: Weeks 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48
- During initial 24 weeks of switch follow-up: switch follow-up Weeks 4, 12, and 24 post– *end of treatment* period
- During extended long-term switch follow-up: Years 1, 1.5, 2, 3, 4, and 5 post- *end of treatment* period

*Subjects may switch at any time between Week 48 and 1 year following Week 48. 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.

The extended long-term follow-up visit at Year 1.5 will be by telephone.

For assessments and procedures required at each visit refer to Table 2 to Table 4.

For visits up to and including Week 48, the visit window is ±3 days.

For visits after Week 48 and up to and including follow-up Week 24, the visit window is ±7 days.

For visits after follow-up Week 24, the visit window is ±28 days.

Any subject who discontinues study treatment should return to complete assessments as per the Week 48/Switch Week 48 visit and enter the post-*end of* treatment follow-up period (see Section 4.6.1).

5.3.1 Efficacy

5.3.1.1 Main Efficacy Assessments

Efficacy (see Section 8.1 for primary and secondary endpoints) will be determined from assessment of HBeAg and HBsAg seroconversion, loss of HBeAg and HBsAg, HBV-DNA, and ALT (see Section 5.4 for laboratory assessment details).

5.3.1.2 Liver Elasticity

At least 50 consenting/assenting subjects at specific sites will take part in a liver elasticity sub-study. For these subjects, liver elastography will be performed at baseline, end of treatment/principal observation period**,** follow-up Week 24, and follow-up Year 2.

Change in the LSM over time will be assessed comparing treated and untreated subjects.

Baseline liver elasticity will also be explored for association with the screening liver biopsy result in these sub-study subjects.

5.3.2 Safety

Safety assessments will include symptom directed physical examination, vital signs, growth, neuro-psychiatric questionnaire (PEG-IFN–treated subjects only, post-baseline), review of concomitant medications, reported AEs and specified safety laboratory assessments of hematology, clinical chemistry, thyroid function, and urinalysis. Additional safety assessments will be determined from tabulations of dose adjustments and premature withdrawals from treatment for safety or tolerability reasons.

All subjects need to have an ophthalmological examination (*consisting of* fundoscopic examination *with dilation*, visual acuity assessment, visual field testing *(confrontation test is recommended for younger children)*, and color visual testing) by an ophthalmologist *(pediatric ophthalmologist is recommended)* within 6 months prior to baseline. *During the study,* subjects treated with PEG-IFN will receive *additional* ophthalmological examination as per the schedules in Table 2 and Table 4. Any subject who develops ocular symptoms should receive a prompt eye examination by an ophthalmologist and additional examinations as necessary.

For females of childbearing potential, a pregnancy test will be performed within 24 hours prior to baseline or switch baseline. This could be performed at the baseline visit, provided that the result is available prior to randomization and commencement of treatment. Pregnancy testing will also be performed at any time secondary amenorrhea of more than 1 week occurs. In addition, subjects treated with PEG-IFN will have pregnancy tests performed as per the schedules in Table 2 and Table 4.

Measurements of growth must be taken using the same instruments in the same individual. A stadiometer with mean of three readings should be used for height measurement. For Group A and C subjects, at Weeks 12, 24, and 36, and for switch subjects at switch baseline, switch week (SW)12, SW24, and SW36 the investigator or

designee will provide IXRS with the subject's height and weight so that the BSA and dose can be provided.

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.

During the extended long-term follow-up period, only the following safety data will be collected:

- Persisting AEs initially reported prior to follow-up Week 24 (including neurological and psychiatric events)
- New-onset SAEs (including neuro-psychiatric events) and non-serious AEs of special interest related to PEG-IFN
- Deaths
- Growth: weight and height
- Thyroid function

5.3.2.1 Neuro-psychiatric Questionnaire

As part of the overall assessment of subjects and their mental state, and collation of neurological and psychiatric AEs, the CDI [50] will be used in subjects ≥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 subject'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 subjects and then post-baseline for treated subjects as per the schedules in Table 2 to Table 4. CDI should be performed prior to the completion of other study assessments. *Note: If a subject 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 17-year-old subjects who turn 18 years old during the study, the CDI should continue to be administered.*

Parents or subjects may not be comfortable with certain sentences, or question the sensitive or personal nature of some sentences, and therefore it should be clearly explained that the CDI is just a tool that all subjects 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 subjects' own language, if available. All subjects should complete the form themselves. For younger children or those with reading difficulties or who are are unable to read, the instructions and items should be read aloud to the child, then the child will select an answer themself. If the CDI Item Form is not available in the subject's own language, a translator may read the instructions and items to the child and then the child will select an answer themself. *The mode of administration (self-administered or translator/caregiver administered) should be clearly*

documented in the clinical records. If subjects feel none of the sentences for an item applies to them, then they should be instructed to choose as best they can. Subjects should be debriefed after the CDI has been completed to address any questions or concerns.

Once the subject 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. *Note: 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 Subjects *with Symptoms of Major Depression or Potential* CDI *Indicators*

Whether the CDI is administered or not, investigators should still assess the mental state of their subjects per their standard clinical practice. If any subject exhibits symptoms of major depression *and/*or if CDI total score is >19 *and/or the subject 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 subject will be referred to a mental health professional (e.g., counsellor). If this is at screening or baseline, then the subject will be excluded from the study. *While in the study, the investigator will determine whether AE criteria have been met and report as an AE on the eCRF, if appropriate (see Section 7.1).* If whilst on study the subject is found to have severe depression, PEG-IFN *must* be permanently discontinued and the subject referred for psychiatric intervention (as per Section 6.2.1 and Section 6.2.5.5).

5.4 LABORATORY ASSESSMENTS

Laboratory assessments post-screening are noted in Table 6 and will be carried out as per the schedules in Table 2 to Table 4.

Table 6 Laboratory Assessments

Hematology[a]	Complete blood count (hemoglobin, hematocrit, total WBC count, differential WBC count [neutrophils, lymphocytes, monocytes, eosinophils, basophils]), platelet count], INR
Clinical chemistry[a]	ALT, AST, GGT, total bilirubin, alkaline phosphatase, total protein, albumin, BUN/urea, creatinine[d], uric acid, total calcium, phosphorus, cholesterol, triglycerides, random glucose, sodium, chloride, potassium
Urinalysis[b]	Dipstick with subsequent microscopic evaluation if positive for blood.
HCG pregnancy test[b]	Urine or serum pregnancy test for females of childbearing potential at any time secondary amenorrhea of more than 1 week occurs. *The result of the baseline pregnancy test must be available prior to randomization and commencement of treatment.*
Thyroid function tests[c]	FT3, FT4, TSH, TPO antibodies [e]
Immunology[c]	ANA [e]
HBV serology and virology[c]	HBeAg, anti-HBe, HBsAg, anti-HBs, quantitative HBsAg and HBeAg, HBV-DNA

[a] 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.

[b] To be performed by local laboratory.

[c] To be performed by central laboratory.

[d] Estimated creatinine clearance will be calculated by the Sponsor at Week 24/SW 24.

[e] PEG-IFN–treated subjects only.

Samples for central analysis will be sent to one or more central laboratories or to the Sponsor for analysis.

Where any analysis is performed by a local laboratory, normal ranges for the local laboratory parameters must be supplied to Roche or designee before the study starts and at any point that the normal ranges are changed.

The results from all hematology and clinical chemistry investigations should be available and reviewed by the investigator or his/her authorized designee before instructing the subject on whether PEG-IFN dosing should continue unchanged or be modified.

See Section 6.2.5 and 7.1.3.1 for follow-up of laboratory abnormalities.

All virological and serological efficacy parameters will be assessed by the central laboratory.

The total volume of blood loss for laboratory assessments (excluding PK and RCR) will be approximately as follows:

- Group A and Group C: 228 mL
- Group B non-switch: 158 mL
- Group B switch: up to 312 mL

The procedures for the collection, handling, and shipping of laboratory samples are specified in the Sample Handling and Logistics Manual for this study. All remaining blood samples will be destroyed no later than 18 months after the final closure of the study database.

The samples for this study should be classified, packed, and shipped as UN3373 Biological Substance, Category B.

5.4.1 Serum Bank and Exploratory HBV Markers

Additional serum bank samples (included in the blood volumes in Section 5.4) will be collected during the course of this study (as per the schedules in Table 2 to Table 4). The primary purpose of these samples is to repeat laboratory tests outlined in the Schedule of Assessments should there be a problem with the original sample. In the event that repeat testing is required, sites will be informed whether the sample should be transferred to the central laboratory for retesting (e.g., HBV serology) or whether it is a test that should be repeated locally (e.g., ALT).

The secondary intention is to use residual serum bank samples for exploratory HBV biomarker analyses. This secondary use of serum bank samples is optional and only applies to subjects who have consented to RCR sample collection and analyses (see Section 5.4.3). After confirmation that serum bank samples are no longer required for repeat testing, any remaining serum bank samples, either at investigational sites or at the central laboratory, may be used for DNA and/or non–DNA biomarker analyses. Samples still at the site may remain stored at the site or can be transferred to the central laboratory for storage until required for biomarker analyses. Example biomarker analyses include viral factors and sequencing and host response factors to infection and treatment. Protection of subject confidentiality will extend to any data generated from the assaying of these samples (see Section 17).

All remaining serum bank samples, either at the site or central laboratory, will be destroyed no later than 18 months after the final closure of the study database.

5.4.2 Pharmacokinetic Assessments

For sites taking part in the PK sub-study, consenting/assenting subjects assigned, randomized or switching to PEG-IFN will have blood samples (approximately 1 mL) collected to evaluate the PK of PEG-IFN during Weeks 1 and 24 pre-dose (0), and 24–48, 72–96, and 168 hours after administration of PEG-IFN. (See also footnote to

Table 7.) Blood samples designated as pre-dose must be collected within 6 hours prior to PEG-IFN administration.

For scheduling purposes, time windows are provided for the first two post-dose samples during Weeks 1 and 24. 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.

Pre-dose samples will also be collected at Weeks 4, 8, and 12 within 6 hours prior to PEG-IFN administration (Table 7). Subjects should take all doses of PEG-IFN associated with both pre- and post-dose PK sampling at the clinic.

The procedure for the collection and handling of blood samples for PK analysis is specified in the Sample Handling and Logistics Manual. The exact date and time of dosing and collection of blood samples will be recorded in the source document and eCRF. The serum concentrations of PEG-IFN will be assessed by a quantitative enzyme-linked immunosorbent assay (ELISA). PK parameters, such as the maximum concentration (C_{max}), area under the curve (AUC), clearance (CL/F) and volume of distribution (V/F), if possible, will be estimated using either non-compartmental analysis or a population approach.

The target exposure is based on the mean exposure observed in adults treated at 180 μg in clinical studies (3334 to 4348 ng • h/mL) and the mean exposure observed in children in Study NR16141 treated at a dose of 180 μg/1.73 $m^2 \times$ BSA (5667 ng • h/mL). 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, PK analysis will be undertaken to ensure exposure is in the appropriate therapeutic range. If data suggest that the exposure is not in the appropriate range, an adjustment to the dosing regimen will be made to meet the target exposure range.

Once PK data up to Week 24/switch Week 24 are available for at least 5 to 10 subjects in each BSA category, PK sampling will be stopped. However, the sub-study may be ceased even if data from a minimum of 5 subjects in each BSA category are not obtained in the case of excessively long recruitment times.

The relationship between PK and PD parameters may also be explored.

Any PK sample residues may be used for analysis of exploratory HBV markers (see Section 5.4.1).

The total volume blood loss for PK assessments will be approximately 14 mL.

Table 7 PK Sampling Schedule

	Baseline/ Switch Baseline	Week 4/ Switch Week 4	Week 8/ Switch Week 8	Week 12/ Switch Week 12	Week 24/ Switch Week 24
0 hour (pre-dose)	x				x
Pre-dose		x	x	x	
24–48 hours post-dose	x				x
72–96 hours post-dose [a]	x				x
168 hours post-dose	x [b]				x

[a] At least 48 hours after the previous blood sample.

[b] Equates to Week 1 visit.

5.4.3 Roche Clinical Repository Specimen(s)

For sites opting to take part, specimens for the RCR will be collected from subjects who give specific consent/assent to participate in this optional research. The results of specimen analysis from the RCR will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for subjects.

RCR samples will be collected as per the schedule in Table 2 to Table 4. For all RCR 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 Sample Handling and Logistics 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/IEC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Specimens for dynamic (non-inherited) biomarker discovery and validation will be used for research purposes to help to better understand the 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). Specimens for dynamic biomarker discovery will be subject to the confidentiality standards described in Section 17. The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Whole blood for isolation of plasma
- Whole blood for RNA expression analysis

Specimens for genetic (inherited) biomarker discovery and validation will be used for research purposes to hopefully help improve subject outcome by predicting which subjects are more likely to respond to specific drug therapies, predicting which subjects are susceptible to developing adverse side effects and/or predicting which subjects are

likely to progress to more severe disease states. Such genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described in Section 17. The following samples will be collected for identification of genetic (inherited) biomarkers:

- One time whole blood sample for DNA isolation

Total blood volume collected for RCR sampling will be approximately as follows:

- Group A and Group C: 36 mL
- Group B non-switch: 36 mL
- Group B switch: up to 54 mL

5.5 SUBJECT MEDICATION DIARY REVIEW

Subjects treated with PEG-IFN will complete a Subject Medication Diary (SMD), which the family will bring to each study visit. The information will be reviewed with the family by the Clinic Coordinator at each study visit. It is mandatory that each PEG-IFN injection dose be recorded in the SMD. The parent/guardian will be instructed to record the date and dose of PEG-IFN. The person giving the PEG-IFN injection must initial the SMD. During the diary review, the reviewer will correct unreadable information and ask the subject to supply missing information. Reviewers will report missing doses, dose adjustments, and treatments stops or restarts on the eCRF. Subject diaries will be maintained with the source documents at each site. See also Section 6.5.2.

6. INVESTIGATIONAL MEDICINAL PRODUCT

PEG-IFN is a chemically modified alpha interferon formed by the covalent attachment of a 40-kD single branched methoxy polyethylene glycol (PEG) moiety to recombinant IFN alfa-2a. Clinical PK studies have shown that PEG-IFN alfa-2a exhibits sustained absorption and low systemic clearance, enabling the maintenance of therapeutic serum concentrations in adults for at least 1 week after a subcutaneous injection of 180 μg of PEG-IFN.

6.1 DOSE AND SCHEDULE OF INVESTIGATIONAL MEDICINAL PRODUCT AND COMPARATOR

Treated subjects will receive PEG-IFN subcutaneously once weekly for 48 weeks with dosing based on the following BSA categories:

Table 8 Dosing 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

6.2 DOSE MODIFICATIONS, INTERRUPTIONS, AND DELAYS

The intention of the protocol is that subjects remain on PEG-IFN until the completion of the allocated treatment period. However, it is possible that some subjects will encounter transient or prolonged adverse effects at some juncture during their participation in the trial leading to adjustment of the PEG-IFN dosage. To minimize the effects of these modifications on the eventual evaluation of the safety, tolerability, and efficacy of test drug regimens, the principles in the following sections will be used to adjust the dose of PEG-IFN.

If consistent with subject safety, doses should not be held or eliminated. This recommendation stems from concerns that extended periods of lowered drug concentrations in the blood may lead to a failure of virological and immunological control reducing the chance of HBeAg seroconversion and sustained response at the conclusion of therapy. When the investigator considers it prudent to hold a dose, consideration needs to be given to informing the Sponsor of the missed scheduled dose and the reasons the dose was withheld. Investigators should consider if adjusting the dose, either transiently or permanently, might be appropriate rather than holding a dose.

6.2.1 Stopping Rules

Individual subject treatment with PEG-IFN *must* be stopped in the event of any of the following:

- Severe hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchoconstriction)
- Severe depression (see also Section 6.2.5.5)
- Absolute neutrophil count $< 0.25 \times 10^9$ cells/L or febrile neutropenia (see also Section 6.2.5.1)
- Platelets $< 25 \times 10^9$ cells/L (see also Section 6.2.5.2)

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) (see also Section 6.2.5.3)*
- *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 (see also Section 7.2.4)*

In the event of discontinuation from treatment, subjects will be encouraged to remain in the 5-year follow-up period (see Section 4.6.1).

6.2.2 Missing Consecutive Doses

If four or more consecutive doses of PEG-IFN are held or otherwise not administered (i.e., the subject has not received study drug for more than 28 days), the subject will be considered intolerant of the study drug or noncompliant, whichever is more appropriate to the clinical situation. No additional study drug may be administered to such subjects without explicit permission from the Sponsor.

6.2.3 Dose Delay

If a PEG-IFN 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., the next dose may be administered as usual on Monday).
- Dose delayed 3–5 days: administer subsequent doses every 5th or 6th day until the subject 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 subject 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 subject every 5th or 6th day until the subject resumes weekly dosing on his or her usual scheduled day.

6.2.4 Dose Reduction Levels

Moderate or severe adverse reactions (clinical and/or laboratory) may require dose reduction of PEG-IFN. Decremental adjustments should be uniform across centers and subjects. Toward this end, the following downward adjustments should be utilized:

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*

Specific dose adjustment guidance for PEG-IFN is provided in Section 6.2.5 for post-treatment neutropenia, thrombocytopenia, elevated serum ALT, BSA change, and depression.

When practical, abnormal laboratory results should be confirmed as soon as possible following notification of the investigator. If appropriate, downward adjustments in one-level decrements should be considered. It should be kept in mind that, whereas these guidelines should be generally followed to promote consistency across centers, other responses by an investigator may be more appropriate in some circumstances. See Section 7.1.1.1 for definitions of intensity of AEs. For laboratory and vital signs abnormalities, “severe” may be considered as any value requiring intervention, further work-up, or more frequent follow-up.

Once the subject'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.
- Subjects 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.

6.2.5 Specific Dose Reduction Guidance

6.2.5.1 Dose Adjustments for Low Absolute Neutrophil Counts

Absolute neutrophil count ($\times 10^9$ 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

6.2.5.2 Dose Adjustments for Low Platelet Counts

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

6.2.5.3 Dose Adjustments for Elevated Serum ALT

ALT	Response
$<5\times$ the ULN	No change.
$5–10\times$ the ULN	Repeat in 1 week. i. If decreased to $<5\times$ the ULN, continue dose but monitor to ensure stability. ii. If persistently $5–10\times$ the ULN on two occasions over 2 weeks, continue dose with one-level adjustment, and monitor ALT until stable or decreasing, then return to full dose iii. If further increased to $>10\times$ the ULN, follow advice under point (ii) below
$>10\times$ the ULN	Repeat in 1 week. i. If decreased to $5–10\times$ the ULN, continue dose with 1 level adjustment, and monitor ALT until stable or decreasing, then return to full dose. ii. If persistently $>10\times$ the ULN, hold dose, and carefully monitor ALT and assess for signs of decompensation. [a] • If there is significant evidence of ALT recovery [b] and there are no signs of decompensation, restart dose with one-level reduction. • PERMANENTLY DISCONTINUE if there are signs of decompensation.

[a] Decompensation is a clinical diagnosis and may be defined as a using a mixture of clinical signs and signs leading to a Child-Pugh score of more than 6 (see Appendix 2), or the presence of oesophageal varices.

[b] Significant decrease in ALT levels may be defined as a progressive decrease in ALT on two serial determinations, with a decline of at least 50% from peak.

6.2.5.4 Dosage Adjustments for BSA Decrease/Increase

Investigators will adjust the dose of PEG-IFN upward or downward to reflect the most current BSA. BSA and dose will be provided by IXRS at Weeks 12, 24, and 36. *Investigators may also assess the patient's BSA (using the Mosteller formula) at other interim timepoints 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 a subject's BSA falls below $<0.51\ m^2$ during treatment, any dose adjustments should be made only after consultation between the investigator and *the Medical Monitor (Appendix 3) or delegate*. The recommended dose will be recorded in the SMD.

6.2.5.5 Dosage Adjustments for Depression

In severe cases of depression, PEG-IFN should be permanently discontinued and the subject referred for psychiatric intervention.

6.3 FORMULATION, PACKAGING AND LABELING

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

Packaging: TBD

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

Study drug packaging will be overseen by the Roche Clinical Trial Supplies Department and bear a label with the identification required by local law, the protocol number, drug identification, and vial contents. The investigator will inform the subject of the dose they are required to take based on their BSA, and this will be recorded in the SMD.

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations.

The study drug must be stored according to the details on the product label. The drug label indicates the storage temperature.

Local packaging in some countries may be different.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

6.4 BLINDING AND UNBLINDING

The study is open label.

6.5 ACCOUNTABILITY OF INVESTIGATIONAL MEDICINAL PRODUCT AND ASSESSMENT OF COMPLIANCE

6.5.1 Accountability of Investigational Medicinal Product

The investigator is responsible for the control of drugs under investigation. Adequate records for the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. Accountability will be assessed by maintaining adequate drug dispensing and return records.

Accurate records must be kept for each study drug provided by the Sponsor. These records must contain the following:

- Documentation of drug shipments received from the Sponsor (date received and quantity).
- Disposition of unused study drug not dispensed to subject.

Study drug will be dispensed according to the schedules in Table 2 and Table 4. A Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the subject to whom the study drug was dispensed
- The date(s) and quantity of the study drug dispensed to the subject
- The date(s) and quantity of the study drug returned by the subject

All records and drug supplies must be available for inspection by the Monitor at every monitoring visit.

Subjects will be asked to return all used drug supply containers at each visit and all unused drug supply containers at the end of treatment as a measure of compliance.

When the study is terminated, the investigator will return any used and unused study drug (i.e., empty, partially used, and unused containers) to the Monitor. The completed Drug Dispensing Log and Drug Return Record(s) will be returned to Roche, unless alternate destruction has been authorized by Roche, or required by local or institutional regulations (Section 6.6). The investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Roche.

6.5.2 Assessment of Compliance

At each visit, compliance with the study requirements will be reinforced.

Subject compliance with taking study drug as required will be assessed by maintaining adequate study drug dispensing records and review of the SMD. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

It is mandatory that each injection (date and volume) be recorded in the drug diary and initialed by the person giving the injection (see Section 5.5). Subjects will be asked to return used drug containers at each visit, along with the drug diary. Returned drug containers will be counted and justified against the diary entries by study site personnel. Each verified injection will be recorded on the eCRF at each visit. Unused study drug should be returned at the end of the treatment period (i.e., Week 48). Under no circumstances should the treatment period for any subject extend beyond the allocated 48 weeks.

6.6 DESTRUCTION OF THE INVESTIGATIONAL MEDICINAL PRODUCT/COMPARATOR

Local or institutional regulations may require immediate destruction of used investigational medicinal product (IMP) for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction.

If there are any issues with the drug, it should be returned to the appropriate Roche clinical trial supplies department for long-term storage and not destroyed.

Written documentation of destruction must contain the following:

- Identity of IMP(s) (and comparators [if applicable]) destroyed
- Quantity of IMP(s) destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed investigational products(s)

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

7.1.1 Clinical Adverse Events

According to the ICH, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Preexisting conditions that worsen during a study are to be reported as AEs.

7.1.1.1 Intensity

All clinical AEs encountered during the clinical study will be reported on the AE eCRF. **Intensity** of AEs will be graded (mild, moderate, severe) and reported in detail on the eCRF.

Mild	discomfort noticed but no disruption of normal daily activity
Moderate	discomfort sufficient to reduce or affect daily activity
Severe	inability to work or perform normal daily activity

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events should be used to assist in the assessment of intensity.

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

Note that events that are considered as life threatening should be reported as an SAE (see Section 7.1.1.3) and the intensity would be reported as “severe” on the eCRF.

7.1.1.2 Drug–Adverse Event Relationship

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event 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 subject 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

7.1.1.3 Serious Adverse Events (Immediately Reportable to Roche)

An SAE is any experience that suggests a significant hazard, contraindication, side effect, or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

- Is fatal (results in death**; note: death is an outcome, not an event)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

****The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.**

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

7.1.1.4 Other Safety Findings Requiring Expedited Reporting

Other safety findings may require expedited reporting depending on local legislation, e.g., a major safety finding from a newly completed animal study (such as carcinogenicity).

7.1.2 Treatment and Follow-up of Adverse Events

Subjects experiencing AEs should be treated by accepted clinical procedures. If the use of medications excluded by protocol is deemed necessary, the subject may need to be discontinued from the test regimen after consultation with Roche. All AEs should be followed until resolved or stabilized.

7.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results electronic form page ([eForm]) of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such on the AE eForm (see Section 7.2.2).

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE eForm in the eCRF:

- Is considered an SAE
- Results in discontinuation from study treatment
- Results in a requirement for a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

This applies to any protocol and non–protocol-specified safety and efficacy laboratory result from tests performed after the first dose of study drug, which falls outside the laboratory reference range and meets the clinical significance criteria.

This does not apply to any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria [these will be analyzed and reported as laboratory abnormalities]; those which are considered AEs of the type explicitly exempted by the protocol; or those which are a result of an AE that has already been reported.

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 35% is direct bilirubin) or
- 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 and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE (Section 7.2.2) or a non-serious AE of special interest (Section 7.2.3).

7.1.3.1 Follow-up of Abnormal Laboratory Test Values

Clinically significant laboratory abnormalities should prompt a repeat measure no less frequently than every 2 weeks or as clinically indicated, with appropriate clinical

management, until they return to normal or baseline levels, and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF. See also Section 6.2.5 for specific guidance.

7.2 HANDLING OF SAFETY PARAMETERS

7.2.1 Reporting of Adverse Events

All AEs (related and unrelated) occurring during the treatment/principal observation period and initial 24 weeks of follow-up must be reported. During the extended long-term follow-up period, only persisting AEs, new-onset SAEs *and* non-serious AEs of special interest related to PEG-IFN, and deaths will be reported.

7.2.2 Reporting of Serious Adverse Events (immediately reportable)

Any clinical AE or abnormal laboratory test value that is serious (as defined in Section 7.1.1.3) and that occurs during the study, regardless of the treatment arm, occurring from the enrollment visit (start of study screening procedures), including extended long-term follow-up must be reported to Roche **within 1 working day** of the investigator becoming aware of the event (expedited reporting).

For initial reports of serious adverse events, investigators should record all case details that can be gathered within 1 working day on the Adverse Event eCRF and submit the report via the Electronic Data Capture (EDC) system. A report will be generated and sent to Roche Safety by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event CRF and Fax Cover Page should be completed and faxed immediately to Roche Safety. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

After informed consent/assent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). **After first study drug, all SAEs must be reported.**

Unrelated SAEs must be collected and reported during the study treatment/principal observation period and initial 24 weeks of follow-up.

Related SAEs **must** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. *Every effort should be made to follow all SAEs considered to be related to the study drug or study-related procedures until a final outcome can be reported.*

Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to investigators at each site and associated IRB/IEC when the following conditions occur:

- The event must be an SAE.

- There must be a certain degree of probability that the event is an adverse reaction from the administered drug.
- The adverse reaction must be unexpected, that is to say, not foreseen in the SPC text (Summary of Product Characteristics [for an authorized medicinal product]) or the Investigator's Brochure (for an unauthorized medicinal product).

When all subjects at a particular site are off treatment as defined by the protocol:

- Only individual SUSAR reports originating in that particular trial will be forwarded to the site and associated IRB/IEC on an expedited basis;
- Individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the Informed Consent Form/assent, will be reported in an expedited manner to all investigators and IRBs/IECs;
- SUSAR reports originating from other trials using the same IMP will be provided as six monthly SUSAR Reports to investigators and IRBs/IECs where long-term follow-up studies are carried out, unless they are considered significant.

This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2. Complete information can be found in Appendix 3.

7.2.3 Reporting of Non-serious Events of Special Interest

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; as per SAE reporting procedure in Section 7.2.2). 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 (Section 7.1.3)
- Suspected transmission of an infectious agent by the study drug

7.2.4 Pregnancy

A female subject must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the Sponsor, using the Pregnancy Report eCRF. The investigator should counsel the subject, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator. Subjects that become pregnant during the treatment period will be withdrawn from the treatment period and continue into the follow-up period.

Pregnancy occurring in the partner of a male subject participating in the study should be reported to the investigator and the Sponsor. The partner should be counseled, the risks

of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

NOTE: The investigator should fill out a Pregnancy Report eCRF only if the pregnant partner has signed a Pregnant Partner Data Release Form.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety or its designee within 1 working day after learning of the pregnancy.

7.3 WARNINGS AND PRECAUTIONS

Alpha interferons, including PEG-IFN, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Subjects should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn from subjects with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping PEG-IFN therapy.

To date, no teratology or reproduction studies have been conducted in humans with PEG-IFN. Primate teratology studies indicate an increased incidence of spontaneously aborted fetuses in pregnant rhesus monkeys (*Macaca mulatta*) receiving high doses of intramuscular Roferon®-A [51]. Studies with Roferon®-A in non-pregnant rhesus monkeys have shown menstrual cycle irregularities, including prolonged menstrual periods. Male fertility and teratological evaluations have yielded no significant adverse effects to date. However, sexually active males will be excluded or discontinued from this study if not utilizing reliable contraception during the treatment/principal observation period and during the initial 24-week follow-up period.

Interferons are human proteins that show a substantial degree of species specificity, making extrapolation of animal study data to humans of questionable value. Investigations have been conducted in normally cycling healthy females using non-recombinant human leukocyte interferon. Results demonstrate a significant reduction of serum estradiol and progesterone concentrations during the treatment interval [52].

There are no adequate, controlled studies of any IFN in pregnant females. Therefore, extreme care must be taken to avoid pregnancy during the study in female subjects, and female partners of male subjects taking PEG-IFN. Sexually active females will be excluded/discontinued from this study if not utilizing effective contraception at enrollment and will be discontinued from study treatment if not using effective contraception during the initial 24-week follow-up period. Females who are pregnant or breast-feeding will also be excluded. A pregnancy test will be performed for each female of childbearing potential prior to baseline and switch baseline, and at any time secondary amenorrhea of more than 1 week occurs. In addition, subjects treated with PEG-IFN will have a pregnancy test performed according to the schedules in Table 2 and Table 4. If

pregnancy occurs in a subject or partner of a subject during the PEG-IFN treatment period or up to 3 months after PEG-IFN treatment, the cases should be handled as described in Section 7.2.4.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 PRIMARY AND SECONDARY STUDY ENDPOINTS

8.1.1 Primary Endpoints

- HBeAg seroconversion (loss of HBeAg and presence of anti-HBe) at the 24-week post-*end of* treatment/principal observation period follow-up visit

8.1.2 Secondary Endpoints

- 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, 24 weeks after end of treatment/principal observation period, and 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 1, 2, 3, 4, and 5 years after end of treatment/principal observation period.
- Descriptive change from baseline in liver elasticity (for subjects enrolled in the liver elasticity sub-study) at the end of treatment/principal observation period, and 24 weeks and 2 years after end of treatment/principal observation period.

8.1.3 Safety

Safety of the treatment will be evaluated by AEs (including SAEs and non-serious AEs of special interest), laboratory tests, vital signs (blood pressure, heart rate, temperature), and growth (weight and height).

8.1.4 Pharmacokinetic

PK parameters (e.g., CL/F, V/F, AUC, C_{max}, etc.) of PEG-IFN will be evaluated in subjects following administration of a new BSA-based dosing regimen over the first 24 weeks of treatment.

8.2 STATISTICAL AND ANALYTICAL METHODS

8.2.1 Statistical Model

8.2.1.1 Primary Variables

The primary efficacy parameter is HBeAg seroconversion (defined as absence of HBeAg and presence of HBeAb) determined 24 weeks after the end of treatment/principal

observation period. Subjects with missing values for this parameter will be considered non-responders.

8.2.1.2 Secondary Variables

All secondary variables will be determined at 24 weeks after the end of treatment/principal observation period and at 1, 2, 3, 4, and 5 years after the end of treatment/principal observation period.

- Loss of HBeAg (defined as absence of HBeAg)
- HBsAg seroconversion (defined as loss of HBsAg and presence of anti-HBs)
- Loss of HBsAg (defined as absence of HBsAg)
- Quantitative serum ALT
- Proportion of normal serum ALT (defined as ALT measure $\leq$ ULN)
- 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 endpoints: HBeAg seroconversion and HBV-DNA $<$ 100,000 copies/mL ($<$ 20,000 IU/mL)
- Combined endpoints: HBeAg seroconversion and HBV-DNA $<$ 10,000 copies/mL ($<$ 2,000 IU/mL)
- HBeAg seroconversion (defined as absence of HBeAg and presence of HBeAb)

8.2.2 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.

8.2.3 Hypothesis Testing

Testing of the primary endpoint consists of a superiority test for the ITT population of HBeAg seroconversion determined 24 weeks after the end of treatment in Group A compared with HBeAg seroconversion determined 24 weeks after the principal observation period in Group B. The primary analysis will be done using a Cochran-Mantel-Haenszel test using stratification factors of genotype (A vs. non-A) and ALT ($<$ 5 $\times$ the ULN and $\geq$ 5 $\times$ the ULN).

8.2.4 Analysis Populations

8.2.4.1 ITT Population

For Group A, the ITT population shall include all subjects who receive at least one dose of study medication. 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.

8.2.4.2 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. Efficacy and safety data will be reported from all subjects entering the switch arm if at least one dose of study medication was taken.

8.2.4.3 Group C

Subjects who have advanced fibrosis (diagnosed on liver biopsy, see Appendix 1) which is not decompensated will receive PEG-IFN in an advanced fibrotic arm (Group C). Efficacy and safety data will be reported from all subjects in Group C if at least one dose of study medication was taken.

8.2.5 Efficacy Analysis

The primary efficacy analysis will compare efficacy in Group A with Group B. 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 (with strata of A and non-A) and ALT ($< 5 \times$ the ULN and $\geq 5 \times$ the 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. Descriptive statistics of secondary endpoints loss of HBeAg, HBsAg seroconversion, loss of HBsAg, proportion of normal serum ALT, suppression of HBV-DNA, and combined endpoints will be summarized by Groups A, B, and C separately. Exploratory p-values will be presented using Fisher's exact test.

Quantitative serum ALT and quantitative HBV-DNA will be summarized by timepoints numerically and graphically over time. No formal statistical tests are planned. Graphs of secondary endpoints and corresponding 95% confidence intervals over time by group will be displayed.

For subjects in the liver elasticity sub-study, LSM will be measured at baseline, end of treatment/principal observation period, and at 24 weeks and 2 years after the end of treatment to assess change in liver elasticity over time. These results in subjects receiving treatment (Group A) will be compared with parallel measurements in the untreated control arm (Group B). For the comparison with liver biopsy at baseline, associations with liver stiffness will be explored using liver biopsy fibrosis score. Continuous outcomes will be studied using Pearson correlation, and potential

categorizations will be investigated as well. Confidence intervals will be provided as needed. No formal statistical tests will be carried out.

8.2.5.1 Exclusion of Data from Analysis

8.2.5.1.1 Intent-to-Treat Population

All subjects randomized will be included in the ITT population, as defined in Section 8.2.4.1.

Subjects will be assigned to groups as randomized for analysis purposes.

Subjects will be excluded if they do not meet ITT criteria, as defined in Section 8.2.4.1.

8.2.5.2 Interim Analysis

No efficacy interim analyses are planned.

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, PK analysis will be undertaken to ensure exposure is in the appropriate therapeutic range. If data suggest that the exposure is not in the appropriate range, an adjustment to the dosing regimen will be made to meet the target exposure range (see Section 5.4.2).

See Section 10 on review of safety data by a Data Safety Monitoring Board (DSMB).

8.2.5.3 Safety Data Analysis

The primary safety analysis will compare safety in Group A with Group B *at 24 weeks post-end of treatment/end of untreated observation*. The safety data of Group A and Group B will be qualitatively evaluated alongside subjects in Group C and the switch arm.

- *Incidence, nature, and severity of serious and non-serious AEs (including neurological and psychiatric events)*
- *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 and weight)*

The following safety outcome measures will be assessed using descriptive statistics at 1, 2, 3, 4, and 5 years post-end of 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 and weight)*

AEs: 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 (including thyroid function) 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.

8.2.6 Other Analyses

8.2.6.1 Pharmacokinetic Analysis

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, coefficients of variation, medians, and ranges.

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

The relationship between PK and PD parameters may be explored.

9. DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operational procedures.

Data for this study will be recorded via an EDC system using eCRF. It will be transcribed by the site from the paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial except where stated in this protocol. Sites will receive training and a manual for appropriate eCRF completion. (See also Section 15.4.) Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug dispensing log by the investigator.

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Roche database will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the eCRF at the site for resolution by the investigator.

Throughout the study the Study Management Team will review data according to the integrated Data Review Plan.

9.1 ASSIGNMENT OF PREFERRED TERMS AND ORIGINAL TERMINOLOGY

For classification purposes, the lowest level terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the MedDRA terminology for AEs and diseases and Genentech's Drug Dictionary for treatments.

10. STUDY COMMITTEES

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.

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 LOCAL REGULATIONS/DECLARATION OF HELSINKI

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the subject. For studies conducted in the EU/European Economic Area (EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC). For studies conducted in the United States of America or under a U.S. Investigational New Drug (IND), the investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects," and part 56, "Institutional Review Boards".

In other countries where a "Guideline for Good Clinical Practice" exists, Roche and the investigators will strictly ensure adherence to the stated provisions.

12.2 INFORMED CONSENT/ASSENT

12.2.1 Main Study Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain signed informed consent from each parent/legal guardian of subjects prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

If children are old enough to understand the risks and benefits of the study, they should also be informed and should also provide their written assent. *Patients within the specified age range who are legally 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, if required by national legislation.* With regard to the donation of a specimen(s) by the minor that will be stored in the RCR this same principle will apply. If the minor is not old enough to form an opinion or assess this information, the legal representative/guardian will replace the minor in recognizing his/her rights and responsibilities until he/she reaches legal age.

The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The eCRFs for this study contain a section for documenting informed consent/assent, and this must be completed appropriately. If new safety information results in significant

changes in the risk/benefit assessment, the informed consent/assent should be reviewed and updated if necessary. All subjects (including those already being treated) and their parent/legal guardian should be informed of the new information, given a copy of the revised informed consent/assent and give their consent/assent to continue in the study.

12.2.2 RCR Informed Consent

The Informed Consent/Assent Form will contain a separate section that addresses participation in the RCR. It also covers use of serum bank samples for exploratory HBV biomarker analyses. The investigator or authorized designee will explain to each subject the objectives, methods, and potential hazards of participation in the RCR. Subjects 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 subject's agreement to provide optional RCR specimens. Subjects who decline to participate will check a “no” box in the appropriate section and will not provide a separate signature.

The investigator should document whether or not the subject has given consent/assent to participate by completing the RCR Research Sample Informed Consent 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.

12.3 INDEPENDENT ETHICS COMMITTEE (IEC)/INSTITUTIONAL REVIEW BOARD (IRB)

The protocol, informed consent/assent, and any accompanying material provided to the subject in the United States will be submitted by the investigator to an IRB for review. For EEA member states, the Sponsor will submit to the Competent Authority (CA) and IEC, the protocol and any accompanying material provided to the subject. In both the United States and EEA member states, the accompanying material may include subject information sheets, descriptions of the study used to obtain informed consent/assent, and terms of any compensation given to the subject as well as advertisements for the trial.

An approval letter or certificate (specifying the protocol number and title) from the IEC/IRB must be obtained before study initiation by the investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, informed consent/assent, or material provided to the subject after receipt of the IEC/IRB approval must also be submitted by the investigator in the United States and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review 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 IRB/EC and, if applicable, an appropriate regulatory body. If a site is not granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study. In the United States, Roche submits an IND Annual Report to the Food and Drug Administration according to local regulatory requirements and timelines.

12.4 ROLE OF THE SCIENCE AND ETHICS ADVISORY GROUP

In addition to an internal review body, an independent Science and Ethics Advisory Group, consisting of experts in the fields of biology, ethics, sociology, and law, will advise Roche regarding the use of RCR specimens and on the scientific and ethical aspects of handling genetic information.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the Sponsor and the investigator (investigator representative[s] in the case of a multicenter trial). Protocol modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the Associate PD Group Medical Director/Clinical Pharmacologist and Biostatistician.

All protocol modifications must be submitted to the appropriate IEC or IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor[s], change of telephone number[s]).

14. CONDITIONS FOR TERMINATING THE STUDY

Both the Sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the investigator will assure that adequate consideration is given to the protection of the subjects' interests. The appropriate IRB/IEC and regulatory agencies should be informed accordingly.

15. STUDY DOCUMENTATION, CASE REPORT FORMS AND RECORD KEEPING

15.1 INVESTIGATOR'S FILES / RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories 1) Investigator's Study File, and 2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, schedule of assessments, IEC/IRB and governmental approval with correspondence, sample informed consent/assent, drug records, staff curriculum vitae, and authorization forms and other appropriate documents/correspondence, etc.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, electrocardiogram (ECG), electroencephalogram (EEG), X-ray, pathology and special assessment reports, signed informed consent/assent forms, consultant letters, and subject screening and enrollment logs. The investigator must keep the documents as described above on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

ICH Good Clinical Practice (GCP) guidelines require that Investigators maintain information in the study subject’s records which corroborate data collected on the eCRF(s). Completed eCRFs will be forwarded to Roche.

15.2 SOURCE DOCUMENTS AND BACKGROUND DATA

The investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 AUDITS AND INSPECTIONS

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development Quality Assurance Unit or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

15.4 ELECTRONIC CASE REPORT FORMS

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

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive subject data for his or her site in a readable format on a compact disc that must be kept with the study records.

15.5 FINANCIAL DISCLOSURE

The investigator(s) will provide the Sponsor with sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (LSLV).

16. MONITORING THE STUDY

It is understood that the responsible Roche monitor [or designee] will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the subject received the study drug assigned by the randomization center (by controlling the written confirmation of the randomization by IXRS). The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The investigator [or deputy] agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

RCR specimens will be tracked in a manner consistent with GCP 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 subject participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/IEC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to Roche, e.g., subjects' written consent/assent forms, in strict confidence.

Roche already maintains rigorous confidentiality standards for clinical studies by "coding" (i.e., assigning a unique subject ID number at the investigator site) all subjects enrolled in Roche clinical studies. This means that subject names are not included in data sets that are transmitted to any Roche location.

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure subject confidentiality for RCR specimens (see Section 5.4.3). These processes also apply to any central laboratory carrying out biomarker analysis on serum bank samples (see Section 5.4.1). Upon receipt by the RCR, all specimens are "single-coded" then each genetic specimen is "double-coded" by replacing the subject 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 subject 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 or any other biomarker specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Subject medical information associated with RCR or any other biomarker 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 subject, unless permitted or required by law.

18. CLINICAL STUDY REPORT

A clinical study report (CSR) will be written and distributed to health authorities as required by applicable regulatory requirements.

Note: EU Regulation (EC) No.1901/2006, states: For pediatric studies the CSR must be distributed to the applicable health authorities within 6 months of completion of the study.

19. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Roche will comply with the requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche 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, Roche 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 Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Data derived from RCR or any other biomarker specimen analysis on individual subjects will not be provided to study investigators, except where explicitly stipulated in a study protocol (e.g., if the result is an enrollment criterion). Exceptions may be granted (e.g., if biomarker data would be linked to safety issues). The aggregate results of any research conducted using RCR or any other biomarker 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 or any other biomarker will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Appendix 1
Liver Biopsy Scores

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

Scores considered as advanced fibrosis will be Metavir fibrosis 3, Knodell fibrosis score 3, Modified Ishak fibrosis score 4, Batts & Ludwig score 3, *or Scheuer score 3*. Subjects with these scores will be assigned to Group C.

Scores considered as cirrhosis will be Metavir fibrosis 4, Knodell fibrosis score 4, Modified Ishak fibrosis score 5 and 6, Batts & Ludwig score 4, *or Scheuer score 4*. Subjects 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

0. no fibrosis
1. fibrous portal expansion
3. bridging fibrosis (portal-portal or portal-central linkage)
4. cirrhosis

MODIFIED ISHAK FIBROSIS SCORE

0. no fibrosis
1. fibrous expansion of some portal areas, with or without short fibrous septa
2. fibrous expansion of most portal areas, with or without short fibrous septa
3. fibrous expansion of most portal areas, with occasional portal to portal (P-P) bridging
4. fibrous expansion of portal areas, with marked bridging (P-P) as well as portal-central (P-C)
5. marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)
6. cirrhosis, probable or definite

Appendix 1
Liver Biopsy Scores (cont.)

BATTS & LUDWIG

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 fibrotic portal tracts

2. Periportal or portal -portal septa but intact architecture

3. Fibrosis with architecture distortion but no cirrhosis

4. Probable or definite cirrhosis

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, Burns, and Saunders (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
ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect, or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- Is fatal (results in death) (Note: Death is an outcome, not an event.)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe.)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one in which the nature or severity is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For serious adverse events, possible causes of the event are indicated by selecting one or more options. (Check all that apply.)

- Pre-existing/underlying disease – specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g., accident, new or intercurrent illness) – specify

Appendix 3
ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 (cont.)

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or that comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test "drug," should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs eform of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor:

See provided forms for details of *study* administrative and contact information*, including the Local Monitor*.

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

ROCHE HEADQUARTERS CONTACT for Medical Emergencies:

Medical Monitor Contact Information

Primary Contact

Medical Monitor: [redacted], MD

Telephone No.: [redacted]

Mobile Telephone No.:

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Secondary Contact

Medical Monitor: [redacted], *MBChB Dip Pharm. Med*

Telephone No.: [redacted]

Mobile Telephone No.: