U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	BLA 103964
Drug Name:	Pegasys® (peginterferon alfa-2a, RO 25-8301)
Indication(s):	Treatment of HBeAg positive pediatric patients 3 years to < 18 years of age
Applicant:	Hoffmann-La Roche Inc.
Date(s):	Received: 12/15/16 PDUFA: 10/15/17
Review Priority:	Standard (10 months)
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Keywords: Clinical trials, HBV, Cochran-Mantel-Haenszel test, Common odds ratio

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1. EXECUTIVE SUMMARY

In this submission the Applicant, Hoffmann-La Roche Inc., seeks to provide evidence to extend the labeling of Pegasys to include HBeAg positive pediatric patients 3 to < 18 years of age. The evidence is derived from a randomized, controlled, parallel-group, open-label, Phase 3 superiority trial designed to evaluate the efficacy and safety of Pegasys injected once weekly for 48 weeks compared to an untreated control.

A total of 151 patients without advanced liver fibrosis were randomized 2:1 to Pegasys or the untreated control group. Ten patients with advanced fibrosis were assigned to Pegasys treatment and received study drug. A summary of the findings at 24 weeks after treatment completion are presented in Table 1. The efficacy of Pegasys compared to untreated control for the primary endpoint of HBeAg seroconversion has been demonstrated based on the result that the odds of seroconversion are greater among patients in Pegasys group compared to those in the untreated control group. Additionally, among the 10 patients with advanced fibrosis who were assigned to receive Pegsys treatment, 3 subjects had HBeAg seroconversion at the follow-up visit of Week 24 with 95% confidence interval of (6.7%, 65.2%).

Table 1: HBeAg seroconversion rates for the two treatment groups

	Pegasys (N=101)	Control (N=50)	OR (95%CI)	p-value
Primary Endpoint				
HBeAg seroconversion	26 (25.7%)	3 (6%)	5.43 (1.54, 19.2)	0.0043

2. INTRODUCTION

2.1 Overview

Pegasys® (peginterferon alfa-2a, RO 25-8310) was approved by the Agency in 2005. It provides treatment to adult patients with HBe antigen (HBeAg) positive and HBeAg negative chronic hepatitis B (CHB) with compensated liver disease. It is reported that pediatric patients have increased lifetime risk of CHB sequelae due to the prolonged duration of infection compared with adults, while therapeutic options for pediatric patients with CHB are more limited than those available for adults. In 2005, the Agency requested the Applicant conduct a post market pediatric study for Pegasys. Study YV25718 was designed and conducted subsequently to evaluate efficacy and safety of Pegasys when administered to HBeAg positive CHB children 3 to <18 years of age. In this submission, the Applicant submitted a labeling supplement with clinical data for YV25718 to support the extension of the Pegasys (indicated as PEG-IFN in the following part of the review) indication to include HBeAg positive pediatric patients 3 years of age and older.

2.2 Data Sources

The data were submitted electronically and are located in \\CDSESUB1\evsprod\BLA103964\0235\m5\datasets\yv25718\analysis\legacy\datasets .

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the data in this NDA is acceptable, and the reviewer was able to access the information.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

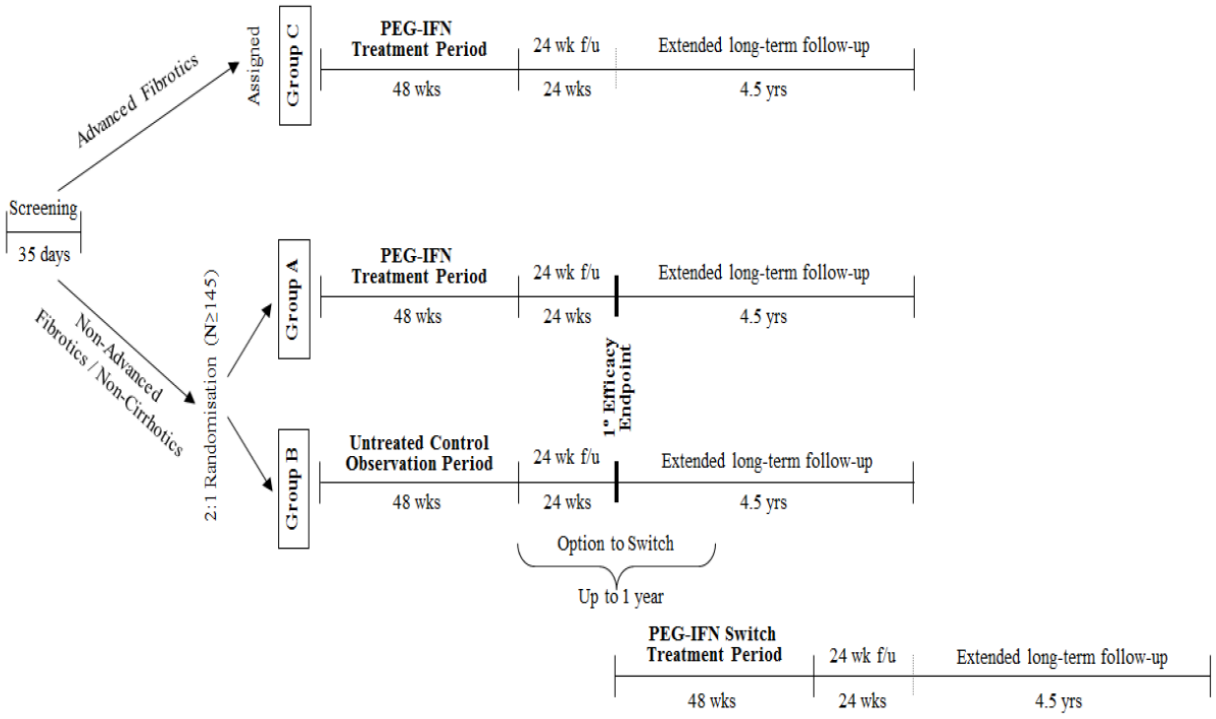
Study YV25718 is a Phase 3, randomized, controlled, parallel-group, open-label study that compares PEG-IFN with untreated control. This study is currently ongoing for the extended long-term follow-up period. Specifically, patients without advanced fibrosis were randomized 2:1 to PEG-IFN (Group A) or untreated control (Group B). Patients with advanced fibrosis were assigned to PEG-IFN treatment group (Group C). Patients in Groups A and C received PEG-IFN subcutaneously once weekly for 48 weeks with a dose according to body surface area (BSA) categories (Table 2). For Group B, after completing 48 weeks of a principal observation period, PEG-IFN was offered to the patients who still had positive HBeAg once weekly for 48 weeks. The duration of the study is about 6 years for Group A, Group B non-switch, and Group C which includes a 1 year treatment/principal observation period, 24 week follow-up period for the primary analysis, and an additional 4.5 years of follow-up. For Group B, the duration is approximately 8 years, with a 1 year treatment/principal observation period, up to 1 year follow-up period while deciding whether to switch, a 1 year switch treatment period, and 5 years of follow-up. For this submission, only data up to 24 weeks of follow-up are included. All patients are planned to be followed for an additional 4.5 years to assess the long term efficacy response and monitor the safety profile (Figure 1).

Table 2: PEG-IFN dosing regimen

Dose (μg)	BSA range (m^2)
65	0.54-0.74
90	0.75-1.08
135	1.09-1.51
180	>1.51

Source: Clinical Overview by Applicant

Figure 1: Study design



Source: Summery of Clinical Efficacy by Applicant

The primary objective of this study was to compare HBeAg seroconversion between Group A and B at 24 weeks after the treatment/principal observation period. The secondary objective was to evaluate short term and long term efficacy and safety of PEG-IFN between Group A and B, and to evaluate pharmacokinetics in PEG-IFN treated patients.

A brief outline of the study is presented in Table 3.

Primary endpoint of the study was HBeAg seroconversion evaluated at 24 weeks after the end of treatment/principal observation.

Secondary endpoints were also evaluated at the same time point as for the primary endpoint, and they are listed as follows:

- Loss of HBeAg
- HBsAg seroconversion (loss of HBsAg and presence of anti-HBs)
- Loss of HBsAg
- Proportion of patients with normal ALT
- Suppression of HBV-DNA to < 20,000 IU/mL, < 2,000 IU/mL, undetectable, and change from baseline

- Combined endpoint of HBeAg seroconversion and HBV-DNA < 20,000 IU/mL, and combined endpoint of HBeAg seroconversion and HBV-DNA < 2,000 IU/mL.
- Quantitative values of serum ALT, HBV-DNA, HBeAg, and HBsAg, and their change from baseline.

Table 3: Summary of Trial to be assessed in the Statistical Review

Trial ID	Design	Study Population	Treatment/ Sample Size	Endpoint/Analysis
YV25718	Phase 3, randomized, controlled, parallel-group, open-label study to evaluate efficacy and safety of Pegasys	Pediatric patients 3 to < 18 years of age with HBeAg-positive CHB	Group A: N= 101; Group B: N=50; Group C: N=10	Primary: HBeAg seroconversion at 24 weeks after the end of treatment/principal observation. The Cochran-Mantel-Haenszel estimates of the common odds ratio was adjusted by stratification factors (genotype A vs. non-A, and baseline ALT level <5×ULN vs. >=5×ULN), and reported with 95% confidence intervals.

3.2.2 Statistical Methodology

The primary efficacy endpoint, HBeAg seroconversion at 24 weeks after treatment completion, was evaluated using Cochran-Mantel-Haenszel (CMH) estimates of the common odds ratio adjusted by stratification factors (genotype A vs. non-A, and baseline ALT level <5×ULN vs. >=5×ULN) and accompanied by the associated 95% confidence intervals. HBeAg seroconversion was defined as absence of HBeAg and presence of anti-HBe. Patients without either HBeAg or anti-HBe at follow-up Week 24 were counted as non-responders. Patients in Group B who switched to PEG-IFN after Week 48 and prior to 24 weeks post-observation period were also counted as non-responders.

Binary secondary efficacy endpoints were also assessed at follow-up Week 24. Fisher's exact test was used for these binary endpoints. Descriptive statistics were used to summarize continuous lab values over time. There was no multiplicity adjustment specified for evaluating secondary endpoints in the statistical analysis plan.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 151 patients without advanced liver fibrosis were randomized to Group A (N=101) and B (N=50) and received treatment. 12 patients with advanced liver fibrosis were assigned to PEG-IFN. Among them, 10 patients received study drug. There were 5 (10%) patients who prematurely discontinued from the study. All of them were from Group B. The reasons for

discontinuation were adverse event (1 subject) and withdrawal of consent (4 subjects) (Table 4).

Table 4: Patient disposition

	Group A	Group B	Group C
Subjects Randomized/Assigned	101	50	12
Subjects Randomized and Received at Least One Dose of Treatment	101	50	10
Subjects Prematurely Discontinuing Study Treatment	0	5 (10%)	0
Reasons for Prematurely Discontinuing Study Treatment			
Adverse Event		1 (2%)	
Withdraw Consent		4 (8%)	

Source: reviewer's analysis.

Demographic and baseline characteristics were similar between Group A and B. The majority of the subjects randomized to the two groups were 12 years of age and older, male, and Asian. In addition, the majority had BSA ≥1.09 m^2, ALT < 5xULN at baseline, HBV genotype C, and baseline fibrosis score as F1. Compared to Group B, Group A patients generally had higher mean height and weight for the age percentiles.

Compared to patients randomized to Group A and B, patients enrolled in Group C were generally younger with the majority less than 12 years old. The majority fell in the category of 0.75-1.08 m^2 for BSA, and a slightly higher mean height and weight for the age percentiles was noted. Ninety percent of the patients had a fibrosis score as F3 at baseline (Tables 5, 6).

Table 5: Patient demographic characteristics

	Statistic	Total (N=161)	Group A (N=101)	Group B (N=50)	Group C (N=10)
Age (Year)	n	161	101	50	10
	Mean	10.4	10.4	11.2	6.7
	SD	4.73	4.57	5.01	3.27
	Median	11	11	13	6
	Min, Max	3.0, 17.0	3.0, 17.0	3.0, 17.0	3.0, 12.0
Age Group	n (%)	161	101	50	10
< 5		27 (16.8)	14 (13.9)	9 (18.0)	4 (40.0)
5 - 12		55 (34.2)	39 (38.6)	11 (22.0)	5 (50.0)
>= 12		79 (49.1)	48 (47.5)	30 (60.0)	1 (10.0)
Sex	n (%)	161	101	50	10
Male		104 (64.6)	64 (63.4)	32 (64.0)	8 (80.0)
Female		57 (35.4)	37 (36.6)	18 (36.0)	2 (20.0)

Race	n (%)	161	101	50	10
White		49 (30.4)	32 (31.7)	15 (30.0)	2 (20.0)
Black		9 (5.6)	7 (6.9)	1 (2.0)	1 (10.0)
Asian		96 (59.6)	56 (55.4)	33 (66.0)	7 (70.0)
Other		7 (4.3)	6 (5.9)	1 (2.0)	
Body Surface Area	n (%)	161	101	50	10
0.54-0.74		20 (12.4)	9 (8.9)	9 (18.0)	2 (20.0)
0.75-1.08		46 (28.6)	31 (30.7)	9 (18.0)	6 (60.0)
1.09-1.51		43 (26.7)	30 (29.7)	12 (24.0)	1 (10.0)
>1.51		52 (32.3)	31 (30.7)	20 (40.0)	1 (10.0)
Height for age Percentile	n	161	101	50	10
	Mean	56.3	58.2	50.4	66
	SD	30.23	29.79	31.59	24.84
	Median	62.6	61.9	60	72.1
	Min, Max	0.0, 99.6	0.0, 99.6	0.1, 98.9	24.9, 99.6
Weight for age Percentile	n	161	101	50	10
	Mean	52.2	54	47.7	57
	SD	30.76	30.85	30.26	32.96
	Median	54.2	57.9	42.7	66.6
	Min, Max	0.3, 99.7	0.3, 99.3	0.3, 99.7	2.9, 96.9

Source: reviewer's analysis.

Table 6: Baseline disease characteristics

	Statistic	Total (N=161)	Group A (N=101)	Group B (N=50)	Group C (N=10)
ALT Group	n (%)	161	101	50	10
< 5xULN		142 (88.2)	91 (90.1)	41 (82.0)	10 (100.0)
5-10xULN		17 (10.6)	8 (7.9)	9 (18.0)	
>=10xULN		2 (1.2)	2 (2.0)		
HBV Genotype	n (%)	161	101	50	10
A		13 (8.1)	9 (8.9)	3 (6.0)	1 (10.0)
B		28 (17.4)	21 (20.8)	6 (12.0)	1 (10.0)
C		63 (39.1)	34 (33.7)	23 (46.0)	6 (60.0)
D		51 (31.7)	31 (30.7)	18 (36.0)	2 (20.0)
E & other		6 (3.7)	6 (5.9)		
Fibrosis Score	n (%)	161	101	50	10
F0		19 (11.8)	13 (12.9)	6 (12.0)	
F1		79 (49.1)	51 (50.5)	27 (54.0)	1 (10.0)

F2		53 (32.9)	36 (35.6)	17 (34.0)	
F3		9 (5.6)			9 (90.0)
HBV DNA (log10 IU/mL)	n	161	101	50	10
	Mean	8.1	8.1	8.1	7.9
	SD	0.98	0.99	0.99	0.98
	Median	8.2	8.2	8.1	8.1
	Min, Max	4.2, 11.0	4.2, 11.0	4.2, 9.6	5.7, 9.1
HBeAg (log10 IU/mL)	n	144	92	43	9
	Mean	2.7	2.7	2.6	2.3
	SD	0.59	0.5	0.65	0.98
	Median	2.8	2.9	2.8	2.6
	Min, Max	0.4, 4.1	1.5, 4.1	1.0, 3.5	0.4, 3.6
HBsAg (log10 IU/mL)	n	154	101	43	10
	Mean	4.3	4.3	4.4	4.2
	SD	0.69	0.69	0.73	0.52
	Median	4.4	4.4	4.5	4.2
	Min, Max	1.3, 5.6	1.3, 5.5	2.2, 5.6	3.6, 5.2

Source: reviewer's analysis.

3.2.4 Results and Conclusions

As shown in Table 7, 26 patients (25.7%) in Group A and 3 patients (6%) in Group B had HBeAg seroconversion at follow up Week 24, with an odds ratio of 5.43 and 95% CI: (1.54 to 19.2), and a p-value 0.0043 (using CMH test). Thirty-three patients in Group B switched to PEG-IFN after 48 weeks of the principal observation period. Among them, 29 patients did not complete Week 24 follow-up. For the 17 patients in Group B who did not switch, 6 patients did not complete 24 weeks follow-up (5 patients had early discontinuation, and 1 patient had HBeAg seroconversion result as "no" at follow-up Week 12). All of those 35 patients who did not have follow-up Week 24 data were counted as non-responders for the primary analysis according to Applicant. A published paper (Liaw, 2009) shows the natural HBeAg seroconversion rate for children >3 years is 4-5% per year, which is consistent with the observed HBeAg seroconversion rate for Group B.

Results from secondary binary endpoints are also listed in Table 7. Numerically, the findings further support the efficacy of PEG IFN. Of note, the Applicant reported p-values for the secondary endpoints which were not adjusted for multiplicity.

Within Group C, 3 patients (30%, with 95% CI 6.7% to 65.2%) achieved HBeAg seroconversion at 24 weeks after treatment completion, which is similar to the seroconversion rate in Group A (Table 8).

Table 7: Primary and secondary efficacy results comparing two treatment groups

	Group A (N=101)	Group B (N=50)	OR (95%CI)	p-value
Primary Endpoint				
HBeAg seroconversion	26 (25.7%)	3 (6%)	5.43 (1.54, 19.2)[1]	0.0043
Secondary Endpoint				
Loss of HBeAg	26 (25.7%)	3 (6%)	5.43 (1.52, 29.32)[2]	
HBsAg seroconversion	8 (7.9%)	0 (0%)		
Loss of HBsAg	9 (8.9%)	0 (0%)		
Normal ALT	52 (51.5%)	6 (12%)	7.78 (2.91, 24.05) [2]	
HBV-DNA < 20000 IU/mL	34 (33.7%)	2 (4%)	12.18 (2.85, 108.26) [2]	
HBV-DNA < 2000 IU/mL	29 (28.7%)	1 (2%)	19.74 (3.02, 822.19) [2]	
HBV-DNA undetectable	17 (16.8%)	1 (2%)	9.92 (1.45, 422.73) [2]	
HBeAg seroconversion and HBV-DNA < 20000 IU/mL	23 (22.8%)	2 (4%)	7.08 (1.61, 64.02) [2]	
HBeAg seroconversion and HBV-DNA < 2000 IU/mL	20 (19.8%)	1 (2%)	12.1 (1.8, 511.5) [2]	

Source: reviewer's analysis.

[1] Cochran-Mantel-Haenszel estimates of the common odds ratio and 95% CI, adjusted by stratification factors: genotype A vs. non-A, and baseline ALT level <5×ULN vs. >=5×ULN.

[2] Exact odds ratio and confidence limits.

Table 8: Binary outcomes for Group C

	Group C (N=10)	
	Frequency	95% CI[1]
HBeAg seroconversion	3 (30%)	6.7%, 65.2%
Loss of HBeAg	3 (30%)	6.7%, 65.2%
HBsAg seroconversion	0	
Loss of HBsAg	0	
Normal ALT	7 (70%)	34.8%, 93.3%
HBV-DNA < 20000 IU/mL	7 (70%)	34.8%, 93.3%
HBV-DNA < 2000 IU/mL	7 (70%)	34.8%, 93.3%
HBV-DNA undetectable	3 (30%)	6.7%, 65.2%
HBeAg seroconversion and HBV-DNA < 20000 IU/mL	3 (30%)	6.7%, 65.2%
HBeAg seroconversion and HBV-DNA < 2000 IU/mL	3 (30%)	6.7%, 65.2%

Source: reviewer's analysis.

[1] 95% CI was constructed using Clopper-Pearson method.

Compared to untreated Group B, viral markers including HBV DNA, HBeAg, and HBsAg for Group A decreased over time during the treatment period. Those changes in Group C appeared to be consistent with what was observed in Group A (Figures 2-4).

Mean ALT change from baseline increased after study/treatment initiation through Week 12 and then declined during treatment period for both Groups A and B. For Group C, there was no apparent ALT change for the first 12 weeks, and then a decline was observed through the end of the treatment (Figure 5).

Figure 2: Log10 HBV DNA, Change from Baseline and 95% CI

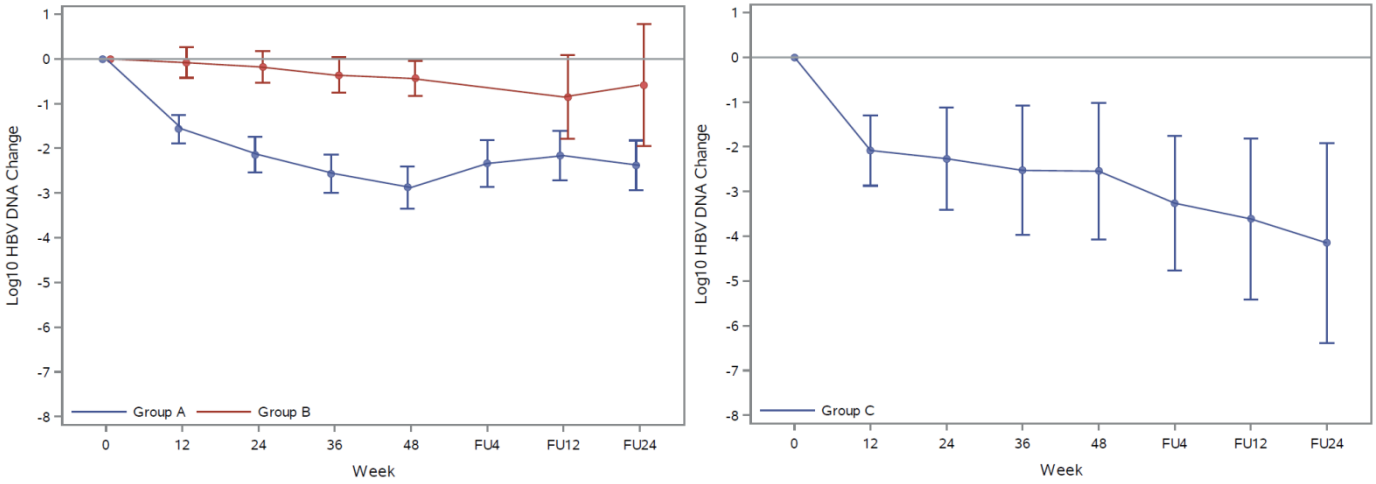


Figure 3: Log10 HBeAg DNA, Change from Baseline and 95% CI

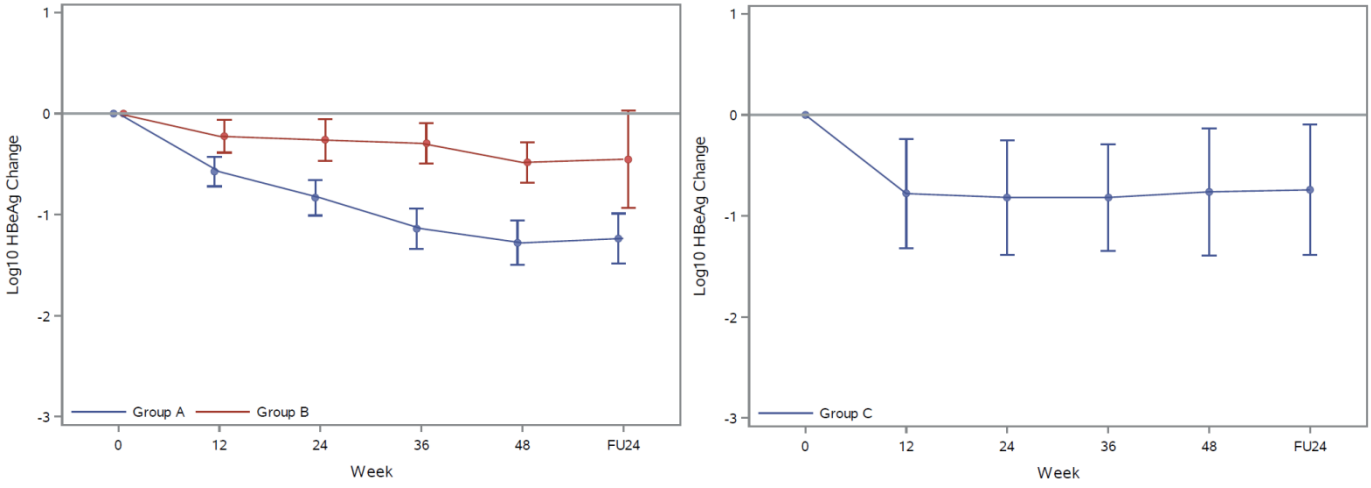


Figure 4: Log10 HBsAg DNA, Change from Baseline and 95% CI

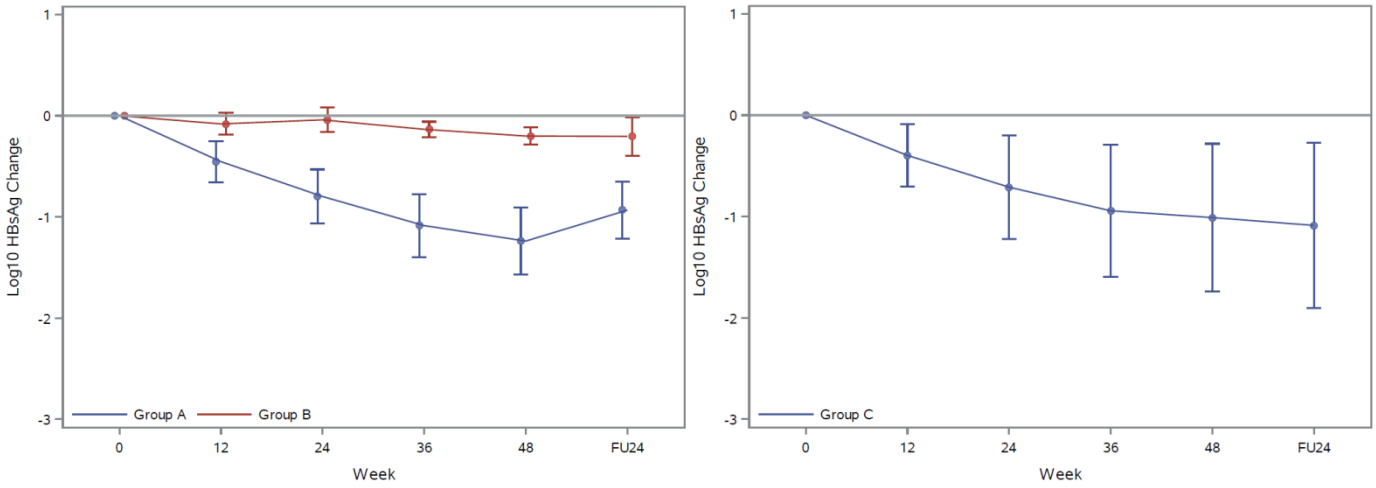
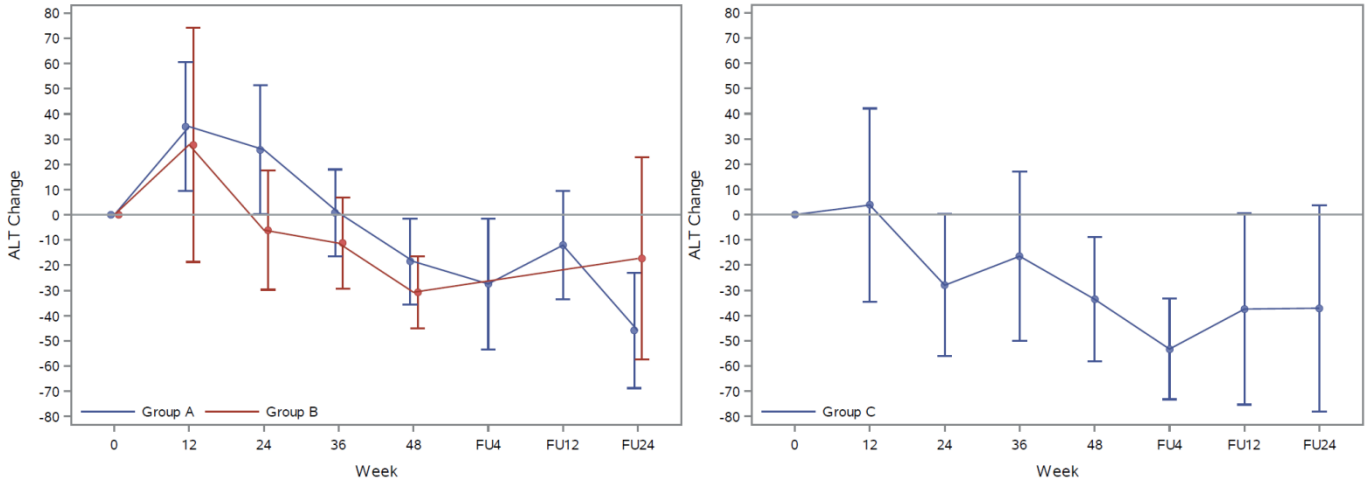


Figure 5: ALT, Change from Baseline and 95% CI



3.3 Evaluation of Safety

Please refer to the clinical review for details.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For the subgroup analysis, the numbers of patients (with proportion and 95% CI) with HBeAg seroconversion are presented (Table 9). The results were relatively consistent across age groups, sex, race, body surface area (BSA), and baseline disease status categories for the treatment difference between groups A and B. Group A and C had similar HBeAG seroconversion rates for the subgroups. Results from subgroup analysis should only be considered exploratory due to small sample sizes.

Table 9: HBeAg seroconversion by subgroups

	Group A (N=101)	Group B (N=50)	Group C (N=10)
Age Group			
< 5	6 (42.9%)	0	2 (50%)
5 - 12	10 (25.6%)	1 (9.1%)	1 (20%)
>= 12	10 (20.8%)	2 (6.7%)	0
Sex			
Male	16 (25%)	2 (6.3%)	3 (37.5%)
Female	10 (27%)	1 (5.6%)	0
Race			
White	5 (15.6%)	1 (6.7%)	1 (50%)
Black	1 (14.3%)	0	0
Asian	19 (33.9%)	2 (6.1%)	2 (28.6%)
Other	1 (16.7%)	0	0
Body Surface Area			
0.54-0.74	3 (33.3%)	0	1 (50%)
0.75-1.08	11 (35.5%)	1 (11.1%)	2 (33.3%)
1.09-1.51	7 (23.3%)	1 (8.3%)	0
>1.51	5 (16.1%)	1 (5%)	0
ALT Group			
< 5xULN	24 (26.4%)	1 (2.4%)	3 (30%)
5-10xULN	2 (25%)	2 (22.2%)	0
>=10xULN	0	0	0
HBV Genotype			
A	3 (33.3%)	1 (33.3%)	0
B	7 (33.3%)	0	1 (100%)
C	13 (38.2%)	1 (4.3%)	1 (16.7%)
D	3 (9.7%)	1 (5.6%)	1 (50%)
E & other	0	0	0
Fibrosis Score			
F0	4 (30.8%)	0	0
F1	11 (21.6%)	1 (3.7%)	1 (100%)
F2	11 (30.6%)	2 (11.8%)	0
F3	0	0	2 (22.2%)

Source: reviewer's analysis. Note: each cell presents number of patient with HBeAg seroconversion (percentage).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The Applicant claimed that the PEG IFN group was significantly better than the untreated control group for some of the secondary endpoints that had p-values < 0.05. However, those p-values were not adjusted for multiplicity resulting in the potential inflation of the type-I error rate. Moreover, some of those secondary endpoints may not be clinically relevant.

5.2 Collective Evidence

The submitted data for Study YV25718 provided evidence of the efficacy of Pegsys at follow up Week 24 for the treatment of HBV infected pediatric patients:

- The HBeAg seroconversion rate in the PEG-IFN treated patients was statistically significantly higher than the rate among untreated patients.
- Results for the secondary endpoints were supportive of treatment effect that favored PEG-IFN over untreated control.
- The advanced liver fibrosis patients treated with PEG-IFN had similar HBeAg seroconversion rates as compared to those without advanced fibrosis.

5.3 Conclusions and Recommendations

The results from the submitted study supported the efficacy of Pegsys at follow up Week 24 for treating HBeAg positive pediatric patients 3 years of age and older.

5.4 Labeling Recommendations

(b) (4)

. We recommend those (b) (4) be removed.

Reference

Liaw YF, HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. Hepatol Int. 2009 Sep;3(3):425-33. doi: 10.1007/s12072-009-9140-3.

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/s/

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09/08/2017

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