CLINICAL REVIEW

Date	September 5, 2017
From	Andreas Pikis, M.D. Medical Officer Division of Antiviral Products/Office of Antimicrobial Products
Through	Mary Singer, M.D., Ph.D. Medical Team Leader
Subject	Clinical Review
BLA # **Supplement#**	BLA 103964 Supplement 5270
Applicant	Hoffmann-La Roche (c/o Genentech, Inc.)
Date of Submission	December 15, 2016
PDUFA Goal Date	October 15, 2017
Proprietary Name / Non-Proprietary Name	PEGASYS® (Peginterferon alfa-2a)
Dosage form(s) / Strength(s)	Available as single-dose injection in the following forms: 180 µg/mL in a vial 180 µg/0.5 mL in a prefilled syringe 180 µg/0.5 mL in an autoinjector 135 µg/0.5 mL in an autoinjector
Applicant Proposed Indication(s)/Population(s)	Treatment of non-cirrhotic pediatric patients 3 years of age and older with HBeAg-positive chronic hepatitis B infection and evidence of viral replication and elevations in serum alanine aminotransferase (ALT)
Recommendation on Regulatory Action	Approval with recommended revisions in the proposed Package Insert

1. Introduction

This supplemental Biologics License Application (sBLA) includes the Clinical Study Report for the Phase 3 trial YV25718, which compared the efficacy and safety of PEGASYS (PEG-IFN) to a no-treatment control in non-cirrhotic pediatric patients 3 years of age and older with HBeAg (+) chronic hepatitis B (CHB) infection and evidence of viral replication and elevations in serum alanine aminotransferase (ALT). This submission is in response to the Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) issued on May 13, 2005, requiring an assessment of the safety and efficacy of peginterferon alfa-2a versus a no-treatment control in 110 pediatric patients with HBeAg(+) chronic hepatitis B (CHB) infection and compensated liver disease.

2. Background

Although the introduction of universal immunization programs and blood-donor screening in several countries has dramatically decreased the incidence of hepatitis B virus (HBV) infection, HBV remains a major cause of human morbidity and mortality. Of the 2 billion individuals infected by HBV, more than 360 million people worldwide are chronically infected by HBV. The prevalence of CHB infection is high in South East Asia and Sub-Saharan African (5-10%), whereas the prevalence of HBV infection is low (< 1%) in the United States and West Europe.

Mother-to-child transmission is the major route of HBV infection in children. The risk of chronic infection is higher for newborns who acquire the infection perinatally (90%) and infants and children less than 5 years of age (25-30%) than for adolescents or adults (< 5%).

Pediatric use information for many approved drugs, including antiviral drugs against HBV, is needed. In general, children have fewer therapeutic options than adults due to lack of pediatric formulations and information to guide clinicians in dosing children. Currently, 8 drugs have been approved for the treatment of CHB infection in adults and only 5 of the 8 drugs are also approved for children, most of them for children ≥ 12 years of age. Interferon alfa-2b, lamivudine, and entecavir are the only drugs approved for children less than 12 years of age. These agents are categorized as interferons or nucleos(t)ide analogues. Interferons are used for a defined self-limited course, whereas treatment with nucleos(t)ide analogues can be long-term (often indefinite). FDA-approved drugs for adults and children are summarized in Table 1.

Table 1. FDA-approved drugs for treatment of CHB infection in adults and children

Drug	**Approved Pediatric Age Range**	**Comments**
Interferons		
Interferon alfa-2b (INTRON A)	≥ 1 year	Advantages: Short treatment; no resistance Disadvantages: Route and frequency of administration (subcutaneously 3 times weekly); adverse reactions In adults, interferon alfa-2b has been replaced by pegylated interferon which is administered once a week.
Peginterferon alfa-2a (PEGASYS)	Currently not approved	In this submission the Applicant seeks indication for pediatric patients ≥ 3years of age
Nucleos(t)ide analogues		
Lamivudine (EPIVIR-HBV)	≥ 2 years	Low barrier to HBV resistance
Telbivudine	≥ 16 years	Low barrier to HBV resistance
Adefovir	≥ 12 years	Low barrier to HBV resistance Efficacy has not been demonstrated in subjects 2 to < 12 years of age
Entecavir	≥ 2 years	High barrier to HBV resistance

Tenofovir disoproxil fumerate	≥ 12 years	High barrier to HBV resistance
Tenofovir alafenamide	Not approved	High barrier to HBV resistance

Peginterferon alfa-2b (PEGINTRON) is not approved for the treatment of chronic hepatitis B infection

PEGASYS (PEG-IFN) is approved for the treatment of chronic hepatitis C (CHC) infection as part of combination therapy with other hepatitis C antiviral drugs in patients 5 years of age and older. In 2005, PEG-IFN was approved as monotherapy for the treatment of CHB infection in adult patients. Upon approval of PEG-IFN for adult patients with CHB infection, a PREA PMR was issued asking the Sponsor to assess the safety and efficacy of PEG-IFN versus no-treatment control in 110 pediatric HBeAg(+) chronically infected with the hepatitis B virus, who have compensated liver disease. In fact, this sBLA is in response to this PREA PMR.

3. Product Quality

In the United States, PEGASYS is available as single-dose injection in the following forms:

180 µg/mL in a vial
180 µg/0.5 mL in a prefilled syringe
180 µg/0.5 mL in an autoinjector
135 µg/0.5 mL in an autoinjector

This sBLA contains no new chemistry and manufacturing data. Please refer to the original NDA reviews for additional information.

4. Nonclinical Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with this sBLA. Please refer to the original BLA reviews for background information.

5. Clinical Pharmacology

A pharmacokinetic (PK) substudy was conducted under Study YV25718 to investigate whether the body surface area (BSA) category-based dosing regimen of PEG-IFN in pediatric patients with CHB infection provides PEG-IFN exposure similar to that observed in adults.

In adults with chronic hepatitis B (CHB) infection PEG-IFN is licensed at a dose of 180 µg administered subcutaneously once weekly for 48 weeks duration. In the United States, the approved dose of PEG-IFN for pediatric patients with CHC infection is 180 µg/1.73 m^2 x BSA.

(b) (4)

[redacted]

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(b) (4)

A total of 31 subjects (available data from 30 subjects) participated in the pharmacokinetic substudy. The pharmacokinetic substudy population was relatively well balanced with respect to age and BSA category. Plasma samples for pharmacokinetic analysis were obtained at Week 1 and Week 24 pre-dose (0), 24-48, 72-96, and 168 hours after the administration of PEG-IFN.

Based on the pharmacokinetic data obtained from Study YV25718 and pharmacokinetic data from 4 studies in adult patients, a population pharmacokinetic model of PEG-IFN was developed for both adult and pediatric patients. When using this model to predict the AUC steady-state levels (AUC_{ss}) and comparing the AUC_{ss} values between adults and pediatric patients, the BSA category-based regimen of PEG-IFN in pediatric patients provided AUC_{ss} values as those in adults. Further, the AUC_{ss} values were found to be comparable among the BSA-based dosing categories.

Of note, as at the time of this review, the Division is still discussing with the Applicant whether the dosing regimen for pediatric patients with CHB (b) (4)

For more details please see the clinical/pharmacology review by Drs. Su-Young Choi and Simbarashe Zvada.

6. Clinical Microbiology

Independent efficacy analyses were performed by Sung Rhee, Ph.D., the clinical virology reviewer. The results were similar to those provided by the Applicant.

For more details please see the review by Dr. Rhee.

7. Clinical/Statistical-Efficacy

Study YV25718: A phase IIIb parallel-group, open-label study of pegylated interferon alfa-2a (PEG-IFN), monotherapy compared to untreated control in children with HBeAg positive chronic hepatitis B in the immune active phase

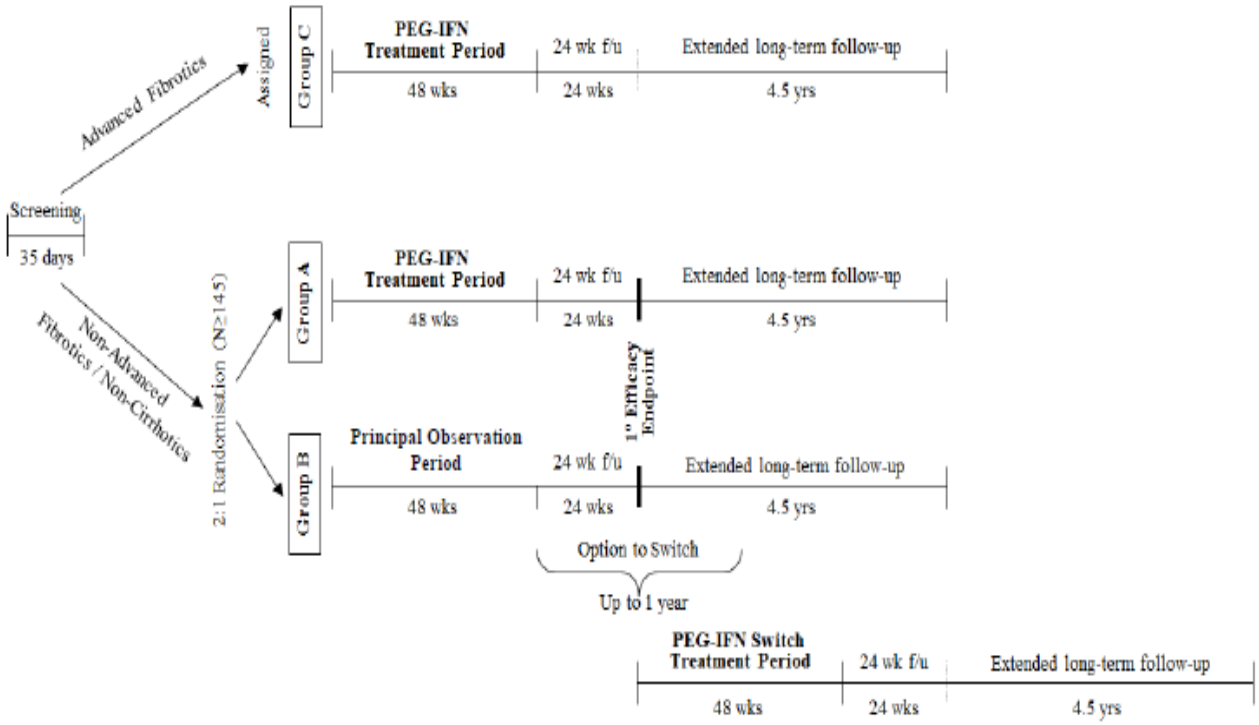
This was a randomized, controlled, open-label multinational study designed to compare the efficacy and safety of PEG-IFN to a no-treatment control in 110 pediatric HBeAg(+) patients chronically infected with the HBV and with compensated liver disease. The study was conducted at 37 centers in 12 countries. The primary objective of the study was 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. The primary endpoint was assessed at 24 weeks after the 48-week treatment/principal observational period.

A total of 151 subjects 3 to < 18 years of age chronically infected with hepatitis B virus and without advanced fibrosis were randomized in a 2:1 ratio to receive PEG-IFN (Group A, n=101) or untreated control (Group B, n=50). Subjects with advanced fibrosis were assigned to PEG-IFN treatment group (Group C, n=10). Subjects in Groups A and C (n=111) were treated with PEG-IFN once weekly for 48 weeks according to BSA categories. Subjects in Group B were observed for 48 weeks (principal observation period). Subjects in Group B had the choice to switch to treatment with PEG-IFN after Week 48 of the principal observation period. All subjects were followed for 24 weeks post-treatment (Groups A and C, or post-principal observation period.

All subjects with advanced fibrosis (Group C) were treated with PEF-IFN because it was not considered ethically acceptable to leave patients with advanced fibrosis without treatment.

After the Week 24 follow-up visit, subjects from Group A and C entered a long-term follow-up period lasting up to 5 years after the end of treatment. Results from the patients in Group B who switched to active treatment and the results of the long-term follow-up period for Groups A and C will be included in the final study report. A schematic overview of the trial design is shown in the following figure.

Figure 1. Schematic overview of Study YV25718.



Eligible subjects met all of the following inclusion criteria:

- Male or female patients aged 3 to <18 years old at baseline
- Positive HBsAg for more than 6 months
- Positive HBeAg and detectable HBV-DNA at screening (patients must have had > 10,000 copies/mL [>2,000 IU/mL] as measured by polymerase chain reaction [PCR])
- A liver biopsy performed within 2 years prior to baseline to confirm the presence of advanced fibrosis or exclude cirrhosis. For patients with advanced fibrosis, a liver biopsy had to have been performed within 9 months prior to baseline.
- Compensated liver disease (Child-Pugh Class A clinical classification)
- Elevated serum ALT > upper limit of normal (ULN) but ≤ 10 x 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.

A patient who met any of the following criteria was excluded from the study:

- Patients with cirrhosis (current treatment guidelines do not recommend interferon treatment for cirrhotic patients with chronic hepatitis B because of the risk of hepatic decompensation associated with hepatic flares due to interferon treatment)
- Patients who have received investigational drugs or licensed treatments with anti-HBV activity within 6 months prior to baseline
- Known hypersensitivity to PEG-IFN

- Positive test results at screening for hepatitis A virus immunoglobulin M antibody, anti-HCV antibody, anti-HDV antibody, or anti-HIV antibody
- History or other evidence of a medical condition associated with chronic liver disease other than chronic hepatitis B
- History or other evidence of bleeding from esophageal varices
- Decompensated liver disease 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 patients to have ultrasound within 6 months prior to baseline)
- Screening alfa-fetoprotein ≥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
- Evidence of renal impairment
- Autoimmune hepatitis
- History of immunologically-mediated disease including, 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
- 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 > 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 would be needed at any time during the study
- Coagulopathy (International Normalized Ratio >1.5), hemoglobinopathy, hemophilia, or history of severe illness or other blood disorders that would make patient unsuitable for the study
- History of seizure disorder requiring treatment with anticonvulsant medication (excluding febrile seizures)
- History or other evidence of severe retinopathy (all patients 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 patient, 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 were 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 had a positive urine or serum pregnancy test result within 24 hours of baseline, or who were breast-feeding

Dosage and administration: Treated patients (Group A and C) received PEG-IFN subcutaneously once weekly for 48 weeks with dosing based on BSA categories as shown in Table 2.

Stopping rules: Treatment with PEG-IFN was stopped in the event of any of the following events:

- 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 PEG-IFN was also considered in the event of:

- Evidence of hepatic decompensation (e.g., Child-Pugh Class B or C clinical classification 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

Dose reduction levels: Specific dose reduction was also defined in the protocol for moderate or severe reactions (depression, low absolute neutrophil count, low platelet count, and elevated serum ALT).

Disposition of subjects and baseline characteristics:

One hundred and fifty-one patients with no advanced fibrosis were randomized to Group A (PEG-IFN treatment arm; n=101) or Group B (untreated arm; n=50).

Group A: Ninety-nine patients completed both the 48-week treatment period and the 24-week follow-up period. The remaining two patients prematurely discontinued treatment; one patient withdrew on Day 57 because of increased transaminases > 10 x ULN considered by the investigator related to study drug and the other one at Week 24 of treatment due to physician's

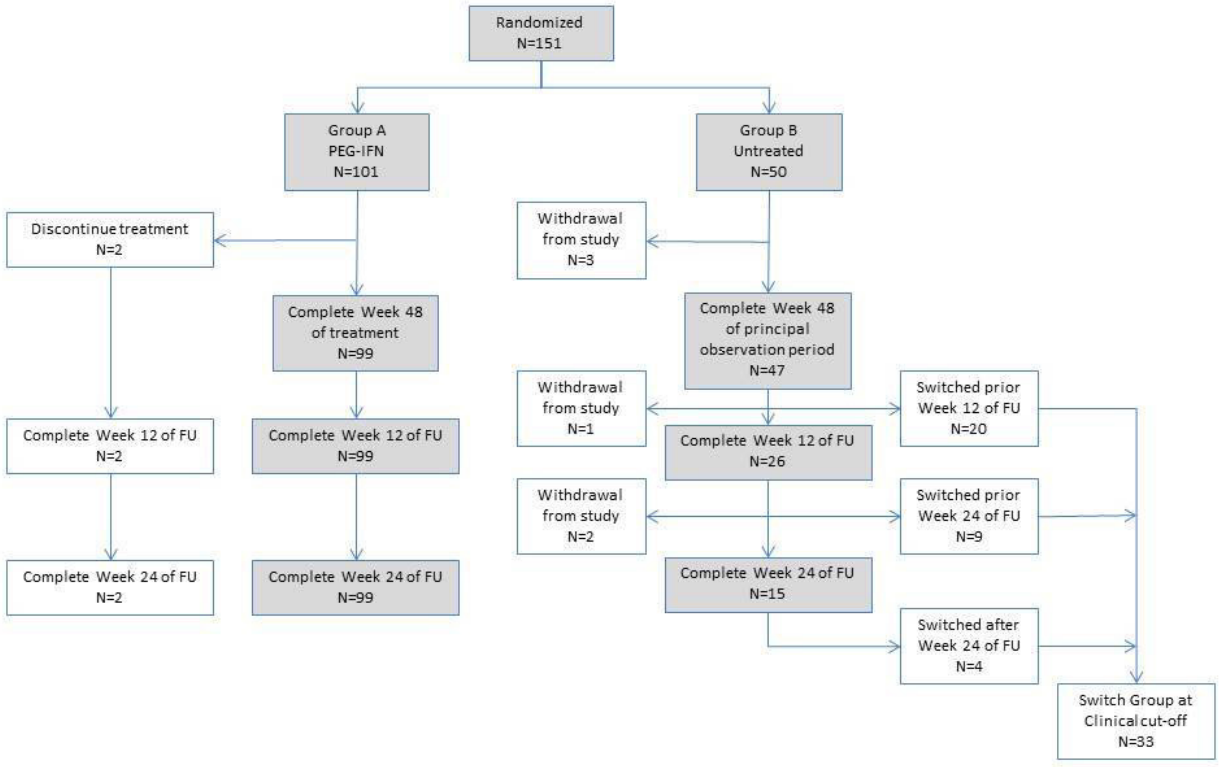
decision (the physician considered treatment unnecessary as patient responded to treatment although the patient did not meet the criterion for HBeAg seroconversion).

Group B: Of the 50 subjects in Group B, three withdrew from the study before Week 48 of the principal observation period. Of the 47 subjects who completed the 48 week principal observation period, 29 switched to active treatment (group D) before completing the Week 24 follow-up period, two subjects withdrew from the study and one subject had no visit after Week 12 of the follow-up period. Thus, in Group B, only 15 subjects had a visit at follow-up Week 24. After the end of Week 24 of the follow-up period, four additional subjects switched to PEG-IFN treatment (Group D). Therefore, the switch arm (Group D) comprised a total of 33 subjects.

Group C: All 10 patients completed the 48-week treatment period and the 24-week follow-up period.

A summary of patient disposition for Group A and Group B is shown in Figure 2.

Figure 2. Patient Disposition – ITT patients (Group A and Group B)



Subject demographics and baseline disease characteristics are shown in Table 3.

Table 3. Subject demographics and baseline disease characteristics (ITT population)

Characteristics	**Group A (PEG-IFN) N=101**	**Group B (no-treatment) N=50**	**Group C (advanced fibrosis) N=10**
Age (years)			
Number of subjects	101	50	10
3 to < 5	14 (14%)	9 (18%)	4 (40%)
5 to < 12	39 (39%)	11 (22%)	5 (50%)
12 to < 18	48 (47%)	30 (60%)	1 (10%)
Sex			
Number of subjects	101	50	10
Male	64 (63%)	32 (64%)	8 (80%)
Female	37 (37%)	18 (36%)	2 (20%)
Race			
Number of subjects	101	50	10
Asian	56 (55%)	33 (66%)	7 (70%)
Black or African American	7 (7%)	1 (2%)	1 (10%)
White	32 (32%)	15 (30%)	2 (20%)
Other	6 (6%)	1 (2%)	-
HBV DNA (log_{10} IU/mL)			
Number of subjects	101	50	10
Mean (SD)	8.09 (0.99)	8.06 (0.99)	7.87 (0.98)
Median	8.25	8.12	8.12
Range	4.24 -10.99	4.18 - 9.55	5.66 - 9.10
HBeAg (log_{10} PEIU/mL)*			
Number of subjects	92	43	9
Mean (SD)	2.74 (0.50)	2.57	2.34 (0.98)
Median	2.86	2.76	2.61
Range	1.46 - 4.10	1.05 - 3.45	0.41 – 3.61
HBsAg (log_{10} IU/mL)			
Number of subjects	101	44	10
Mean (SD)	4.31 (0.69)	4.38 (0.72)	4.23 (0.52)
Median	4.41	4.48	4.16
Range	1.34 – 5.51	2.24 – 5.63	3.63 – 5.24
ALT at baseline (x ULN)			
Number of subjects	101	50	10
< 1	7 (7%)	5 (10%)	-
1 to < 2	41 (41%)	19 (38%)	3 (30%)
2 to < 5	43 (42%)	17 (34%)	7 (70%)
5 to < 10	8 (8%)	9 (18%)	-
≥ 10	2 (2%)	-	-
HBV genotype			
Number of subjects	101	50	10

A	9 (9%)	3 (6%)	1 (10%)
A & B	1 (1%)	-	-
A & D	1 (1%)	-	-
B	21 (21%)	6 (12%)	1 (10%)
C	34 (33%)	23 (46%)	6 (60%)
D	31 (31%)	18 (36%)	2 (20%)
E	4 (4%)	-	-

*PEIU= for Paul Ehrlich Institute Unit of measure of HBeAg

Reviewer's comment: The majority of the patients were male, Asian (approximately half of the patients were enrolled in China), and were infected with HBV genotype C. In general, Group A and Group B were comparable with regards to patient demographics and baseline disease characteristics. Small differences were observed but are considered acceptable given the small number of subjects in each group.

Analysis of Primary Endpoint

The primary efficacy endpoint in Study YV25718 was HBeAg seroconversion at 24 weeks after the end of treatment (Group A) or the principal observation period (group B). At this time-point, 26 patients (26%) in Group A had HBeAg seroconversion compared to 3 patients (6%) in the untreated group (Group B). This difference was statistically significant (*P* value = 0.004 based on Cohran-Mantel-Haenszel estimates (Table 4)

Table 4. HBeAg seroconversion in Study SV25718 (ITT population; Groups A and B)*

Primary endpoint	**Group A (PEG-IFN) N=101**	**Group B (no-treatment) N=50**	**Odds Ratio** (95% CI)**	**P-value**
HBeAg seroconversion	26 (26%)	3 (6%)	5.43 (1.54, 19.2)	0.0043

*Subjects switched to PEG-IFN treatment during the post-principal observation period and before the Week 24 follow-up were considered as non-responders.
**Based on Cochran-Mantel-Haenszel test, stratified by genotype (A vs. non-A) and baseline ALT (< 5 × ULN and ≥ 5 x ULN)

In Group C, three of the 10 patients (30%) with advanced fibrosis treated with PEG-IFN for 48 weeks had HBeAg serocnversion at 24 weeks after the end of treatment, a rate similar to the HBeAg seroconversion rate observed in Group A.

Reviewer's comment: The 26% HBeAg seroconversion observed in Study SV25718 is slightly lower than the 32% HBeAg seroconversion observed in the adult registrational trial WV16240. This difference may be due to the higher proportion of patients with HBV genotype D in the pediatric study (31% versus 3%) compared to adults. HBV genotype D infection is considered a difficult-to-treat population.

Analysis of Major Secondary Endpoints

The key secondary efficacy results in Study SV25718 are summarized in the following table.

Table 5. Major secondary efficacy endpoints in Study SV25718 (ITT population; Groups A and B)

Endpoints	Group A (PEG-IFN) N=101	Group B (No-Treatment) N=50	Odds Ratio* (95% CI)	p-value
HBsAg seroconversion	8 (8%)	0 (0%)	-	0.052
Loss of HBsAg	9 (9%)	0 (0%)	-	0.030
Loss of HBeAg	26 (26%)	3 (6%)	5.43 (1.52, 29.32)	0.003
ALT normalization	52 (52%)	6 (12%)	7.78 (2.91, 24.05)	< 0.0001
HBV-DNA <20000 IU/mL	34 (34%)	2 (4%)	12.18 (2.85, 108.3)	< 0.0001
HBV-DNA <2000 IU/mL	29 (29%)	1 (2%)	19.74 (3.02, 822.2	< 0.0001
HBV-DNA undetectable	17 (17%)	1 (2%)	9.92 (1.45, 422.7)	0.006
HBeAg seroconversion and HBV-DNA <20000 IU/mL	23 (23%)	2 (4%)	7.08 (1.61, 64.02)	0.002
HBeAg seroconversion and HBV-DNA <2000 IU/mL	20 (20%)	1 (2%)	12.10 (1.80, 511.5)	0.002

*Exact odds ratio and confidence limits.

Reviewer's comment: Statistically significant response rates at Week 24 of follow-up were observed in Group A compared with Group B. The only secondary endpoint that did not reach statistical significance was HBsAg seroconversion (p=0.052), even though a higher response rate was observed in Group A (8% in Group A versus 0% in group B).

The treatment difference between Group A and Group B was relatively consistent across age groups, gender, race, and baseline disease characteristics.

The efficacy results in Group C were in line with Group A and are summarized in Table 6.

Table 6. Efficacy results in patients with advanced fibrosis

Endpoints	Group C (advanced fibrosis) N=10
Primary endpoint	
HBeAg seroconversion	3 (30%)
Secondary endpoints	
HBsAg seroconversion	0 (0%)

Loss of HBsAg	0 (0%)
Loss of HBeAg	3 (30%)
ALT normalization	7 (70%)
HBV-DNA <20000 IU/mL	7 (70%)
HBV-DNA <2000 IU/mL	7 (70%)
HBV-DNA undetectable	3 (30%)
HBeAg seroconversion and HBV-DNA <20000 IU/mL	3 (30%)
HBeAg seroconversion and HBV-DNA <2000 IU/mL	3 (30%)

Efficacy conclusions: Study YV25718 was undertaken to compare the efficacy of PEG-IFN to a no-treatment control in non-cirrhotic pediatric patients 3 years of age and older with HBeAg seropopositive chronic hepatitis B infection in the immune-active phase. The results of the study demonstrated the superiority of PEG-IFN administered subcutaneously once weekly for 48 weeks over no treatment.

For more details with regards to efficacy please see the reviews by Dr. Hengrui Sun, the statistical reviewer, and Dr. Sung Rhee, the clinical virology reviewer.

8. Safety

The safety profile of PEG-IFN is well characterized. Until now, more than (b) (4) people have been exposed to this drug in the context of CHC or CHB infection. PEG-IFN is currently labeled with warning language regarding neuropsychiatric, cardiovascular, endocrine, ophthalmologic, cerebrovascular disorders and bone marrow suppression. The safety evaluation of this submission is based on the safety data of the 111 patients in Study YV25718 treated with PEG-IFN; 101 patients with no advanced fibrosis (Group A) and 10 patients with advanced fibrosis (Group C). The majority of the patients received the planned 48 weekly doses as indicated by the median number of received doses which was 48. When indicated, and in order to provide context, the safety data from Study YV25718 were compared with safety data from studies with the same indication (adult studies WV16240 and WV1624 in patients with CHB infection) or with safety data from studies with a similar population (Study NV17424 for the treatment of chronic hepatitis C in pediatric patients 5 years of age and older).

- Study WV16240 in adult CHB HBeAg positive patients and Study WV16241 in adult CHB HBeAg negative patients (in these studies, patients were randomized to receive PEG-IFN plus placebo, PEG-IFN + lamivudine, or lamivudine monotherapy for 48 weeks with a 24-week follow-up period; only data from the PEG-IFN arms [180 µg once weekly for 48 weeks] were used for comparison).

- Study NV17424 in pediatric patient 5 to 18 years of age with chronic hepatitis C infection (in this study, treatment-naïve pediatric patients with CHC infection were randomized to receive either combination treatment with PEG-IFN [180 µg/1.73 m^2 x BSA once weekly] plus ribavirin [15 mg/kg/day] or PEG-IFN monotherapy for 48 weeks followed by a 24-week treatment-free period. Patients with detectable HCV RNA levels

at Week 24 of treatment were unblinded and those receiving PEG-IFN monotherapy were allowed to switch to combination therapy. These patients received PEG-IFN for 72 weeks

and were not counted for safety comparison. Thus, the safety population compared to Study YV25718 includes 55 subjects in the combination treatment arm and 31 subjects in the monotherapy arm who received PEG-IFN for maximum of 48 weeks).

In Study YV25718, all adverse events were presented using preferred terms from MeDRA version 18.1. Adverse events were graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.

Overall, most of the patients (86%) in the pooled safety population (Group A and C) in Study YV25718 experienced at least one AE most of which (81%) were considered related to study medication. Six subjects (5%) experienced at least one serious AE (SAE), and 8 subjects experienced a severe AE. An overview of AEs in patients in Study YV25718 is summarized in the following table.

Table 7. Overview of safety: Pooled safety population (Group A and C) and No Treatment Group (Group B)*

	PEG-IFN (Group A and C) N=111	**No treatment (Group B) N=49**
Patients with any AE	96 (86%)	27 (55%)
Patients with a treatment-related AE	90 (81%)	1 (2%)**
Patients with a serious AE	6 (5%)	1 (2%)
Patients withdrawn from study due to an AE	0	1 (2%)
Patients with AE leading to dose modification or interruption	8 (7%)	0
Patients with severe AE	8 (7%)	0
Patients with AE leading to withdrawal from treatment	1 (1%)	0
Deaths	0	0

*Results should be interpreted with caution given the less frequent visits in Group B, the shorter follow-up in patients in Group B due to patients switching to PEG-IFN treatment after Week 48 of principal observation period, and the potential bias due to the open-label design.
**This AE was ongoing at the time of switching to PEG-IFN and it was erroneously reported as related to study drug

A summary of AEs occurred in at least 10% of patients is shown in Table 8.

Table 8. Most common adverse events (≥ 10% of patients)

Adverse event	**PEG-IFN (N=111)**
Pyrexia	57 (51%)
Headache	34 (31%)
Abdominal pain	19 (17%)
Cough	17 (15%)

Vomiting	17 (15%)
Influenza-like illness	15 (14%)
ALT increased	11 (10%)
AST increased	11 (10%)
Rash	11 (10%)

Overall, most of the AEs described in Study YV25718 have been well described with PEG-IFN use in the pivotal adult studies for the treatment of CHB infection (WY16240 and WV16241) and the pediatric study NV17424 for the treatment of pediatric patients with CHC infection.

Deaths: No deaths were reported during the study

Nonfatal serious adverse events: Six patients (all of them from Group A) experienced 7 SAEs (Table 8). Three of the 6 patients with SAEs were ≥ 12 years of age. All SAEs resolved by Week 24 of follow-up and none of them led to PEG-IFN dose modification or interruption. In the adult CHB pivotal studies, 27 patients (6%) experienced SAEs, and in the pediatric CHC study one patient (3%) in the PEG-IFN monotherapy arm and two patients (4%) in the PEG-IFN + ribavirin arm experienced an SAE.

Table 9. Serious adverse events in Group A and C

Patient No	Age (years)/Sex	Adverse Event	Related to PEG-IFN
1101	17/F	↑ALT, AST	Yes
1601	6/M	*Microsporum* infection (scalp)	No
1602	12/M	Osteochondrosis	No
1606	7/W	Latent tuberculosis	No
2006	13/M	Acute tonsillitis	No
3903	4/M	Pneumonia	No

Adverse events or laboratory abnormalities led to dose modification or interruption of study drug: Twenty-nine subjects (26%) experienced an AE or laboratory abnormality that led to a dose modification. The most common abnormalities that led to dose modification were elevated transaminases (13 subjects) and low absolute neutrophil count (14 subjects). Similar findings were observed in the adult pivotal studies and the pediatric CHC study with neutropenia and transaminasemia being the most common abnormalities.

In the adult CHB studies 40% of subjects experienced an AE or laboratory abnormality that lead to dose modification. In the pediatric hepatitis C study, 36% of patients in the PEG-IFN + ribavirin arm and 35% in the PEG-IFN monotherapy arm required dose modification.

Patients with AEs leading to withdrawal from study treatment: One patient (1%) withdrew from study treatment. This was a 5-year-old girl who experienced ALT and AST > 10 x ULN which were considered by the investigator related to study medication. These events resolved after 40 days and the patient continued follow-up. In the adult CHB pivotal studies, 21 patients (5%) experienced adverse events or laboratory abnormalities that led to withdrawal from study treatment whereas in the pediatric CHC study 12 patients (14%) experienced AEs that led to withdrawal from study treatment; 7 (13%) in the PEG-IFN+ ribavirin arm and 5 (16%) in the PEG-IFN monotherapy arm.

Adverse events of special interest:

Modified Hy's law criteria (defined as ALT or AST > 3 x baseline in combination with total bilirubin > 2 x ULN or with clinical jaundice): No patient met the modified Hy's law criteria.

Neuropsychiatric disorders: Twelve patients (11%) reported 16 psychiatric disorder adverse events. Insomnia was reported by 3 subjects, listlessness and altered mood by two subjects and all other events by one subjects each. Depressed mood and depression were reported by one patient each. Both of these events were mild in intensity and did not lead to dose modification. All psychiatric events resolved by Week 24 of the follow-up period. The incidence of psychiatric adverse events in Study YV25718 was lower compared to the incidence reported in the adult pivotal studies and the pediatric study for CHC infection. In the adult pivotal studies for CHB infection, 17% of patients in the PEG-IFN monotherapy arms experienced psychiatric disorder adverse events. The most common psychiatric AEs were insomnia and depression which were observed in 8% and 4%, respectively.
In the pediatric CHC study, 16 patients (29%) in the PEG-IFN+RBV arm and 10 patients (32%) in the PEG-IFN monotherapy arm experienced psychiatric disorders. The most common psychiatric AEs were insomnia (13% and 19%, respectively) and depression (7% and 16%, respectively).

Forty-one patients (37%) in the pooled safety population (Group A and Group C) experienced an AE in the Nervous system disorder SOC. The most common was headache (31%) followed by dizziness (6%). Headache was also the most common AE in the Nervous system disorder observed in the adult pivotal CHB studies and the pediatric CHC study (27% and 53%, respectively).

Ophthalmological disorders: Thirteen patients (12%) in the pooled safety population experienced 23 eye AEs during the study. Most of these events were mild in intensity. The most common were eye pain (3 subjects), allergic conjunctivitis (2 subjects), and hypermetropia (2 subjects). Of the 23 ophthalmologic AEs, 4 were considered related to study drug (eye pain, eyelid edema, retinal hemorrhage, and retinal edema). None of these events led to study drug discontinuation or dose modification, and all of them resolved by the end of the follow-up

period. The occurrence of AEs in Study YV25718 is in line with previous experience in adult CHB studies and the pediatric CHC study.

Thyroid disorders: No cases with hypothyroidism or hyperthyroidism were reported in the pooled safety population. In the adult pivotal CHB studies, 3 patients (< 1%) experienced hypothyroidism and 6 patients (1%), hyperthyroidism. In the CHC study, 2 subjects (2%) experienced hypothyroidism and were treated with levothyroxine.

Laboratory abnormalities of special interest: The most notable changes from baseline were changes in WBC counts, platelet counts, hemoglobin levels, and increases in the transaminases. These changes were not unexpected based on the known safety profile of PEG-IFN.

Neutropenia: The occurrence of neutropenia in the pooled safety population (Group A and Group C) of Study YV25718 is consistent with that observed in the adult pivotal studies for CHB infection. Five percent of patients had their lowest neutrophil count < 0.5 x 10^9/L (none of them below 0.25 x 10^9/L) and 15% reached a nadir in the range of 0.5 - < 0.75 x 10^9/L. These changes reversed after drug discontinuation. Neutrophil counts < 0.75 x 10^9/L were managed with dose modification (PEG-IFN dose was modified in 14 of the 111 patients [13%] subjects due to low ANC). The low ANC was not associated with severe or serious infections.

In the adult studies in patients with CHB infection the incidence of subjects with neutrophil counts < 0.5 x 10^9/L and between 0.5 - < 0.75 x 10^9/L was 5% and 15%, respectively.

Lymphopenia: A total of 14 patients (13%) had their lowest lymphocyte count in the range between 0.5 - < 1.0 x 10^9/L and 1 patient had lowest count < 0.5 x 10^9/L (this patient had no infection and dose modification was not required). In the adult studies for CHB infection lymphocyte counts < 0.5 x 10^9/L were observed in 3% of subjects. In the CHC study lymphocyte account < 0.5 x 10^9/L was observed in 2% of patients.

Anemia: None of the patients had hemoglobin levels < 85 g/L, and only 4 patients (4%) had levels in the range of <100 to 85 g/L.

In the adult studies, the occurrence of Hgb levels < 100 g/L was 5%. The occurrence of Hgb levels < 100 g/L in the pediatric CHC study was 13% (no difference between the PEG-IFN monotherapy arm and the PEG-IGN+RBV arm). None of the patients in the pediatric CHC study had Hgb levels < 85 g/L.

Thrombocytopenia: Post-baseline platelet counts in the range of 50.0 - < 75.0 x 10^9/L and 20.0 - < 50.0 x 10^9/L were reported in one patient each. These cases recovered to normal range without any dose modification. In the pediatric CHC study (Study NV 17424), one patient (3%) in the PEG-IFN+RBV arm and no patients in the PEG-IFN arm had a platelet count in the range of 50.0 - < 75.0 x 10^9/L. No patient in either arm had platelet levels < 50.0 x 10^9/L.

ALT elevations/ALT flares: In Study YV25718, enrolled subjects were in the active-phase of the disease. As defined in the inclusion criteria, patients had to have ALT > ULN but ≤ 10 x ULN. Highest post-baseline values greater than 5.0 x ULN were reported in 65 patients (59%) in the

pooled safety population; 43 patients had ALT levels > 5.0 – 10.0 x ULN and 22 subjects > 10 x ULN. In all but 2 of the patients with post-baseline ALT levels > 5.0 x ULN, ALT levels returned/were returning to baseline at Week 24 of the follow-up period. The two patients had peak ALT levels at Week 24 of the follow-up period. None of the ALT flares met the modified Hy's law criteria and there was no evidence of hepatic decompensation.

Although elevated ALT levels could be attributed to many causes of liver damage, they may also be a marker of disease activity in patients with CHB infection. ALT flares can occur during treatment or off-treatment and have been correlated to clinical outcome. ALT flares associated with decreasing HBV DNA levels may indicate treatment effectiveness; whereas ALT flares associated with rising/stable HBV DNA levels may indicate treatment failure. Based on the most recent definition, ALT flares are categorized as follows:

- Grade 1 - ALT level ≥5-≤10 x ULN and>2x baseline
- Grade 2 - ALT level >10x ULN and>2x baseline

In Study YV25718 (pooled safety population), and using the above definition, ALT flares were higher during the treatment period (38/111, 34%) compared to the off-treatment period (16/111, 14%). Most of the ALT flares observed during the treatment period (24 of 38, 63%) were associated with concurrent decline in HBV DNA levels (≥ 1 $\log_{10}$) compared to lower proportion of post-treatment ALT flares (5 of 16, 31%). In addition, HBeAg seroconversion at Week 24 of the follow-up period was more common in patients with on-treatment ALT flares associated with HBV-DNA decline (11 of 24, 46%) compared to those without HBV-DNA decline (2 of 14, 14%).

Thyroid function abnormalities: No consistent changes were seen in thyroid laboratory measurements. The majority of thyroid laboratory abnormalities were isolated (and single) events of high FT3 not accompanied by TSH or FT4 abnormalities. Only two of these events were reported as an AE (two high TSH abnormalities) and they did not require treatment.

Growth parameters: The effects of interferons on growth represent a safety issue of particular concern among pediatric patients. Previous pediatric trials with alpha interferons have identified growth delay during treatment followed by "catch-up" growth in most of the patients. Growth parameters were measured in Study YV25718; however, long-term follow-up data are not available. At Week 48 of treatment, 11% of subjects in the pooled safety population (Group A and C) were more than 15 percentiles below their baseline weight curve and 6% were more than 15 percentiles below their baseline height curve. At Week 24 of the follow-up period, 12% of subjects were more than 15 percentiles below their baseline weight curve and 12% were more than 15 percentiles below their baseline height curve. A summary of the growth parameters is shown in the following table.

Table 10. Summary of growth parameters in pediatric patients in Study YV25718

Growth parameter	YV25718 (CHB)	
	Groups A+C	Group B*
Height:		
Number of patients with >15 percentile drop from baseline at Week 48 of treatment	7/108 (6%)	1/47 (2%)
Number of patients with >15 percentile drop from baseline at Week 24 of the follow-up period	13/110 (12%)	1/15 (7%)
Weight:		
Number of patients with >15 percentile drop from baseline at Week 48 of treatment	12/108 (11%)	4/47 (9%)
Number of patients with >15 percentile drop from baseline at Week 24 of the follow-up period	13/110 (12%)	3/15 (20%)

*Week 24 of the follow-up period includes data from patients who continued to be off PEG-IFN treatment.

Reviewer's comment: No clinically significant changes in height and weight were observed over time (comparing Groups A and C to Group B) through Week 24 of the follow-up period for pediatric patients treated with PEG-IFN for CHB infection. Of note, StudyYV25718 is ongoing; after the Week 24 of the follow-up visit, patients in Group A and C entered a long-term follow-up period (up to 5 years after the end of treatment). Results from these patients and from patients in Group B who switched to PEG-IFN treatment will be included in the final clinical study report.

Safety conclusions: In summary, the safety profile of PEG-IFN in treatment of non-cirrhotic pediatric patients 3 years of age and older with HBeAg seropositive CHB infection in the immune-active phase appears to be consistent with that observed in adult patients with CHB infection as well as with pediatric patients with CHC infection. No new safety signals were identified.

9. Advisory Committee Meeting

An Advisory Committee was not held for this sBLA.

10. Pediatrics

On May 13, 2005, PEGASYS was approved for use in adults with chronic hepatitis B infection. In that approval letter, FDA waived the requirements for neonates and infants. The requirement to study pediatric patients 2 to 17 years of age was deferred to a postmarketing requirement under the Pediatric Research Equity Act (PMR#2322-1). This PREA PMR required the Applicant to:

2322-1: Assess the safety and efficacy of peginterferon alfa-2a versus a no-treatment control in 110 pediatric HBeAg positive patients chronically infected with the hepatitis B virus, who have compensated liver disease.

The Division believes that the submitted data from Study YV25718 fulfilled the PREA requirements for PMR# 2322-1.

11. Other Relevant Regulatory Issues

Compliance with Good Clinical Practices: The Applicant states the study was conducted according to accepted ethical standards based on the precepts established by the declaration of Helsinki. The study was conducted with the approval of Ethics Committees or Institutional Review Boards and informed consent was obtained from all subjects.

Submission Quality and Integrity: At the request of the Division of Antiviral Products, the Office of Scientific Investigations (OSI) audited three study sites; two sites in China and one in Ukraine. These sites were selected based on enrollment; Site 251541 (China) enrolled 38 subjects, Site 255265 (China) enrolled 10 subjects, and Site 238773 (Ukraine) enrolled 10 subjects. In addition, response rate at Site 251541 (53%) was much higher than the overall study response. The final classification from the clinical inspections at Sites 251541 and 255265 is No Action Indicated. Data from these sites are acceptable for use in support of this sBLA. The final report from the inspection of Site 238773 is pending at the time of this review. However, preliminary report from OSI suggested that no problems were identified.

Financial Disclosures: In compliance with the rule on Financial Disclosure by Clinical Investigators, the Applicant provided financial interest information for 186 out of 191 principal investigators and sub-investigators who participated in Study YV25718. According to the Applicant, none of the 186 clinical investigators and sub-investigators had a proprietary interest in the product or a significant equity interest in the Sponsor as defined in 21 CFR 54.2(b). The Applicant was unable to obtain financial disclosure for 5 investigators (one principal investigator and 4 sub-investigators) despite a detailed due diligence process. The Applicant provided the

names of these 5 investigators and the reason why the information could not be collected (see Appendix).

Recommendations for post-market requirements and commitments: A postmarketing requirement will be issued asking the Applicant to collect long-term data from patients enrolled in Study YV25718 related to the effects of PEG-IFN on growth and other safety parameters. The Applicant will be asked to collect data on growth and other safety parameters for at least 3 years after the Week 24 follow-up period. The Applicant will be also asked to collect data on the hepatitis B serological markers for at least 3 years after the Week 24 follow-up period.

Recommendations for post-market risk evaluation and mitigation strategies: No specific Risk Management activities are recommended.

12. Labeling

Key labeling changes included the following sections:

- INDICATIONS AND USAGE: This section was modified to include the indication of PEGASYS in pediatric patients 3 years of age and older with HBeAg-positive CHB infection.
- DOSAGE AND ADMINISTRATION: This section was modified to include the recommended dosage for pediatric patients with CHB infection.
- WARNINGS AND PRECAUTIONS: The subsection of "Impact on Growth to Pediatric Patients" was modified to include the growth changes (height and weight) observed in Study YV25718.
- ADVERSE REACTIONS: The subsection "Clinical Trials Experience" was modified to add information on the adverse reactions observed in Study YV25718.
- USE IN SPECIFIC POPULATIONS: This section was modified in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). The subsection of "Pediatric Use" was also modified to add information on the use of PEGASYS for the treatment of pediatric patients 3 to 17 years of age with CHB infection.
- CLINICAL STUDIES: Subsection 14.4 was modified to provide a brief presentation of Study YV25718.

13. Recommendations

The data submitted from Study YV25718 support the use of PEG-IFN for the treatment of non-cirrhotic pediatric patients 3 years of age and older with HBeAg seropositive CHB infection in the immune-active phase. The results of this study demonstrated the superiority of PEG-IFN administered once weekly for 48 weeks over no treatment. No new safety signals were identified

during the study. Overall, the safety profile of PEG-IFN was consistent to that observed in the registrational trials in adult patients with CHB infection and to that observed in the pediatric study with CHC infection.

APPENDIX

Clinical Investigator Financial Disclosure
Review Template

Application Number: sBLA 103964/5270

Submission Date: December 15, 2016

Applicant: Hoffmann-La Roche (c/o Genentech, Inc.)

Product: PEGASYS® (Peginterferon alfa-2a)

Reviewer: Andreas Pikis

Date of Review: September 5, 2017

Covered Clinical Study (Name and/or Number): YV25718

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: Principal investigators: 45; sub-investigators: 146		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 5 (one principal		

investigator and 4 sub-investigators		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The Applicant adequately examined financial disclosure information from 186 out of 191 principal investigators and sub-investigators for the covered clinical trial, and completed FDA Form 3454 for Financial Certification. The Applicant certified that, as the sponsor of the submitted trial, the Applicant has not entered into any financial arrangement with the listed clinical investigators (*list was included in the submission*) whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity interest in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The Applicant was unable to obtain a financial disclosure for 5 investigators (one principal investigator and 4 sub-investigators) despite a detailed due diligence process. These 5 investigators were not available to sign the forms despite multiple attempts by the Applicant. The Applicant provided the names of these investigators and the reason that the information could not be collected.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREAS PIKIS
09/08/2017

MARY E SINGER
09/08/2017
I concur with Dr. Pikis' assessment and recommendations for approval of this efficacy supplement.