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 # / Supplement:	21356/57
Drug Name:	VIREAD® (Tenofovir Disoproxil Fumarate [TDF])
Indication(s):	Treatment of chronic Hepatitis B infection in pediatric patients 2 to < 12 years of age
Applicant:	Gilead Sciences, Inc.
Date(s):	Submitted date: 06/14/2018
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Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Karen Qi, Ph.D.
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Keywords: chronic hepatitis B infection, Cochran-Mantel-Haenszel test, confidence interval based on inverting a two-sided test

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1. EXECUTIVE SUMMARY

Gilead has submitted a supplemental New Drug Application (sNDA) 21356 in support of approval of TDF for the treatment of chronic hepatitis B (CHB) infection in pediatric subjects aged 2 to < 12 years. The application included an interim Week 48 clinical study report for Study GS-US-174-0144 (referred as Study 0144 hereafter), an ongoing Phase 3, randomized and double-blinded study. Pediatric patients were randomized in a 2:1 ratio to receive either TDF or placebo daily for 48 weeks. All patients switched to receive open-label TDF after Week 48. The primary efficacy endpoint was the proportion of subjects with HBV DNA < 69 IU/mL at Week 48. The study demonstrated that a significantly greater proportion of subjects in the TDF group achieved HBV DNA < 69 IU/mL at Week 48 compared with the placebo group (77% vs. 7%). TDF treatment also led to a higher proportion of subjects with ALT normalization at Week 48 than placebo (66% vs. 15% by central lab standard). The two treatment groups had similar proportion of subjects with HBeAg loss (30% vs. 28%) and proportion of subjects with HBeAg seroconversion (25% vs. 24%) at Week 48. There were no statistical issues and the reviewer concluded that results from Study 0144 provided adequate evidence of efficacy of TDF in treatment of pediatric subjects aged 2 to < 12 years infected with CHB.

2. INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health problem. It is estimated that 257 million people worldwide are infected with HBV according to WHO (http://www.who.int/news-room/fact-sheets/detail/hepatitis-b). It can result in either acute or chronic infection. Chronic hepatitis B (CHB) infection can cause chronic liver infection which can develop into liver cirrhosis or liver cancer. Children infected with HBV are more likely to develop chronic infection than adults. Approximately 30 to 50% children infected HBV before the age of 6 years develop chronic infections, whereas less than 5% adults infected HBV lead to chronic infections.

TDF was approved for the treatment for the treatment of CHB in adults and pediatric patients 12 years of age and older as well as for the treatment of HIV-1 infection in adults and children 2 years of age and older. In order to address the postmarketing requirement of assessing TDF for the treatment of CHB infection in pediatric patients aged 2 to < 12 years of age, the applicant conducted Study 0144. This sNDA included the interim Week 48 clinical study report for Study 0144. The statistical reviewer evaluated the efficacy results presented in the interim clinical study report. The summary of the key elements of the study design are displayed in Table 1.

2.1 Overview

Table 1: List of Study Included in Review

Study	Design	Treatment Period	Follow-up Period	Randomization and Treatment Arm	Study Population
GS-US-174-0144	randomized, double-blind, placebo-controlled, multicenter, international	double-blind treatment phase was 48 weeks[1]	All subjects switched to open-label TDF treatment for 144 weeks after receiving double-blind treatment.	Subjects were randomized in a 2:1 ratio to the following two treatment arms: Treatment A: TDF orally (PO) once daily (n=60); Treatment B: matching placebo PO once daily (n=30).	Pediatric subjects (aged 2 to < 12 years at the time of enrollment) with chronic hepatitis B

[1]The double-blind treatment phase was 72 weeks in the original protocol. Protocol Amendment 3 reduced to 48 weeks. Amendment 3 also specified that subjects who were beyond Week 48 of their randomized treatment would switch to open-label TDF at the Week 72 visit and continue treatment until Week 192.

2.2 Data Sources

The original submitted data for the NDA were located in \\CDSESUB1\evsprod\NDA021356\0778\m5\datasets\gs-us-174-0144. The applicant's information responses to the clinical team's query of results for the age subgroups were located in \\CDSESUB1\evsprod\NDA021356\0796.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the data in this NDA was good, and the reviewer was able to conduct analyses without any concerns with the data submission.

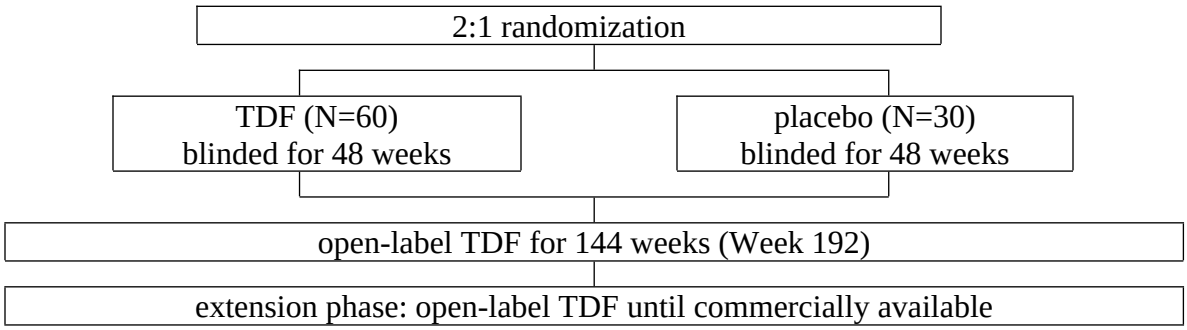
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study was entitled "A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection." Ninety TDF-naïve subjects were randomized in a 2:1 ratio to receive either TDF once daily or placebo once daily for 48 weeks. The recommended oral dose of TDF for HIV infected pediatric subjects ≥ 2 years is 8 mg/kg of body weight to a maximum of 300 mg daily. The same dosage was selected for this study. Subjects who weighed ≥ 17 kg and were able to swallow tablets received weight-based TDF as a 150, 200, 250 or 300 mg tablet or matching placebo tablet once daily. Subjects who weighed ≥ 17 kg but were unable to swallow tablets and subjects who

weighed < 17 kg received weight-based TDF as oral powder or matching placebo powder. The randomization was stratified by age (< 6 years, ≥ 6 years) and geographic region (North America/Europe and Asian). Figure 1 displays the study schema.

Figure 1: Study Schema



In the original protocol, the double-blind treatment was 72 weeks and the primary efficacy endpoint was proportion of subjects achieving HBV < 69 IU/mL at Week 72. In Protocol Amendment 3, due to the difficulty in enrolling subjects and the aim to limit exposure of subjects to placebo, the double-blind treatment was shortened to 48 weeks and the primary efficacy endpoint was changed from Week 72 to Week 48. The amendment specified that all subjects would switch to receive open-label TDF treatment up to Week 192 upon completing 48 weeks of blinded treatment, and that subjects who were beyond Week 48 under the previous protocol would switch to open-label TDF at Week 72. In Protocol Amendment 4, an extension phase was added, where all subjects who completed the study were offered to continue receiving open-label TDF until the time that TDF became commercially available for subjects of their age and weight in the country of their enrollment.

Plasma HBV NDA levels, laboratory analyses, vital signs, adverse events and concomitant medications were measured at screening, baseline, Weeks 4, 8, every 8 weeks thereafter up to Week 96, and then every 12 weeks thereafter up to the end the study (or at early discontinuation or during the extension phase, if applicable). HBV serology, including HBsAg, HBeAg, and reflex hepatitis B e antibody and hepatitis B surface antibody, were assessed at screening, baseline, and every 12 weeks through the end of study.

The primary efficacy endpoint was the proportion of subjects with HBV DNA < 69 IU/mL (400 copies/mL) at Week 48. The primary efficacy endpoint was the same as in the trials for adult patients.

The key secondary efficacy endpoint was the proportion of subjects with HBeAg seroconversion at Week 48. The definition of HBeAg seroconversion at Week 48 included 1) HBeAg loss defined as change of HBeAg test result from positive at baseline to negative at Week 48 with HBeAb negative or missing at baseline, and 2) change of

HBeAb test result from negative or missing at baseline to positive at Week 48. The other secondary efficacy endpoints evaluated at Week 48 were as follows:

- proportion of subjects with normal ALT
- proportion of subjects with normalization of ALT defined as change from abnormal ALT at baseline to normal ALT at Week 48
- composite endpoint of proportion of subjects with HBV DNA < 69 IU/mL and normal ALT
- proportion of subjects with HBV DNA < 29 IU/mL (169 copies/mL)
- proportion of subjects with HBsAg loss defined as change of HBsAg < 0.07 IU/mL result at Week 48 with HBsAg ≥ 0.07 Iu/mL at baseline and baseline HBsAb negative or missing
- proportion of subjects with seroconversion defined as HBsAg loss and change of HBsAb negative or missing at baseline to HBsAb positive at Week 48
- sequence changes from baseline within the HBV polymerase for subjects who were viremic (i.e., HBV DNA ≥ 69 IU/mL)

3.2.2 Statistical Methodologies

A. Efficacy Population

The efficacy analyses were conducted based on the dataset including all randomized subjects who have received at least one dose of study drug.

B. Analysis Windows

Study Day 1 was defined as the day when the first dose of blinded study drug was taken. Subject visits might not occur on the protocol specific days. Observations were assigned to analysis windows for the purpose of analyses. The lower limit of a visit window was defined as half of the duration of time between the previous study visit and the specific study visit, while the upper limit of a visit window was defined as half of the duration of time between the specific study visit and the one afterwards. Table 8 and Table 9 in appendix displays the analysis windows for endpoints related to HBV DNA, ALT and HBV serology.

C. Efficacy Analysis

The Cochran-Mantel-Haenszel (CMH) test controlling for the age at baseline (< 6, ≥ 6 years) and region (North America/Europe, Asia) was applied to compare the treatment difference in the primary efficacy endpoint between the two treatment groups. In the analysis, the missing data was imputed as failures. Fisher's exact test was also used to analyze the primary endpoint as a sensitivity analysis.

A sequential gatekeeping procedure was used. The key secondary efficacy endpoint of the proportion of subjects with HBeAg seroconversion at Week 48 would be tested at a

significant level of 0.05 only if the primary efficacy endpoint of the proportion of subjects with HBV DNA < 69 IU/mL at week 48 was statistically significant at a 0.05 level.

The subgroup analyses for the primary efficacy endpoint were planned to be conducted in the following subgroups:

- Baseline ALT: a) ≤ 2 x ULN, and b) > 2 x ULN
  - By AASLD normal range (ULN is 30 U/L for pediatric subjects)
  - By central lab normal range (ULN is 34 U/L for females between 2-15 years old or males between 1-9 years old and 43 U/L for males between 10-15 years old)
- Gender: a) male, and b) female
- Age at baseline: a) < 6 years old, and b)
- Region: a) Asia, and b) North America/Europe
- Baseline HBV DNA: a) <8 $\log_{10}$ IU/mL, and b) ≥ 8 $\log_{10}$ IU/mL

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows the patient disposition. All randomized subjects except for one placebo subject received at least one dose of study drug. Approximately 93% subjects in the TDF group and 90% in the placebo group completed the 48-week double-blind treatment. In the TDF group, subjects discontinued the drug due to consent withdrawal and noncomplicance. In the placebo group, subjects discontinued due to AE or consent withdrawal.

Table 2: Patient Disposition at Week 48

	TDF	Placebo
Randomized	60	30
Treated	60 (100%)	29 (100%)
Completed study treatment	56 (93%)	26 (90%)
Discontinued study treatment	4 (7%)	3 (10%)
AE	0	2 (7%)
Subject noncompliance	1 (2%)	0
Withdrew consent/assent	3 (5%)	1 (3%)

Source: Table 9 in Study GS-US-174-0144 Interim Week 48 Clinical Study Report

Table 3 and Table 4 display patient demographic and selected baseline disease characteristics in both groups. Among all randomized and treated subjects, the average age (standard deviation [SD]) was 6 (2.8) years. The majority of the subjects were male (56%) and Asian (65%).

All subjects were HBsAg positive at baseline. All subjects except for four subjects in TDF group were HBeAg positive at baseline. A greater proportion of subjects in the place group had received prior HBV treatment as compared to the subjects in the TDF groups, primarily with interferon alfa and/or lamivudine.

Table 3: Demographics and Selected Baseline Characteristics (All Treated)

	TDF (N=60)	Placebo (N=29)	Total (N=89)
Age			
Mean (SD)	6 (2.5)	7 (3.2)	6 (2.8)
Median	6	7	6
Q1, Q3	4, 8	5, 10	4, 9
Min, Max	2, 11	2, 12	2, 12
< 6 years	22 (37%)	11 (38%)	33 (37%)
≥ 6 years	38 (63%)	18 (62%)	56 (63%)
Gender			
Male	33 (50%)	17 (59%)	50 (56%)
Female	27 (45%)	12 (41%)	39 (44%)
Race			
Asian	41 (68%)	17 (59%)	58 (65%)
Indian	9 (15%)	5 (17%)	14 (16%)
Non-Indian	32 (53%)	12 (41%)	44 (49%)
Black or African American	4 (7%)	1 (3%)	5 (6%)
White	15 (25%)	11 (38%)	26 (29%)
Ethnicity			
Not Hispanic/Latino	60 (100%)	29 (100%)	89 (100%)
Region			
North America/Europe	27 (45%)	13 (45%)	40 (45%)
Asia	33 (55%)	16 (55%)	49 (55%)
Weight (kg)			
Mean (SD)	23 (8.8)	26 (12.1)	24 (10.0)
Median	21	23	21
Q1, Q3	16, 28	17, 35	16, 28
Min, Max	10.5, 51	11, 55	10.5, 55.0

Source: Table11 in Study GS-US-174-0144 Interim Week 48 Clinical Study Report

Table 4: Selected Baseline Disease Characteristics (All Treated)

	TDF (N=60)	Placebo (N=29)	Total (N=89)
HBV DNA (log_{10} IU/mL)			
Mean (SD)	8.1 (0.7)	8.1 (1.3)	8.1 (0.9)
Median	8.2	8.3	8.2
Q1, Q3	7.8, 8.6	7.9, 8.8	7.8, 8.7
Min, Max	5.7, 9.4	2.6, 9.2	2.6, 9.4
HBsAg			
Positive	60 (100%)	29 (100%)	89 (100%)
HBeAg			
Positive	56 (93%)	29 (100%)	85 (96%)
Negative	4 (7%)	0	4 (4%)
HBeAb			
Positive	4 (7%)	0	4 (4%)
Negative	56 (93%)	29 (100%)	85 (96%)

(to be continued)

Table 4: Selected Baseline Disease Characteristics (All Treated) (continued)

ALT – Central lab			
≤ 1.5 x ULN	9 (15%)	6 (21%)	15 (17%)
> 1.5 x ULN to 5 x ULN	37 (62%)	19 (66%)	56 (63%)
> 5 x ULN to 10 x ULN	10 (17%)	4 (14%)	14 (16%)
>10 x ULN	4 (7%)	0	4 (4%)
ALT – AASLD[1]			
≤ 1.5 x ULN	7 (12%)	5 (17%)	12 (13%)
> 1.5 x ULN to 5 x ULN	35 (58%)	18 (62%)	53 (60%)
> 5 x ULN to 10 x ULN	14 (23%)	5 (17%)	19 (21%)
>10 x ULN	4 (7%)	1 (3%)	5 (6%)
Previous HBV Medication exposure			
Yes	10 (17%)	12 (41%)	22 (25%)
No	50 (83%)	17 (59%)	67 (75%)

Source: Table11 in Study GS-US-174-0144 Interim Week 48 Clinical Study Report
[1]AASLD = American Association for the Study of Liver Diseases

3.2.4 Efficacy Results

Table 5 presents the applicant's results for the primary efficacy endpoint. The proportion of subjects with HBV DNA < 69 IU/mL at Week 48 was approximately 77% in the TDF group and 7% in the placebo group. There was a statistically significant treatment difference in favor of TDF. The reviewer agreed with the applicant's results.

Table 5: Results for Primary Efficacy Endpoint (All Treated)

	TDF (N=60)	**Placebo (N=29)**	**Treatment Difference**	
			Difference (95% CI[1])	**p-value[2]**
HBV DNA < 69 IU/mL at Week 48	77% (46/60)	7% (2/29)	70% (51%, 82%)	<0.001

Source: Table15 in Study GS-US-174-0144 Interim Week 48 Clinical Study Report
[1]The exact 95% CI based on inverting a two-sided test was calculated by the statistical reviewer
[2]based on 2-sided CMH test adjusted for age at baseline and region

The applicant's results for selected secondary efficacy endpoints are summarized in **Error! Reference source not found.** and highlighted as follows:

- The two groups had similar results in the following endpoints at Week 48: proportion of subjects with HBeAg loss, proportion of subjects with HBeAg seroconversion and proportion of subjects with HBsAg loss.
- No subjects in either group achieved HBsAg seroconversion.
- Higher proportion of subjects in the TDF arm achieved normalized ALT compared to the placebo group, either by central lab or AASLD standard.
- There was a higher proportion of subjects with HBV DNA < 69 IU/mL and normalized ALT in the TDF group as compared to the placebo group.

The reviewer agreed with the applicant's results.

Table 6: Results for Selected Secondary Efficacy Endpoints (All Treated)

Efficacy Endpoints at Week 48	TDF (N=60)	Placebo (N=29)	Difference in Proportion (95% CI[1])
HBeAg loss[2]	30% (17/56)	28% (8/29)	3% (-19%, 22%)
HBeAg seroconversion[2]	25% (14/56)	24% (7/29)	1% (-20%, 19%)
HBsAg loss[3]	3% (2/60)	3% (1/29)	0% (-15%, 9%)
HBsAg seroconversion[3]	0% (0/60)	0% (0/29)	n/a
HBV DNA < 29 IU/mL	72% (43/60)	7% (2/29)	65% (46%, 77%)
Normalized ALT (Central lab)[4,5]	66% (38/58)	15% (4/27)	51% (29%, 66%)
Normalized ALT (AASLD)[4,6]	52% (31/60)	18% (5/28)	34% (12%, 51%)
Normal ALT (Central lab)[5]	65% (39/60)	17% (5/29)	48% (27%, 64%)
Normal ALT (AASLD)[6]	52% (31/60)	17% (5/29)	34% (13%, 51%)
HBV DNA < 69 IU/mL and normal ALT (Central lab)[5]	53% (32/60)	7% (2/29)	46% (27%, 61%)
HBV DNA < 69 IU/mL and normal ALT (AASLD)[6]	47% (28/60)	7% (2/29)	40% (21%, 54%)

Source: Tables 16, 17, 18, 15.9.3.1 and 15.9.5.1 in Study GS-US-174-0144 Interim Week 48 Clinical Study Report
[1]The exact 95% CIs based on inverting a two-sided test were calculated by the statistical reviewer.
[2]excluding subjects who were with HBeAg negative and HBeAb positive at baseline
[3]excluding subjects who were with HBsAg negative and HBsAb positive at baseline
[4]excluding subjects who were with normal ALT at baseline
[5]Central lab normal ALT: ≤ 34 U/L for females 2-15 years or males 1-9 years, and ≤ 43 U/L for females 10-15 years
[6]AASLD normal ALT: ≤ 30 U/L for males and females 0-12 years

3.3 Evaluation of Safety

Please refer to the review report by the clinical reviewer Dr. Samer El-Kamary.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Table 7 summarizes the results for the preplanned subgroup analyses for the primary efficacy endpoint. Subjects receiving TDF treatment had consistently higher percent of subjects achieving HBV DNA < 69 IU/mL at Week 48 than placebo subjects across the subgroups.

Table 7: Subgroup Analyses for Primary Efficacy Endpoint (All Treated)

	TDF (N=60)	Placebo (N=29)	Difference (95% CI[1])
ALT at baseline (AASLD)			
≤ 2 x ULN	53% (9/17)	22% (2/9)	31% (-12%, 60%)
> 2 x ULN	86% (37/43)	0% (0/20)	86% (67%, 94%)
ALT at baseline (Central lab)			
≤ 2 x ULN	60% (12/20)	20% (2/10)	40% (0%, 66%)
> 2 x ULN	85% (34/40)	0% (0/19)	85% (65%, 93%)
Age			
< 6 years	55% (12/22)	9% (1/11)	45% (10%, 67%)
≥ 6 years	89% (34/38)	6% (1/18)	84% (61%, 93%)

(to be continued)

Table 7: Subgroup Analyses for Primary Efficacy Endpoint (All Treated) (continued)

Region			
North America/Europe	63% (17/27)	0% (0/13)	63% (36%, 78%)
Asia	88% (29/33)	13% (2/16)	75% (47%, 89%)
HBV DNA at baseline			
< 8 $\log_{10}$ IU/mL	88% (22/25)	25% (2/8)	63% (25%, 85%)
≥ 8 $\log_{10}$ IU/mL	69% (24/35)	0% (0/21)	69% (50%, 81%)

Source: Table19 in Study GS-US-174-0144 Interim Week 48 Clinical Study Report
[1]The exact 95% CIs based on inverting a two-sided test were calculated by the statistical reviewer.

It was noticed that the treatment difference between TDF and placebo groups was smaller in the subgroup of younger children compared to that in the subgroup of older children. The clinical team requested the applicant provide the potential reasons for the lower response rate for TDF treatment in the younger children than that in the older children. The applicant's responses are highlighted as follows:

1) In the < 6 years old subgroup, 10 out of 22 subjects (45%) receiving TDF treatment were considered treatment failure at Week 48, including five subjects (23%) who had missing data at Week 48 and five subjects (23%) who did not achieve HBV DNA < 69 IU/mL at Week 48.

    a. Of the five subjects who had missing data at Week 48, four subjects withdrew from the study before Week 48 and one subject remained in the study. The subject remaining in the study missed Week 48 visit, achieved HBV DNA < 69 IU/mL at Week 40, and remained HBV DNA < 69 IU/mL at all subsequent time points when assessed through Week 144.

    b. Of the five subjects who did not achieve HBV DNA < 69 IU/mL at Week 48, three subjects had delayed treatment response and achieved HBV DNA < 69 IU/mL after Week 48.

2) In the ≥ 6 years old subgroup, no subjects had missing data at Week 48.

In summary, the updated data showed that 4 out of the 10 subjects receiving TDF treatment in the < 6 years old subgroup who were considered treatment failure at Week 48 actually achieved HBV DNA < 69 IU/mL after Week 48. In the reviewer's opinion, the updated data for these subjects should not be used in the Week 48 analysis since the updated data are unavailable for the remaining subjects in the study.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no statistical issues.

5.2 Collective Evidence

The sNDA included an interim Week 48 clinical study report for Study 0144 for evaluation of safety and efficacy of TDF compared with placebo for the treatment of CHB infection in pediatric patients aged 2 to < 12 years. In the primary efficacy analysis, the proportion of subjects with HBV DNA < 69 IU/mL at Week 48 significantly higher than the placebo group. In addition, the TDF treatment yielded a greater proportion of ALT normalization at Week 48 compared with the placebo patients. The two treatment groups had similar results in the following secondary efficacy endpoints at Week 48: proportion of subjects with HBeAg loss, proportion of subjects with HBe Ag seroconversion, proportion of subjects with HBsAg loss, and proportion of subjects with HBs seroconversion.

5.3 Conclusions and Recommendations

The reviewer concluded that results from Study 0144 indicated that TDF treatment was effective in treatment of pediatric subjects aged 2 to <12 years.

6. Appendix

Table 8: Analysis Windows for HBV DNA and ALT

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	41
Week 8	56	42	83
Week 16	112	84	139
Week 24	168	140	195
Week 32	224	196	251
Week 40	280	252	307
Week 48	336	308	363
Week 56	392	364	419
Week 64	448	420	475
Week 72	504	476	531
Week 80	560	532	587
Week 88	616	588	643
Week 96	672	644	713
Week 108	756	714	797
Week 120	840	798	881
Week 132	924	882	965
Week 144	1008	966	1049
Week 156	1092	1050	1133
Week 168	1176	1134	1217
Week 180	1260	1218	1301
Week 192	1344	1302	1385

Source: Table 3-2 in Statistical Analysis Plan for Study GS-US-174-0144

Table 9: Analysis Windows for HBV Serology and qHBsAg

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 16	112	2	167
Week 32	224	168	279
Week 48	336	280	391
Week 64	448	392	475
Week 72	504	476	531
Week 80	560	532	615
Week 96	672	616	713
Week 108	756	714	797
Week 120	840	798	881
Week 132	924	882	965
Week 144	1008	966	1049
Week 156	1092	1050	1133
Week 168	1176	1134	1217
Week 180	1260	1218	1301
Week 192	1344	1302	1385

Source: Table 3-4 in Statistical Analysis Plan for Study GS-US-174-0144

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