DEPARTMENT OF HEALTH AND HUMAN SERVICES

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STATISTICAL REVIEW AND EVALUATION

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PRODUCT NAME: HEPLISAV (Hepatitis B Virus Vaccine)

SPONSOR: Dynavax Technologies Corporation

INDICATION: Prevention of infection caused by all known subtypes of hepatitis B virus in adults age 18 through 70 years

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1 EXECUTIVE SUMMARY

1.1 Overview. This study evaluates the safety and efficacy of HEPLISAV, a new vaccine under clinical development by Dynavax Technologies Corporation, for the prophylaxis of Hepatitis B virus (HBV). The vaccine comprises 1018 ISS adjuvant and recombinant HBsAg derived from Hansenula polymorpha yeast cells. HEPLISAV, intended to be administered as 2 vaccinations at Weeks 0 and 4, was compared to the licensed Engerix-B (GlaxoSmithKlline) administered as 3 vaccinations at Weeks 0, 4, and 24. The maximum duration of a subject's participation in the study was 56 weeks, which included a screening period up to 4 weeks prior to the first vaccination, a 24-week treatment period with injections administered at Weeks 0, 4, and 24, and a follow-up of 28 weeks. The evaluation was a non-inferiority comparison with seroprotection rate (SPR) as the primary immunogenicity endpoint. The study groups were randomized, parallel, conducted in two pivotal trials, where each trial enrolled about 2400 healthy, adolescent, and adult subjects with ages ranging 11-70 years. The review results are summarized in Table 1.1, with details provided in the main body of the review. In essence, both pivotal trials demonstrated non-inferiority of the HEPLISAV's immune response measured in SPR, compared to the Engerix-B vaccine. The pre-specified non-inferiority margin of -10% on the SPR difference (HEPLISAV – Engerix-B) was far exceeded by the observed 95% CI lower bounds of +10.6% and +14.7% (Table 1.1, col. 4) in the two pivotal trials, respectively.

Additionally, despite both trials meeting the primary immunogenicity endpoint, study DV2-HBV-10 yielded somewhat higher immunogenicity results in SPR and GMC and by arms (Table 1.1 cols. 2,3,5,6), compared to the other study DV2-HBV-16. This may be partly due to the younger-age coverage of 11-55 years in the former study compared to the age coverage of 40-70 years in the latter, and as it will be seen later (from Table 2.3.3b and Table 3.3.3), the relatively younger age group had higher levels of immune response.

Table 1.1: Seroprotection rate[*] (SPR,%) and Geometric Mean Concentrations (GMC) in HEPLISAV and Engerix-B arms, by Studies (Per-Protocol Population)

Study	SPR HEPLISAV	SPR Engerix-B	SPR Difference (HEPL-Eng) (95% CI)	GMC HEP-LISAV	GMC Engerix-B	GMC Ratio (HEPL/Eng) (95% CI)
(Column=1)	(2)	(3)	(4)	(5)	(6)	(7)
DV2-HBV-10, N=2101[§]	95.1	81.1	14.0[†,b] (10.6, 17.6)	138.2	350.7	0.39 (0.32, 0.48)
DV2-HBV-16, N=1482[§,a]	90.0	70.5	19.6[‡,b] (14.7, 24.7)	93.0	61.4	1.51 (1.12, 2.04)

[*]Primary Efficacy Endpoint, defined as HBsAg ≥ 10 mIU/mL; [§]Allocation ratio (HEPLISAV vs Engerix-B) was 3:1 for DV2-HBV-10 and 4:1 for DV2-HBV-16; [a]Lot consistency subjects; For primary efficacy comparison, [†]HEPLISAV was measured @Week 12 and Engerix-B @ Week 28, [‡] HEPLISAV was measured @Week 12 and Engerix-B @ Week 32. [b]Applicant's results [BLA 125428/0, DV2-HBV-10 (p.63/204), DV2-HBV-16 (p.83/215)], also reproduced by the reviewer.

With regard to safety evaluation, most AEs related to the post-injection local and systemic reactions, did not reveal major differences from the comparator vaccine Engerix-B. Additionally, the study reported 8 adverse events of special interest in the

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HEPLISAV group and 4 in the Engerix-B group. These included potential autoimmune cases (Table 4.3.3), particularly in the HEPLISAV arm, prompting closer examination by the clinical team. Please refer to the medical reviews for assessment of these AEs.

1.2 Pivotal Clinical Studies. Study DV2-HBV-16 investigated the non-inferiority of the immune response to HEPLISAV vaccination as measured by SPR at 8 weeks after the last active dose (Week 12), in healthy subjects 40-70 years of age, and in comparison to the licensed Engerix-B vaccine. For Engerix-B, the SPR was measured at Week 32 following injections at Weeks 0, 4, and 24, i.e., 8 weeks after the last dose. The study was conducted at 29 study centers in the USA and at 3 study sites in Canada. This study also investigated the clinical consistency of three manufacturing lots and evaluated the immnunogenicity bridging between these lots combined and a different lot that had "minor" differences in manufacturing process. Another pivotal study DV2-HBV-10 also evaluated the non-inferiority of the seroprotection rate (SPR) of HEPLISAV at Week 12, following injections at Weeks 0 and 4, to the SPR at Week 28 following injection with Engerix-B at Weeks 0, 4, and 24, in healthy subjects 11-55 years of age (18-55 years in Germany). This study was conducted at 14 study centers in Canada and 7 study centers in Germany.

1.3 Reviewer's Main Conclusions and Recommendations

1. Overall, the BLA demonstrated that, in both pivotal studies, the primary immunogenicity endpoint of seroprotection with HEPLISAV vaccine met the non-inferiority criterion when compared with Engerix-B vaccine. From Table 1.1, with the observed SPRs in the HEPLISAV and Engerix-B arms being respectively 95.1% and 81.1%, the 95% CI lower bound of the difference (HEPLISAV – Engerix-B) was +10.6% in study DV2-HBV-10. In study DV2-HBV-16, such observed lower limit was +14.7%. Both of these lower limits far exceeded the pre-specified margin of -10%, supporting HEPLISAV's non-inferiority in terms of SPR in both studies.

2. The applicant stated that the clinical lot consistency criterion which required the GMC ratios in the three lot-pairs to exclude both a 2/3-fold decrease and 3/2-fold increase could not be established by the pre-specified endpoint of immune response measurements at 4 weeks post last dose (i.e., Week 8) of the HEPLISAV vaccine. However, after data unblinding, the sponsor concluded that lot consistency was shown at Week 12 of the measurements, which is a post-hoc endpoint. However, lot consistency was also demonstrated for several other post hoc time points as well, suggesting that the Week 12 time point result is unlikely to be a statistical fluke. Additionally, the Week 12 time point is believed to be more clinically appropriate and was the same time point that was used for the primary immunogenicity endpoint (which was measured 8 weeks after the last dose), as well as being around the time that antibody titers peaked. The applicant's results for these analyses were, by and large, reproduced in the reviewer's analyses.

3. Immunogenicity bridging was a secondary objective. The BLA, overall, indicates comparable immunogenicities between the old lot TDG006 and the combined three new consistency lots of HEPLISAV, in terms of GMCs (Table 3.5.1). In the per-protocol population, the GMC ratios (new vs old lot) excluded both a 2/3-fold

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decrease and a 3/2-fold increase, supporting the bridging of immunogenicity results at both time points of Week 8 and Week 12. In the MITT population and at these same time points, the respective GMC ratios and confidence bounds were 1.21 (95% CI: 0.95, 1.55) and 1.20 (95% CI: 0.98, 1.47), showing the GMC ratio 95% CIs did not have marked departure from the interval (2/3, 3/2) used for bridging.

4. The excess rate of seroprotection in the HEPLISAV arm compared to Engerix-B persisted regardless of the subject's demographic characteristics and as well at different Weeks of measurements. The details are provided in Table 2.3.3b, Table 2.3.3a, Table 3.3.3, and Table 3.3.4 following major categories of age, gender, and race.

5. As with the seroprotection rate, the HEPLISAV vaccinees showed increased GMC as well compared to the Engerix-B vaccinees, over the study Weeks. The GMC with HEPLISAV rose fast at Week 8 and slowed only at Week 36. Comparatively, the GMC with Engerix-B had much slower rise and ran lower (Table 2.3.4 and Table 3.3.6).

6. Based on the reported post-injection local and systemic reactions and general AEs in the pivotal studies, no concern about the general safety profile is discerned. Two deaths were reported but were considered by the study investigator as unrelated to treatment groups. Additionally, the sponsor reported 8 adverse events of special interest in the HEPLISAV group and 4 in the Engerix-B group. These included potential autoimmune cases (Table 4.3.3), particularly in the HEPLISAV arm. Please refer to the medical reviews for evaluation of these events.

1.4 Statistical Methods

Immunogenicity

The seroprotection was defined as anti-HBsAg serum concentration ≥ 10 mIU/mL measured using the   (b) (4)   immunoassay. The sero-protection rate (SPR) was the percentage of subjects seroprotected at a given visit or Week of measurement post last dose. From pre-specification in study DV2-HBV-16, HEPLISAV would be declared non-inferior to Engerix-B as measured by SPR if the 95% confidence interval lower bound of the difference between HEPLISAV's SPR at Week 12 (8 weeks after the last dose at week 4) and Engerix-B's SPR at Week 32 (8 weeks after the last dose at week 24) exceeds the non-inferiority margin of -10%. For non-inferiority evaluation in study DV2-HBV-10, the Engerix-B's SPR was pre-specified to be measured at Week 28 (4 weeks post the last dose at week 24), instead of at Week 32 as was in study DV2-HBV-16.

To demonstrate clinical lot consistency in three manufacturing lots, the pair-wise 95% CIs for the ratios of GMCs excluded both a 2/3-fold decrease and a 3/2-fold increase per specification. The assessment of this consistency was pre-planned at Week 8 but was changed post-hoc to Week 12. The sponsor's data analysis revealed that the measurements at the pre-planned Week 8 did not satisfy the lot consistency criterion, but did so for measurements at Week 12 and for subsequent time points as well.

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The applicant's calculations for the post-hoc endpoint were, by and large, reproduced in the reviewer's results. In an additional approach which used a single statistic, called Z_{min} (Wiens and Iglewicz 1999), the overall lot consistency was examined and concluded based on the Week 12 data. Of note, the applicant's results whenever used in this review are indicated in the text with reference.

Safety

Based on the pivotal trials, the frequencies of post-injection local and systemic reactions, adverse events (AE), serious adverse events (SAE), AEs of special interest (AESI) with potential link to autoimmune diseases were summarized.

1.5 Major Statistical Findings

Efficacy

1. Based on the two pivotal studies, the BLA demonstrated that the primary immunogenicity endpoint of seroprotection with HEPLISAV met the non-inferiority criterion when compared with Engerix-B. With the observed SPRs in the HEPLISAV and Engerix-B arms being respectively 95.1% (95% CI: 93.9%, 96.1%) and 81.1% (95% CI: 77.5%, 84.4%), the 95% CI lower limit of the observed difference (HEPLISAV – Engerix-B) was +10.7% and far exceeded the pre-specified non-inferiority margin of -10% in study DV2-HBV-10. In study DV2-HBV-16, the point estimate of the SPR difference was 19.6% with 95% CI: (14.6, 24.7) and, again, the lower bound far exceeded the -10% margin, establishing all together the non-inferiority of HEPLISAV with respect to SPR. The applicant's primary efficacy results were reproduced in the reviewer's analyses.

2. The BLA stated that the three consistency lots did not satisfy the clinical lot consistency criterion at the pre-specified time point of Week 8 for measuring the anti-HBsAg results. But with the post-hoc change to Week 12 measurements, which the clinical team believes to be clinically acceptable, the consistency criterion appeared to have been met (Table 3.4.2). For each pairwise comparison between lots, a 95% CI on the ratio of GMC was contained within the limits (2/3, 3/2) -- in other words, the ratio of mean concentrations excluded both a 2/3-fold decrease and a 3/2-fold increase, the bounds that were pre-specified for lot consistency evaluation. The lots were found consistent by the Z_{min} statistic also, a method that tested for overall consistency of the three lots (reviewer's analysis). Satisfying the consistency criterion, the observed value of Z_{min} statistic (1.93) was found larger than its critical value (1.51) in the per-protocol population and as well in the ITT population with Z_{min} value (2.12) exceeding its critical value (1.52).

3. With regard to bridging, the BLA, overall, indicated comparable immunogenicity between the old lot TDG006 and the combined, three consistency lots of HEPLISAV, in terms of GMCs (Table 3.5.1). In the per-protocol population, the GMCs at Week 8 for the combined new lots and old lot were respectively 41.5 (95% CI: 36.1, 47.6) and 36.5 (95% CI: 28.9, 46.2), thereby yielding a GMC ratio of 1.14 (95% CI: 0.86, 1.49).

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For the same population at Week 12, the corresponding results were 93.0 (95% CI: 82.9, 104.2), 81.0 (95% CI: 67.2, 98.0), and 1.15 (95% CI: 0.92, 1.43). The GMC ratios excluded both a 2/3-fold decrease and a 3/2-fold increase, supporting bridging of the immunogenicity results at both time points of Week 8 and Week 12. At these same time points and in the MITT population, the respective GMC ratios and confidence bounds were 1.21 (0.95, 1.55) and 1.20 (95% CI: 0.98, 1.47), showing the GMC ratio 95% CIs did not have marked departure from the interval (2/3, 3/2) supporting, again, the bridging.

Safety

4. Based on the reported safety data in the two pivotal clinical trials in this BLA, no concern about the general safety profile arises. The study, however, reported 8 adverse events of special interest in the HEPLISAV group and 4 in the Engerix-B group. These included potential autoimmune cases (Table 4.3.3), particularly in the HEPLISAV arm. Please refer to the medical reviews regarding these AEs.

2 PROTOCOL DV2-HBV-10

Protocol Title:

A Phase III Safety and Efficacy Study to Compare Immune Responses Following Injection with Either Two Doses of HEPLISAV or Three Doses of Engerix-B.

2.1 OBJECTIVES

- **Primary Immunogenicity Objective**

  To compare the proportion of subjects who achieve seroprotection (based on anti-HBsAg ≥ 10 mIU/mL) when measured at Week 12 following vaccination with HEPLISAV at Weeks 0 and 4 to the proportion of subjects who achieve seroprotection when measured at Week 28 following vaccination with Engerix-B at Weeks 0, 4, and 24. The sero-protection rate (SPR) is the percentage of subjects seroprotected.

- **Secondary Immunogenicity Objective**

  To compare the SPR for HEPLISAV versus Engerix-B when measured at Week 4.

- **Safety Objective**

  To demonstrate the safety and tolerability of vaccination with HEPLISAV when administered to adolescent and adult subjects.

2.2 BACKGROUND AND DESIGN

This was a phase 3, randomized, multi-center, subject- and observer-blind, active-controlled study to compare immune responses following injection with either 2 doses of HEPLISAV or 3 doses of Engerix-B in approximately 2400 healthy adult subjects aged 11 through 55 years of age (18 through 55 in Germany). The study was conducted at 21 sites in Canada and Germany. For non-inferiority evaluation, the study was adequately sized with more than 90% power, using a wider range of plausible SPR values for the comparator arm, Engerix-B. Subjects were randomly allocated to HEPLISAV and Engerix-B with a 3:1 ratio.

The applicant's study design of HEPLISAV/placebo and Engerix-B injections is presented in Table 2.2.1 below. After providing informed consent and meeting eligibility criteria [which include subjects who were serum negative for

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Table 2.2.1: Study Design Scheme Showing Study Weeks/ Visits

Treatment Group	Week -4/ Visit 1	Week 0/ Visit 2	Week 4/ Visit 3	Week 8/ Visit 4	Week 12/ Visit 5	Week 24/ Visit 6	Week 28/ Visit 7/ Termination
1018ISS-HBsAg	Screen	**active vaccine**	**active vaccine**	non-treatment	primary endpoint	**placebo**	non-treatment
Engerix-B	Screen	**active vaccine**	**active vaccine**	non-treatment	non-treatment	**active vaccine**	primary endpoint

hepatitis B virus surface antigen (HBsAg), antibody to hepatitis B surface antigen, and antibody to hepatitis B virus core antigen; had no history of hepatitis B virus (HBV) infection; and, had no prior immunization with any HBV vaccine], all subjects received a total of 3 intramuscular injections (deltoid muscle) administered at Weeks 0, 4, and 24. Subjects assigned to the HEPLISAV group received active vaccine at Weeks 0 and 4. To maintain the study blind, these subjects received saline (placebo) at Week 24 administered in the same manner as the first 2 doses of HEPLISAV. Subjects assigned to Engerix-B received Engerix-B at Weeks 0, 4, and 24. Study injections for all groups were administered in the alternate arm from the previous injection. After completing Week 0, subjects returned to the clinical site at Weeks 4, 8, 12, 24, and 28 to undergo clinical safety evaluations and to have blood drawn for safety laboratory studies and antibody against hepatitis B surface antigen (anti-HBsAg) serum concentrations. A total number of 2428 subjects were enrolled and randomized. The details of the subject disposition and demographics are included in Table 2.2.2 and Table 2.2.3, respectively.

2.2.1 Subject Disposition And Demographics. The subjects were mostly white (> 90.0%), with mean age 40 years and the percentage of women 52.7. About 97% of the subjects in each treatment group completed the study. There were 81 non-completers, and among them the most common reason shown for discontinuation was 'lost to follow-up' (49.4%) followed by 'consent withdrawn' (24.7%).

Table 2.2.2: Subject Disposition, age 11-55 years

All subjects	HEPLISAV N(%)	Engerix-B N(%)	Total N (%)
Randomized	1820 (100)	608 (100)	2428 (100)
Completed study	1757 (96.5)	590 (97.0)	2347 (96.7)
Discontinued	63 (3.5)	18 (3.0)	81 (3.3)
- adverse event	2 (3.2)	2 (11.1)	4 (5.0)
- consent withdrawn	18(28.6)	2 (11.1)	20 (24.7)
- death	0	0	0
- lost to followup	30 (47.6)	10 (55.6)	40 (49.4)
- protocol violation	2 (3.2)	0	2 (2.5)
- non-compliance	3 (4.8)	2 (11.1)	5 (6.2)
- other	8 (12.7)	8 (12.7)	10 (12.4)
Per Protocol Population	1566	535	2101
Intent to Treat Analysis Population	1800	605	2405
Safety Analysis Population	1820	608	2428

Table 2.2.3: Demographic Characteristics: Safety Analysis Population.

Variable	Statistic	HEPLISAV	Engerix-B
[1]Age (years)	N	1820	608
18-39	n (%)	[2]829 (45.5)	[2]277 (45.6)
40-55	n (%)	991 (54.5)	331 (54.5)
Age (years)	N	1820	608
	Mean (sd)	39.7 (9.6)	39.8 (9.1)
	Median	41.0	41.0
	Range[3]	(33.0, 48.0)	(34.0, 47.0)
BMI (kg/m2)	N	1817	607
	Mean (sd)	27.38 (5.81)	27.61 (6.18)
	Median	26.23	26.61
	Range[3]	(23.25, 30.13)	(23.47, 30.59)
Sex :	N	1820	608
Male	n (%)	861 (47.3)	262 (43.1)
Female	n (%)	959 (52.7)	346 (56.9)
Race:	N	1820	608
Caucasian	n (%)	1699 (93.3)	558 (91.8)
Black/AfrAm	n (%)	40 (2.2)	20 (3.3)
Asian	n (%)	43 (2.4)	22 (3.6)
Other	n (%)	38 (2.1)	8 (1.3)

[1]Age is the difference between date of birth and date of consent.
[2] Eleven Heplisav vaccinees and 2 Engerix-B vaccines, all aged 11-17 years, were included in the 18-39 years age group.
[3] (1st quartile, 3rd quartile)

2.2.2 Statistical Methods.

The primary population for analysis of immunogenicity was the per-protocol population (PPP), defined as eligible subjects who received all injections as specified, had serology at their primary endpoint, and did not have major protocol violations. The modified ITT population (MITT) comprised subjects who received at least 1 injection following their baseline anti-HBsAg measurement and had at least 1 post-baseline anti-HBsAg measurement. The safety population comprised enrolled subjects who received at least 1 study injection and had any post-baseline safety data. The primary immunogenicity analysis determined the difference in SPR between HEPLISAV at Week 12 and Engerix-B at Week 28 with a two-sided 95% confidence interval (CI) on the difference (HEPLISAV - Engerix-B) in SPR. If the lower bound of this CI was above the pre-specified non-inferiority criterion (-10%), HEPLISAV would be established as non-inferior to Engerix-B in SPR. All immunogenicity analyses used one-sided tests at the 2.5% level of significance.

2.3 IMMUNOGENICITY RESULTS

Immunogenicity Analysis

Primary Objective.

Seroprotection Rates (SPR). Seroprotection was defined as the post-injection anti-HBsAG ≥ 10 mIU/mL. As the primary immunogenicity endpoint for non-inferiority evaluation based on the Per-Protocol population (PP), the SPR was measured at Week 12 following 2 injections of HEPLISAV and at Week 28 following 3 injections of Engerix-B. Table 2.3.1 presents the applicant's (Per Protocol) and reviewer's analyses (Per Protocol and modified ITT) of the proportion of vaccinees with seroprotection in the HEPLISAV and Engerix-B arms. The applicant's and reviewer's results were close

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and supported identical conclusions, each supporting non-inferiority of HEPLISAV to Engerix-B in terms of SPR.   For example, the applicant reported a 95% CI lower bound of 10.61% on the SPR mean difference (HEPLISAV – Engerix-B) of 13.9%. In the reviewer's analysis for the Per Protocol population, a similar lower bound was 10.7%, based on SPR of 95.1% (95% CI: 93.9%, 96.1%) in the HEPLISAV arm compared to 81.1% (95% CI: 77.5%, 84.4%) in the Engerix-B arm resulting in a mean difference (HEPLISAV-Engerix-B) of 14.0% with 95% CI: (10.7%, 17.6%). Each lower bound, applicant's and reviewer's, far exceeded the pre-specified non-inferiority margin of -10%, and met the non-inferiority criterion. Similar results were found in the reviewer's MITT population analysis as well, where the treatment difference's lower bound 11.6% > -10%, thus supporting non-inferiority.

Table 2.3.1: Seroprotection Rates (%) at WEEK 12 for HEPLISAV and at WEEK 28 for Engerix-B by Study Populations.

Applicant's results

Population	HEPLISAV (WEEK 12) n/N	HEPLISAV (WEEK 12) %	Engerix-B (WEEK 28) n/N	Engerix-B (WEEK 28) %	Mean difference in SPR rates (HEPLISAV – Engerix-B) (95% CI)[1]	Non-inferiority criterion
Per Protocol[*]	1479/1556	95.04	432/533	81.13	13.91 (+10.61, +17.59)	met

Adapted from BLA 125428/0, DV2-HBV-10, Table 11-1, Page 63 of 204. [*]Applicant's Table 11-1 didn't include analysis for ITT pop'n. [1]CI based on analysis adjusted for age groups

Reviewer's results

Population	HEPLISAV (WEEK 12) n/N	HEPLISAV (WEEK 12) % (95% CI)	Engerix-B (WEEK 28) n/N	Engerix-B (WEEK 28) % (95% CI)	Mean difference in SPR rates (HEPLISAV – Engerix-B) (95% CI)[1]	Non-inferiority criterion[2]
Per Protocol	1489/1566	95.1	434/535	81.1	14.0 (+10.7, +17.6)	met
Modified ITT	1687/1767	95.5	479/590	81.2	14.3 (+11.6, +17.8)	met

[1]Asymptotic method, analysis unadjusted for age groups; [2]95% CI lower bound for mean difference > -10%..
Eleven Heplisav vaccinees and 2 Engerix-B vaccines, all aged 11-17 years, were retained instead of being excluded.

Secondary Objective.

The secondary immunogenicity endpoint was the SPR measured 4 weeks after the first injection, i.e., at Week 4, in both the HEPLISAV and Engerix-B arms. The SPR at this time point was 23.7% (N=1556) with HEPLISAV and 3.9% (N=533) with Engerix-B, for the PP population. The rate-difference (HEPLISAV - Engerix-B) had a point estimate of 19.7% with 95% CI: (16.9%, 22.3%). This apparently shows HEPLISAV as being more immunogenic than Engerix-B, even at 4 Weeks after the first vaccine (Table 2.3.2).

Analyses by Weeks.

The evaluation also carried out analyses of additional endpoints measured at different subsequent Weeks.

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1. *Seroprotection Rates (SPR) by Study Weeks and Age Strata.* Table 2.3.2 provides SPRs and their differences observed at different Weeks (4, 8, 12, 24, and 28). The point estimates of the SPR difference between HEPLISAV and Engerix-B had 95% CI lower bound values ranging from 13.7% to 68.8% over the Weeks. This displayed HEPLISAV to be highly immunogenic compared to Engerix-B during the study's course. The overall, higher seroprotection rate from HEPLISAV seems to have persisted within each of the two age strata (18-39 and 40-55 years) as well and by gender and race. These results are detailed in Table 2.3.3a and Table 2.3.3b.

Table 2.3.2: Seroprotection Rates (SPR) at Weeks 8, 12, 24, and 28, Per Protocol Population

Week	HEPLISAV n/N	HEPLISAV SPR(%)	Engerix-B n/N	Engerix-B SPR(%)	Estimated difference in SPR (HEPLISAV-Engerix-B) (95% CI)
Week 4	368/1556	23.7	21/533	3.9	19.7 (16.9, 22.3)
Week 8	1381/1559	88.6	141/533	26.5	62.1 (57.9, 66.0)
Week 12	1489/1566	95.1	120/535	22.4	72.7 (68.8, 76.2)
Week 24	1531/1558	98.3	172/533	32.3	66.0 (61.9, 69.9)
Week 28	1534/1566	98.0	434/535	81.1	16.8 (13.7, 20.4)

The results in Table 2.3.3a also show a pattern of seemingly higher SPR in the younger age group, but among the HEPLISAV vaccinees the age differential apparently attenuated from Week 24 (Figure 2.3.1)).

Table 2.3.3a: Seroprotection Rate (SPR) by Study Weeks and Age Strata*, Per-Protocol Population

Week / Age(yrs) stratum	HEPLISAV N	HEPLISAV SPR(%) (95% CI)	Engerix-B N	Engerix-B SPR (%) (95% CI)
Week 4: 18-39	669	30.5 (27.0, 34.0)	225	5.8 (2.7, 8.9)
Week 4: 40-55	878	18.5 (15.9, 21.0)	306	2.6 (0.8, 4.4)
Week 8: 18-39	673	94.8 (93.1, 96.5)	225	33.3 (27.1, 39.5)
Week 8: 40-55	876	83.8 (81.3, 86.2)	306	21.2 (16.6, 25.9)
Week 12:18-39	675	98.7 (97.8, 99.5)	227	30.0 (24.0, 36.0)
Week 12: 40-55	881	92.3 (90.5, 94.0)	306	17.0 (12.8, 21.2)
Week 24:18-39	673	99.6 (99.0, 100.0)	225	39.6 (33.1, 46.0)
Week 24: 40-55	875	97.3 (96.2, 98.3)	306	27.1 (22.1, 32.1)
Week 28:18-39	675	99.3 (98.6, 99.9)	227	89.0 (84.9, 93.1)
Week 28: 40-55	881	96.9 (95.8, 98.1	306	75.2 (70.3, 80.0)

*Strata defined by sponsor

Table 2.3.3b: Seroprotection Rates (%) at WEEK 12 for HEPLISAV and at WEEK 28 for Engerix-B, by Demographic Characteristics, Per-Protocol Population.

	HEPLISAV N	HEPLISAV SPR(95% CI†)	Engerix-B N	Engerix-B SPR (95% CI)
[1]Age (yrs): 18-39	685	98.7 (97.5, 99.4)	228	89.5 (84.7, 93.1)
Age (yrs): 40-55	881	92.3 (90.3, 94.0)	307	74.9 (70.0, 80.0)
Female	839	96.0 (94.4, 97.2)	313	81.8 (77.0, 85.9)
Male	727	94.1 (92.1, 95.7)	222	80.2 (74.3, 85.2)
Caucasian	1472	95.1 (93.9, 96.2)	493	81.1 (77.4, 84.5)
Black/AfrAm	30	100.0 (88.4, 100.0)	17	88.2 (63.6, 98.5)
Other[2]	64	92.2 (82.7, 97.4)	25†	76.0 (54.9, 90.6)
All	1566	95.1 (93.9, 96.1)	535	81.1 (77.5, 84.4)

[1]Age is the difference between date of birth and date of consent. Eleven Heplisav vaccinees and 2 Engerix-B vaccinees, all aged 11-17 years, were included in the 18-39 years age group. [2] Collapsed category because of smaller frequencies.
† Exact methods.

Figure 2.3.1: SPR by Weeks, in different age-strata in Per-Protocol Population

group   ✳—✳—✳ Engerix-B, Age 18-39   ○—○—○ Engerix, Age 40-55   ◇—◇—◇ HEPLISAV Age 18-39   ⊟—⊟—⊟ HEPLISAV Age 40-55
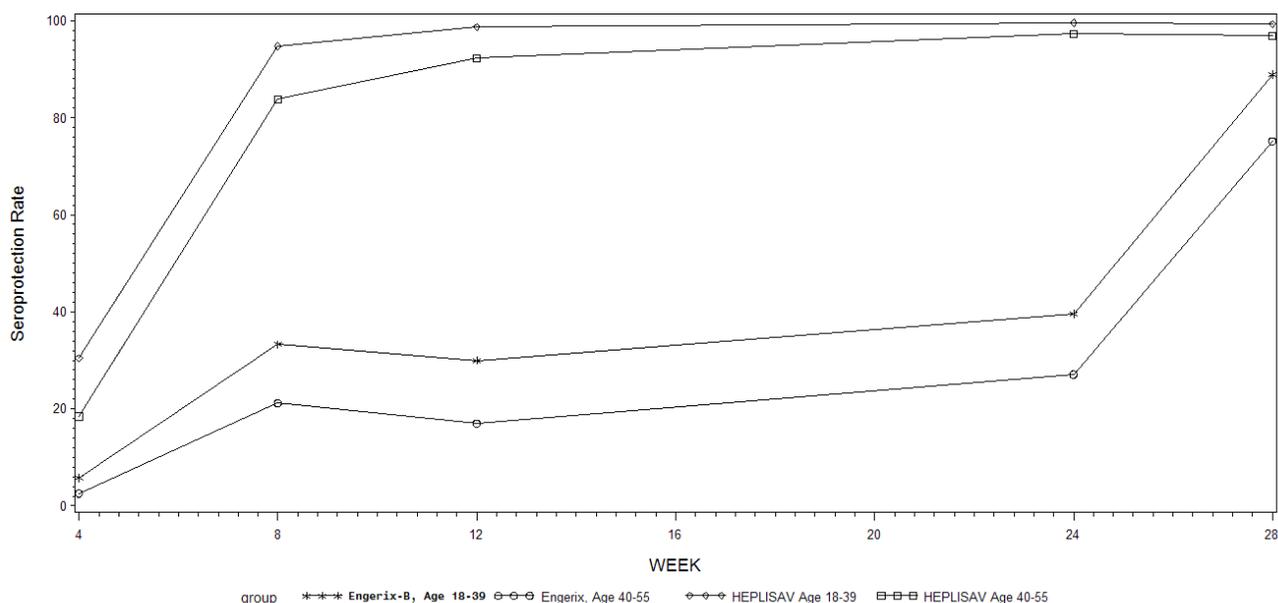
2. *Geometric Mean Concentration (GMC).* The GMCs observed at different time points from Week 4 through Week 28 (Per Protocol population) are presented in Table 2.3.4. At all visits from Week 4 through Week 24, the GMC continued to increase faster with HEPLISAV than with Engerix-B. At Week 28, HEPLISAV and Engerix-B groups reached similar GMCs, 323.20 (95% CI: 301.24, 346.76) and 350.71 (95% CI: 268.07, 458.82), respectively.

Table 2.3.4: GMC by visit, Per Protocol Population, Age 18-55 years.

Week of visit	HEPLISAV N	HEPLISAV GMC (95% CI)	Engerix-B N	Engerix-B GMC (95% CI)
Week 4	1556	5.5 (5.1, 5.9)	533	2.9 (2.8, 3.1)
Week 8	1559	82.3 (75.8, 89.3)	533	6.4 (5.6, 7.4)
Week 12	1566	138.2 (128.8, 148.4)	535	5.4 (4.8, 6.2)
Week 24	1558	345.9 (323.3, 370.1)	533	7.2 (6.3, 8.2)
Week 28	1566	323.2 (301.2, 346.8)	535	350.7 (268.1, 458.8)

3. *Seroprotection Rates (SPR) in Type 2 Diabetes Mellitus Subjects.* Table 2.3.5 presents SPRs among the Type 2 diabetes mellitus subjects by study arms. As the last column indicates, the HEPLISAV vaccinees showed an SPR difference of 49.4% (95% CI: 18.7%, 71.5%) from Engerix-B, in the per-protocol population. Similar difference was noticed for the MITT population also, 51.9% (95% CI: 24.8%, 73.0%).

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Table 2.3.5: Seroprotection Rates (%) in Subjects with Type-2 Diabetes Mellitus at WEEK 12 for HEPLISAV and at WEEK 28 for Engerix-B by Study Populations

Population	HEPLISAV (WEEK 12) n/N	HEPLISAV (WEEK 12) % (95% CI)	Engerix-B (WEEK 28) n/N	Engerix-B (WEEK 28) % (95% CI)	Mean difference in rates (HEPLISAV –Engerix-B) (95% CI)[1]
Per Protocol	38/45	84.4 (70.5, 93.5)	6/17	35.3 (14.2, 61.7)	49.4 (+18.7, +71.5)
Modified ITT	46/54	85.2 (72.9, 93.4)	6/18	33.3 (13.3, 59.0)	51.9 (+24.8, +73.0)

[1] Clopper-Pearson method.

2.4 REVIEWER's SUMMARY

1. The results of the primary immunogenicity endpoint analysis showed that 95.1% (95% CI: 93.9%, 96.1%) of the subjects who had completed full primary vaccination were seroprotected with the experimental HEPLISAV vaccine. In contrast, the proportion of seroprotection in the comparator Engerix-B arm was 81.1% (95% CI: 77.5%, 84.4%). The observed 95% CI lower bound of +10.7% on the difference (HEPLISAV- Engerix-B) in seroprotection rate far exceeded the pre-specified non-inferiority margin of -10%, and thus satisfied the non-inferiority criterion. Similar results were found in the MITT population as well, supporting non-inferiority (Table 2.3.1).

2. The excess rate of seroprotection in the HEPLISAV arm persisted over the study Weeks (Table 2.3.2), regardless of the subject's age categories (Table 2.3.3a) and demographic characteristics (Table 2.3.3b). Compared to Engerix-B, the SPR in HEPLISAV vaccinees rose sharply at Week 8 (Figure 2.3.1). The rate continued to increase at Week 12 and then appeared to have leveled off at Week 24 or later. Also, the rates seemed higher among the younger age group, regardless of the study Week of measurement (Table 2.3.3a).

3. Consistent with SPRs, the HEPLISAV vaccinees showed rapid increase of GMC over the study Weeks, compared to the Engerix-B vaccinees (Table 2.3.4). At all visits from Week 4 through Week 24, the GMC continued to increase faster with HEPLISAV than with Engerix-B. At Week 28, HEPLISAV and Engerix-B reached comparable GMCs: 323.2 (95% CI: 301.2, 346.8) and 350.7 (95% CI: 268.1, 458.8), respectively.

3 PROTOCOL DV2-HBV-16

Protocol Title:

An Observer-Blinded, Randomized, Parallel-Group, Multi-Center Study Comparing the Safety and Immunogenicity of HEPLISAV™ to Licensed Vaccine (Engerix-B®) Among Healthy Subjects 40 to 70 Years of Age.

3.1 OBJECTIVES

Primary

- To demonstrate the noninferiority of the immune response to HEPLISAV vaccination as measured by SPR at 8 weeks after the last active dose (Week 12) compared to the SPR for Engerix-B vaccination at 8 weeks after the last active dose (Week 32).

- To demonstrate lot consistency for immune response as measured by geometric mean concentration (GMC) at 4 weeks after the last active dose (Week 8) among 3 consecutively manufactured lots of HEPLISAV from the manufacturing process after minor modification.

Secondary

- To demonstrate the safety of HEPLISAV in healthy subjects 40 to 70 years of age and to compare the safety profile of HEPLISAV to that of Engerix-B in this population.

- To demonstrate consistency of immune response at 4 weeks after the last active dose (Week 8) between HEPLISAV lots prior to and after minor modifications to the manufacturing process.

- To evaluate the immune response to HEPLISAV vaccination as measured by SPR at 8 weeks after the last active dose (Week 12) compared to Engerix-B vaccination at 8 weeks after the last dose (Week 32) in subjects with a history of type 2 diabetes mellitus on enrollment.

3.2 BACKGROUND AND DESIGN

This was a phase 3, multi center, randomized, observer-blinded, active-controlled, parallel-group study to evaluate immune responses following injection with either 2 doses of HEPLISAV or 3 doses of Engerix-B, planned in approximately 2000 healthy adult subjects 40 to 70 years of age. For non-inferiority evaluation, the study was adequately sized with more than 90% power, using a wide range of plausible SPR values for the comparator arm, Engerix-B. Initially, the subjects were randomly assigned to receive

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HEPLISAV lot TDG006 (lot prior to minor manufacturing process modifications), 1 of the 3 consistency lots of HEPLISAV (TDG008 TDG009 TDG010), or Engerix-B at a 3:1:1:1:1 ratio. After reaching the target enrollment of 400 subjects for lot TDG006, the subjects were randomized to receive 1 of the 3 consistency lots or Engerix-B at a 1:1:1:1 allocation until the enrollment was complete. The overall allocation ratio of HEPLISAV to Engerix-B was 4:1. For the primary objective of non-inferiority, the allocation ratio of the 3 consistency lots to Engerix-B was 3:1. The randomization was stratified by age (ages 40 to 49 years, 50 to 59 years, and 60 to 70 years) and by site.

The applicant's study design of HEPLISAV/placebo and Engerix-B injections is presented in Table 3.2.1 below. Basically, after providing informed consent and meeting eligibility criteria, all subjects received a total of 3 intramuscular injections (deltoid muscle) administered at Weeks 0, 4, and 24. Subjects assigned to the HEPLISAV group received 0.5 mL HEPLISAV at Weeks 0 and 4. To maintain the study blind, these subjects received 0.5 mL saline (placebo) at Week 24 administered in the same manner as the first 2 doses of HEPLISAV. Subjects assigned to Engerix-B received 1.0 mL Engerix-B at Weeks 0, 4, and 24. Study injections for all groups were administered in the alternate arm from the previous injection. After completing Week 0, subjects returned to the clinical site at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 44, and 52 to undergo clinical safety evaluations and to have blood drawn for safety laboratory studies and antibody against hepatitis B surface antigen (anti-HBsAg) serum concentrations. A total number of 2452 subjects were screened and randomized.

Table 3.2.1: Study Design

Week/Visits	HEPLISAV	Engerix-B
Injection period		
Week 0, Visit 1	**Active Dose 1**	**Active Dose 1**
Week 4, Visit 2	**Active Dose 2**	**Active Dose 2**
Week 8, Visit 3	Non-treatment	Non-treatment
Week 12,Visit 4	Primary endpoint for mmunogenicity	Non-treatment
Week 18,Visit 5	Non-treatment	Non-treatment
Week 24,Visit 6	**Placebo dose 3**	**Active Dose 3**
Post-Injection period		
Week 28, Visit 7	Follow up	Follow up
Week 32, Visit 8	Follow up	Primary endpoint for immunogenicity
Week 36, Visit 9	Follow up	Follow up
Week 44, Visit 10	Follow up	Follow up
Week 52, Visit 11	Follow up	Follow up

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3.2.1 Subject Disposition And Demographics

Details of the subject disposition and demographics are included in Table 3.2.2 and Table 3.2.3, respectively.

Table 3.2.2: Subject Disposition

All subjects	HEPLISAV [1]Consistency lots N (%)	HEPLISAV [2]Lot TDG006 N (%)	Engerix-B N (%)	Total N (%)
Screened	-	-	-	3793
Randomized	1441 (100)	529 (100)	482 (100)	2452 (100)
Completed study	1335 (92.6)	484 (91.5)	450 (93.4)	2269 (92.5)
Discontinued	106 (7.4)	45 (8.5)	32 (6.6)	183 (7.5)
- adverse event	1 (0.9)	0	0	1 (0.6)
- consent withdrawn	30(28.3)	15 (33.3)	12 (37.5)	57 (31.5)
- death	0	1 (2.2)	1 (3.1)	2 (1.1)
- lost to followup	53 (50.0)	28 (62.2)	13 (40.6)	94 (51.4)
- protocol violation	3 (2.8)	0	1 (3.1)	4 (2.2)
- non-compliance	5 (4.7)	1 (2.2)	3 (9.4)	9 (4.9)
- other	14 (13.2)	0	2 (6.3)	16 (8.7)
Per Protocol Population	1123	390	359	1872
Intent to Treat Analysis Population	1426	522	475	2423
Safety Analysis Population	1441	529	482	2452

[1] Lot TDG008, Lot TDG009 and Lot TDG010 for primary efficacy evaluation;   [2] Lot to be used for bridging with consistent lots

Table 3.2.3: Demographic Characteristics: Modified Intent to Treat Population.

Variable	Statistics	HEPLISAV[1]	Engerix-B
Age[2](years)	N	1426	475
	Mean (sd)	54.0 (7.8)	53.9 (7.8)
	median	54.0	54.0
	range[3]	(48.0, 60.0)	(47.0, 60.0)
BMI (kg/m2)	N	1424	474
	Mean (sd)	30.1 (6.4)	30.0 (6.5)
	median	28.9	28.8
	range	(25.7, 33.6)	(25.5, 33.0)
Sex:	N	1426	475
Male	% (n)	47.8 (681)	49.0 (233)
Female	% (n)	52.2 (745)	51.0 (242)
Races:	N	1426	475
Caucasian	% (n)	83.0 (1183)	83.2 (395)
Black/AfrAm	% (n)	14.8 (211)	14.1 (67)
Asian	% (n)	1.0 (14)	0.8 (4)
Other	% (n)	1.3 (18)	1.9 (9)

[1] Consistency Lots (TDG008, TDG009 and TDG010). [2]Age is the difference between date of birth and date of consent. [3] (1st quartile, 3rd quartile)

3.2.2 Statistical Methods.

The primary population for examining the non-inferiority of immunogenicity was the non-inferiority per-protocol population (PPP), defined as subjects who received all injections as specified, had serology obtained within study visit windows including baseline and primary endpoint, and had no major protocol violations. The sponsor used two other per protocol populations. One was for lot consistency evaluation (LCPP), defined as subjects randomized to 1 of 3 consistency lots of HEPLISAV (TDG008, TDG009, and TDG010) who received the scheduled 2 study injections within the study visit windows, had no major protocol

deviations, and had anti-HBsAg measurements obtained within study visit windows at baseline and Week 8. And the other one was Bridging Study PP population, which comprised all subjects randomized to lot TDG006 or to 1 of 3 consistency lots of HEPLISAV (TDG008, TDG009, and TDG010) concurrently with lot TDG006 who received the scheduled 2 study injections within the study visit windows, had no major protocol deviations, and had anti-HBsAg measurements obtained within study visit windows at baseline and Week 8. The modified intent-to-treat (mITT) population comprised all randomized subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation. The safety population included all subjects who received at least 1 study injection.

The primary immunogenicity analysis determined the difference in SPR between HEPLISAV at Week 12 and Engerix-B at Week 32 with a two-sided 95% confidence interval (CI) on the difference (HEPLISAV - Engerix-B) between arms. If the lower bound of this CI is above the pre-specified non-inferiority criterion (-10%), HEPLISAV would be established as non-inferior to Engerix-B in SPR. All immunogenicity analyses used one-sided tests at the 2.5% level of significance. To demonstrate clinical lot consistency in three manufacturing lots, the pair-wise 95% CIs for the ratios of GMCs were required to exclude both a 2/3-fold decrease and a 3/2-fold increase per specification. These same limits were used in bridging between the three consistency lots combined and an old lot TDG006 of HEPLISAV with slightly different manufacturing process.

3.3 IMMUNOGENICITY RESULTS

Immunogenicity Analysis

Primary endpoint

1. *Seroprotection Rates (SPR).* The primary immunogenicity endpoint for non-inferiority evaluation is the seroprotection rate in the per-protocol (PP) population. Seroprotection was defined as the post-injection anti-HBsAG ≥ 10 mIU/mL. Table 3.3.1 presents the proportion of vaccinees reaching seroprotection (i.e., SPR) in the HEPLISAV and Engerix-B arms, in the PP, and modified ITT populations. The analyses from the PP population were generated by the applicant and were closely reproduced by the reviewer. The reviewer's PP population results (Table 3.3.1, row 1), therefore, are not presented. In the PP population, the SPR was 90.0% (95% CI: 88.1%, 91.7%) in the HEPLISAV arm, compared to 70.5% (95%: 65.5%, 75.2%) in the Engerix-B arm. The observed difference (HEPLISAV-Engerix-B) in SPR was 19.6% with the 95% CI lower bound of +14.7%. This far exceeded the pre-specified non-inferiority margin of -10%, and thus met the non-inferiority criterion. Similar results were obtained in the reviewer's analysis from the MITT population as well, supporting non-inferiority.

Table 3.3.1: Seroprotection Rates (%) at WEEK 12 for HEPLISAV and at WEEK 32 for Engerix-B by Study Populations

Population	HEPLISAV[2] (WEEK 12) n/N	HEPLISAV[2] (WEEK 12) %	Engerix-B (WEEK 32) n/N	Engerix-B (WEEK 32) %	Mean difference in SPR (HEPLISAV –Engerix-B) (95% CI)[1,4]	Non-inferiority criterion[3]
Per Protocol[*,†]	1011/1123	90.0	253/359	70.5	19.6 (+14.7, +24.7)	met
Modified ITT[†]	1250/1402	89.2	318/460	69.1	20.0 (+15.6, +24.7)	met

* **Adapted from** BLA 125428/0, DV2-HBV-16, Table 11-1, Page 83 of 215. The applicant's Table 11-1 didn't include analysis for ITT popn. [†]Reproducced by reviewer as well. [1]CIs based on Newcombe score method with continuity correction, by applicant; [2]Comprised of 3 consistency lots: TDG008, TDG009, and TDG010; [3]95% CI lower bound for mean difference > -10%. [4]CIs based on Clopper-Pearson method by reviewer.

Secondary Endpoints and Additional Analyses.

2. *Seroprotection Rates (SPR) in Type 2 Diabetes Mellitus Subjects.* The SPR among subjects with Type 2 diabetes mellitus was a secondary endpoint. Table 3.3.2 presents SPRs among the HEPLISAV and Engerix-B vaccinees. As the last column indicates, the two vaccines appear to have no statistically significant difference in SPRs among the Type 2 Diabetes Mellitus subjects. Considering the per-protocol population, the SPR among these diabetes subjects was 73.7% in the HEPLISAV arm compared to 63.3% in the Engerix-B arm, resulting in a SPR difference of 10.4% (95% CI: -8.0, +31.1) between arms. The lack of statistical significance in the SPR difference between treatment groups was noticed in the MITT population as well, with CIs not excluding zero.

Table 3.3.2: Seroprotection Rates (%) in Subjects with Type-2 Diabetes Mellitus at WEEK 12 for HEPLISAV[2] and at WEEK 32 for Engerix-B, by Study Populations

Population	HEPLISAV[2] (WEEK 12) n/N	HEPLISAV[2] (WEEK 12) % (95% CI)	Engerix-B (WEEK 32) n/N	Engerix-B (WEEK 32) % (95% CI)	Mean difference in SPR (HEPLISAV –Engerix-B) (95% CI)[1]
Per Protocol	73/99	73.7 (63.9, 82.1)	19/30	63.3 (43.9, 80.1)	10.4 (-8.0, +31.1)
Modified ITT	97/126	77.0 (68.7, 84.0)	22/37	59.5 (42.1, 75.2)	17.5 (- 0.4, +35.8)

[1] Clopper-Pearson method; [2] Comprised of 3 consistency lots: TDG008, TDG009, and TDG010.

3. *Seroprotection Rates (SPR) by Demographic Characteristics and at Study Visits.* The excess rate of seroprotection in the HEPLISAV arm persisted regardless of the subject's demographic characteristics and as well at different measurement Weeks over the trial's course. The details are provided in Table 3.3.3 for different major categories of age, gender, and race and in Table 3.3.4 for study Weeks of measurement.

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Table 3.3.3: Seroprotection Rates (%) at WEEK 12 for HEPLISAV and at WEEK 32 for Engerix-B, by Demographic Characteristics, Per-Protocol Population.

	HEPLISAV N	HEPLISAV SPR(95% CI)	Engerix-B N	Engerix-B SPR (95% CI)
[1]Age (yrs) 40-55	659	94.5 (92.5, 96.1)	202	73.3 (66.7, 79.2)
Age (yrs) 56-70	464	83.6 (79.9, 86.9)	157	66.9 (58.9, 74.2)
Female	586	92.0 (89.5, 94.0)	181	76.8 (70.0, 82.7)
Male	537	87.9 (84.8, 90.5)	178	64.0 (56.5, 71.1)
Caucasian	932	89.2 (87.0, 91.1)	303	71.3 (65.8, 76.3)
Black/AfrAm	165	93.9 (89.1, 97.1)	48	64.6 (49.5, 77.8)
Other[2]	26	96.2 (80.4, 99.9)	8[†]	75.0 (34.9, 96.8)
All	1123	90.0 (88.1, 91.7)	359	70.5 (65.5, 75.2)

[1]Age is the difference between date of birth and date of consent. [2] Collapsed category because of smaller frequencies.
[†] Exact method used.

Table 3.3.4: Seroprotection Rates (%) at Different Weeks, Per Prototocol Population, Age 40-70 years.

WEEK	HEPLISAV n/N	HEPLISAV %	Engerix-B n/N	Engerix-B %	Estimated Difference (HEPLISAV-Engerix-B) (95% CI)
WEEK 04	223/1123	19.9	16/359	4.5	15.4 (12.0, 18.5)
WEEK 08	859/1122	76.6	73/359	20.3	56.2 (51.1, 60.8)
WEEK 12	1011/1123	90.0	61/359	17.0	73.0 (68.5, 77.0)
WEEK 18	1062/1123	94.6	70/359	19.5	75.1 (70.5, 79.1)
WEEK 24	1068/1123	95.1	77/359	21.4	73.7 (68.9, 77.8)
WEEK 28	1064/1122	94.8	260/357	72.8	22.0 (17.4, 27.0)
WEEK 32	1065/1123	94.8	253/359	70.5	24.4 (19.7, 29.4)
WEEK 36	1048/1111	94.3	233/355	65.6	28.7 (23.7, 34.0)
WEEK 44	1030/1103	93.4	211/353	59.8	33.6 (28.4, 39.0)
WEEK 52	1012/1101	91.9	209/354	59.0	32.9 (27.6, 38.3)

Table 3.3.5: Anti-HBsAg Geometric Mean Concentrations (GMC) by HEPLISAV(WEEK 12) and Engerix-B (WEEK 32) Arms and Study Populations.

Population	HEPLISAV N	HEPLISAV GMC (95% CI)	Engerix-B N	Engerix-B GMT (95% CI)	GMC ratio[1] (HEPLISAV/ Engerix-B) (95% CI)
Per Protocol	1123	93.0 (82.9, 104.2)	359	61.4 (41.7, 90.5)	1.51 (1.12, 2.04)
Modified ITT	1402	87.6 (79.0, 97.2)	460	57.1 (40.2, 81.2)	1.53 (1.17, 2.01)

[1] Calculated from $\log_{10}$ transformed Anti-HBsAg concentrations using t-test method

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Table 3.3.6: GMC at different Weeks, Per Protocol Population (age 40-70 years)

Visit	HEPLISAV N	HEPLISAV GMC (95% CI)	Engerix-B N	Engerix-B GMC (95% CI)
WEEK 0	1123	0.16 (0.15, 0.16)	358	0.15 (0.15, 0.16)
WEEK 04	1123	1.34 (1.15, 1.56)	359	0.23 (0.20, 0.28)
WEEK 08	1122	41.46 (36.10, 47.62)	359	0.94 (0.71, 1.24)
WEEK 12	1123	92.98 (82.95, 104.23)	359	0.82 (0.63, 1.06)
WEEK 18	1123	192.22 (173.76, 212.64)	359	0.87 (0.68, 1.12)
WEEK 24	1123	232.66 (210.22, 257.50)	359	0.98 (0.76, 1.26)
WEEK 28	1122	231.97 (209.19, 257.24)	356	88.53 (59.43, 131.87)
WEEK 32	1123	222.30 (200.27, 246.75)	359	61.41 (41.68, 90.48)
WEEK 36	1111	208.57 (187.60, 231.89)	355	46.79 (31.84, 68.75)
WEEK 44	1103	180.13 (161.86, 200.45)	353	27.21 (18.72, 39.55)
WEEK 52	1101	150.72 (134.81, 168.50)	354	19.47 (13.49, 28.09)

4. *Geometric Mean Concentration (mIU/mL).*

The anti-HBsAg geometric mean concentrations (GMC) for subjects by study arms are presented in Table 3.3.5. In the PP population, the HEPLISAV vaccinees showed a GMC of 93.0 (95% CI: 82.9, 104.2) compared to 61.4 (95% CI: 41.7, 90.5) among the Engerix vaccinees, yielding a GMC ratio of 1.51 (95% CI: 1.12, 2.04). Similar results held for the MITT population as well. In measurements taken at different visits during the trial's course, the GMC with HEPLISAV showed continued increase compared to Engerix-B. Visibly, the increase was rapid at WEEK 8, and continued until slowing down from WEEK 32 and thereafter. The results are presented in Table 3.3.6.

3.4 CLINICAL LOT CONSISTENCY

3.4.1 Background. The evaluation of clinical lot consistency was the second primary objective in the study. The primary endpoint of assessing the clinical consistency of three HEPLISAV lots (TDG008, TDG009, and TDG010) was originally planned to be the GMC measured at 4 weeks post last dose of HEPLISAV (Week 8). The sponsor pre-specified that "The lot-to-lot consistency will be established if all 3 CIs for the pairwise ratios of GMCs are embedded in the interval between 2/3 and 1.5" (page 15 of 38, Statistical Analysis Plan Version 1.1, DV2-HBV-16, BLA 125428/0). After unblinding, the data revealed a GMC ratio of 1.19 (95% CI: 0.87, 1.62) for the lot comparison TDG010 vs. TDG008. The ratio was 1.23 (95% CI: 0.90, 1.67) for the comparison TDG010 vs. TDG009. In recognition of these GMC-ratio results, with the CI upper bounds exceeding the 1.5-fold increase, the applicant acknowledged that the lot consistency test "did not meet the pre-specified criteria because the GMC of lot TDG010 was higher than that of the other two lots" (DV2-

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HBV-16, BLA 125428/0, page 84 of 215). Following unblinding, the applicant also discovered that the lot consistency criterion was met at several subsequent time points, of which the earliest one was Week 12. The applicant's Week 12 results on GMC ratios for lot comparisons are presented in Table 3.4.0.

Table 3.4.0: Applicant's results on GMC ratios in pairwise comparisons of HEPLISAV's three consistency lots, at WEEK 12, Lot consistency Per Protocol Populaiton (N=1282).

Comparison	GMC Ratio [1]	95% LCL	95%UCL
Lot TDG008 / Lot TDG009	0.94	0.73	1.21
Lot TDG010 / Lot TDG008	1.17	0.90	1.50
Lot TDG010 / Lot TDG009	1.09	0.85	1.41

[1] 95% CIs of the 3 pair-wise GMC ratios, with GMCs adjusted for lot, center and age category.
Adapted from DV2-HBV-16, BLA 125428/0, page 85 of 215

The applicant subsequently contended that the data collected at Week 12 would be the basis for the lot consistency evaluation, arguing that the study had "error" in planning (page 83 of 215, DV2-HBV-16, BLA 125428/0).

Table 3.4.1: Anti-HBsAg geometric mean concentrations (GMC[1]) at WEEK 12 and individual 95% confidence intervals (CI) in HEPLISAV's three consistency lots.

Population, Statistic	TDG008	TDG009	TDG010
LCPP, N	426	434	422
LCPP, GMC (95% CI)	82.2 (68.9, 98.2)	86.5 (71.0, 105.3)	96.2 (80.4, 115.1)
MITT, N	466	472	464
MITT, GMC (95% CI)	82.1 (69.1, 97.6)	87.1 (72.2, 105.2)	94.2 (78.7, 112.7)

[1]The GMC values are unadjusted and differed by 3.6 to 5.7 from applicant's figures that were adjusted for lot, center and age category.

3.4.2 Descriptive Statistics. Table 3.4.1 presents GMC (95% CI) at Week 12 for each of the three clinical consistency lots, for the Lot Consistency Per Protocol (LCPP) and Modified ITT (MITT) populations. Considering LCPP, which was the primary analysis population, the GMC appears to be the largest with a value of 96.2 (95% CI: 80.4, 115.1) for lot TDG010, followed by 86.5 (95% CI: 71.0, 105.3) for TDG009, and 82.2 (95%CI: 68.9, 98.2) for TDG008. Almost similar levels and trend followed for the MITT population as well.

3.4.3 Comparisons among Lots. The reviewer computed the GMC ratios and their confidence intervals individually for each lot-pair (Table 3.4.2). Table 3.4.2 shows that all three 95% CIs for the pairwise ratios of GMCs were, by and large, contained within the limits 2/3 and 3/2, supporting lot consistency. The overall lot consistency was also considered as met based on the method of Z_{min} statistic (Wiens and Iglewitcz 1999). In the LCPP and MITT populations, the observed values of Z_{min} (and its 5% level critical value) were, respectively, 1.93 (1.51) and 2.12 (1.52) (Table 3.4.2). In both populations, the critical values were exceeded by the observed value of Z_{min} statistic, thus supporting lot consistency.

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Table 3.4.2: Individual confidence intervals of GMC ratios at WEEK 12 in HEPLISAV's three consistency lots, Lot Consistency Per Protocol (LCPP, N=1282) and Modified ITT (N=1402) Populations.

Population	Comparison	GMC Ratio [1]	95% LCL	95%UCL
LCPP	Lot TDG008 / Lot TDG009	0.95	0.73	1.24
LCPP	Lot TDG010 / Lot TDG008	1.17	0.91	1.51
LCPP	Lot TDG010 / Lot TDG009	1.11	0.85	1.45
LCPP	[1]Z_{min} (5% level critical value)	1.93 (1.51)	-	-
MITT	Lot TDG008 / Lot TDG009	0.94	0.73	1.22
MITT	Lot TDG010 / Lot TDG008	1.15	0.89	1.47
MITT	Lot TDG010 / Lot TDG009	1.08	0.83	1.40
MITT	Z_{min} (5% level critical value)	2.12 (1.52)	-	-

[1] 95% CIs of the 3 pair-wise GMC ratios require to be simultaneously within 2/3 and 3/2 for clinical lot consistency. [2] Z_{min} is calculated by the Wiens-Iglewicz method using equivalence margin ±0 176 in log10 scale of titer.

3.4.4 Conclusions. The applicant reported that the lot consistency criterion was not met at the pre-specified time point of Week 8 (4 weeks post last dose) but was met at the post-hoc time point of Week 12 of immunogenicity measurements. The applicant's results at 12 Weeks from the per protocol population supporting lot-consistency (Table 3.4.0) were largely reproduced in the reviewer's results (Table 3.4.2). In both sets of results, the Week 12 data, by and large, showed that the confidence intervals for the GMC ratios in lot-pairs excluded both a 2/3-fold decrease and a 3/2-fold increase. In the reviewer's analyses, the results were corroborated by an additional approach called Z_{min} method and as well with data from the MITT population analysis.

Although the Week 12 analysis was not pre-planned, it is the same time point that was used for the primary immunogenicity endpoint (which was measured 8 weeks after the last dose), as well as being around the time at which the antibody titers peaked. The week 12 lot consistency results were also corroborated by multiple lot consistency analyses performed at various other time points post vaccination.

3.4.5 Reference

Wiens BL and Iglewicz B: On Testing Equivalence of Three Populations. Journal of Biopharmaceutical Statistics, 9(3), 465-483, 1999.

3.5 BRIDGING STUDY

Analyses, Results and Conclusions.

Bridging was an important secondary objective of the study. In Figure 3.5.1 are presented the histograms of log10Anti-HBsAg Concentration results from the old lot TDG006 and the combined, three new consistency lots of HEPLISAV. The log10 results are derived from the Week 8 (1st row panel) and Week 12 (2nd row panel)

measurements. The old lot had minor differences in manufacturing process compared to the new lots. Clearly, the histograms, panel-wise, do not show any marked differences. Table 3.5.1 compares GMC of the combined lots with that of the old lot. At Week 8, the GMC ratio's (new vs old lot) 95% CI upper bound (1.49) was either slightly below the 1.5-fold change (in per-protocol population), or slightly exceeded it (1.55 in MITT population). At Week 12, however, the said upper bound remained below 1.5. Overall, in the per-protocol population, the GMC ratios excluded 2/3-fold decrease and 3/2-fold increase, indicating comparable immunogenicity between the old lot and the combined new lots, at both time points. For the MITT population, the respective GMC ratios and confidence bounds were 1.21 (0.95, 1.55) and 1.20 (95% CI: 0.98, 1.47), showing, again, the GMC ratio 95% CIs were not markedly off of the interval (2/3, 3/2) used for bridging.


Figure 3.5.1. Histograms of Log10 Anti-HBsAg Results by Study Week and HEPLISAV Lots (Per-Protocol Population)
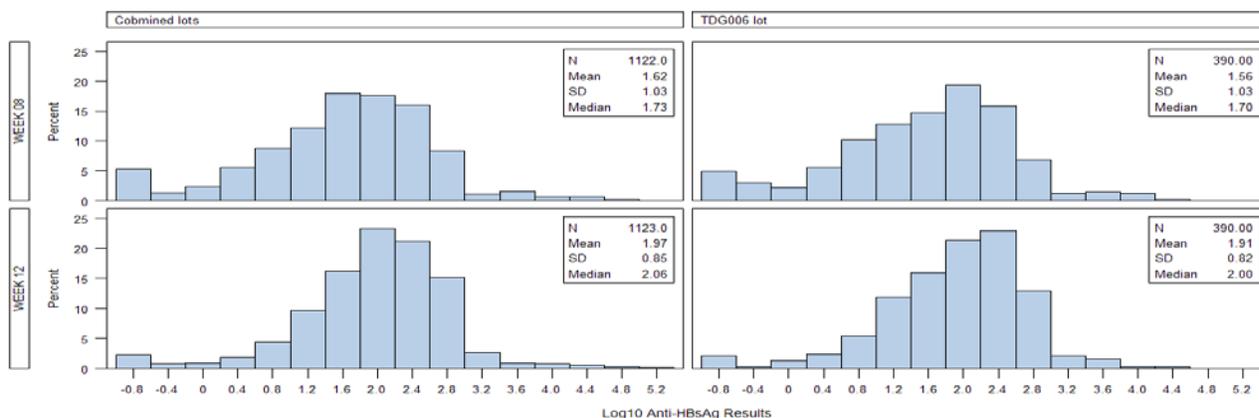
Table 3.5.1: GMC for HEPLISAV's three consistency lots (CoL) combined and for Lot TDG006, at WEEK 8 and WEEK 12

Population	Statistic	WEEK 8 Consistency Lots	WEEK 8 Lot TDG006	WEEK 12 Consistency Lots	WEEK 12 Lot TDG006
LCPP	N	1122	390	1123	390
LCPP	GMC (95% CI)	41.5 (36.1, 47.6)	36.5 (28.9, 46.2)	93.0 (82.9, 104.2)	81.0 (67.2, 98.0)
LCPP	GMC ratio (CoL* vsTDG006) (95% CI)	-	1.14 (0.86, 1.49)	-	1.15 (0.92, 1.43)
MITT	N	1412	510	1402	504
MITT	GMC (95% CI)	39.2 (34.6, 44.5)	32.5 (26.2,40.2)	87.6 (79.0, 97.2)	72.8 (61.3, 86.3)
MITT	GMC ratio (CoL* vsTDG006) (95% CI)	-	1.21 (0.95, 1.55)	-	1.20 (0.98, 1.47)

*CoL=Consistency lots combined, LCPP=Lot Consistency Per Protocol, MITT=Modified ITT.

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3.6 REVIEWER'S SUMMARY

1. Based on the results of the primary immunogenicity endpoint of seroprotection, 90.0% (88.1, 91.7) of the subjects who had completed full primary vaccination showed seroprotection with the experimental HEPLISAV arm. Such seroprotection rate in the comparator Engerix-B arm was 70.5% (95% CI: 65.5%, 75.2%). The observed difference (HEPLISAV- Engerix-B) of 19.6% in seroprotection rate had the 95% CI lower bound of 14.6. This value far exceeded the pre-specified non-inferiority margin of -10% and, thus, met the non-inferiority criterion. Similar results were found in the MITT population as well, supporting non-inferiority (Table 3.3.1).

2. The excess rate of seroprotection in the HEPLISAV arm persisted regardless of the subject's major demographic characteristics and at different measurement Weeks over the trial's course (Table 3.3.3 and Table 3.3.4).

3. As with the seroprotection rate, the HEPLISAV vaccinees showed increased GMC as well compared to the Engerix-B vaccinees (Table 3.3.5). The GMC was 93.0 (95% CI: 82.9, 104.2) in the HEPLISAV arm, compared to 61.4 (95% CI: 41.7, 90.5) in the Engerix-B arm, implying a GMC ratio of 1.51 (95% CI: 1.12, 2.04) for HEPLISAV over Engerix-B. While these results are observed from the per-protocol population, similar results were found from the MITT population also (Table 3.3.5). Additionally, in measurements taken at different visits during the trial's course, the GMC with HEPLISAV showed continued excess compared to Engerix-B. Visibly, the excess was rapid at WEEK 8, and continued until slowing down from WEEK 32 and thereafter. The results are presented in Table 3.3.6.

4. The three consistency lots were reported by the applicant as having not satisfied the lot consistency criterion based on the pre-planned Week 8 immunogenicity measurements. But with the post-hoc change to Week 12 measurements, the three lots were considered to be clinically consistent based on the anti-HBsAg geometric mean concentration ratios (Table 3.4.0, Table 3.4.2). For each pairwise comparison between lots, the 95% CI on the ratio of GMCs was contained within the limits (2/3, 3/2) -- in other words, the ratio of mean concentrations excluded both a 2/3-fold decrease and a 3/2-fold increase, the bounds that were pre-specified for lot consistency evaluation based on the planned Week 8 data. The lots were found consistent by the Z_{min} statistic also, a method that tested for overall consistency of the three lots. Satisfying the consistency, the observed value of Z_{min} statistic (1.93) was larger than its 5% critical value (1.51) in the per-protocol population. Similar was the conclusion from the MITT population as well, with Z_{min} value of 2.12 exceeding its critical value 1.52.

5. The BLA indicated comparable immunogenicity between the old lot TDG006 and the combined three new consistency lots of HEPLISAV, in terms of GMCs (Table 3.5.1). In the per-protocol population, the GMCs at Week 8 for the combined new lots and old lot were, respectively, 41.5 (95% CI: 36.1, 47.6) and 36.5 (95% CI: 28.9, 46.2), yielding a GMC ratio of 1.14 (95% CI: 0.86, 1.49). For the same population at Week 12, the corresponding results were 93.0 (95% CI: 82.9, 104.2), 81.0 (95% CI: 67.2, 98.0) and 1.15 (95% CI: 0.92, 1.43). The applicant also reported for Week 12 a GMC ratio of 1.19 (95% CI: 0.94, 1.51) with GMCs 91.7 and 77.0, respectively, for the

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combined new lots and the old lot IDG006. Overall, the GMC ratios excluded both a 2/3-fold decrease and a 3/2-fold increase, supporting bridging of immunogenicity results at both time points of Week 8 and Week 12.

4 SAFETY

This section provides safety assessment summaries based on safety populations combined from the two pivotal phase 3 trials (HBV-10 and HBV-16), and includes demographic and baseline characteristics, post-injection reactions – local and systemic, adverse events (AE), serious adverse events (SAE), and deaths. Additionally, it presents adverse events of special interest (AESI).   These included potential autoimmune cases.

4.1 DEMOGRAPHICS

Table 4.1.1 provides demographic and baseline characteristics of subjects of age 18 and older, by treatment groups. Due to balance of the distributions of gender, age, BMI, and race across treatments, the overall safety populations by treatment groups were considered to be similar with respect to these characteristics.

Table 4.1.1: Age, Gender and Race by Treatment Group,
All Pivotal Safety Population, Age 18-70

	HEPLISAV (N=3777)	Engerix-B (N=1087)
Men, n (%)	1795 (47.5)	498 (45.8)
Women, n (%)	1982 (52.5)	589 (54.2)
Age 18-39 Yrs, n (%)	818 (21.7)	275 (25.3)
Age 40-55 Yrs, n (%)	2116 (56.0)	614 (56.5)
Age 56-70 Yrs, n (%)	843 (22.3)	198 (18.2)
Age (yrs)		
N	3777	1087
Mean (SD)	47.3 (11.15)	46.0 (10.98)
Median	48.00	46.00
Min - Max	18-70	18-70
BMI < 30 kg/m^2, n(%)	2445 (64.7)	713 (65.6)
BMI ≥ 30 kg/m^2, n(%)	1326 (35.1)	372 (34.2)
White, n(%)	3309 (87.6)	955 (87.9)
Black/Afr American, n(%)	336 (8.9)	89 (8.2)
Asian, n(%)	69 (1.8)	26 (2.4)
Other, n(%)	63 (1.7)	17 (1.6)

Adapted from Table 2.7.4-7, STN 125428, Summary of Clinical Safety, pp. 49.

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4.2 POST-INJECTION REACTIONS

The study reported post-injection reactions which were local (i.e., injection site pain, redness, and swelling) and systemic (i.e., malaise, headache, fatigue, and elevated temperature). As an overview, among vaccinees receiving HEPLISAV, 1612 subjects of a total of 3762 subjects reported local reactions, yielding an overall local reaction rate of 42.8% (95% CI: 41.3%, 44.4%). For Engerix-B, this rate was 41.1% (95% CI: 38.1%, 44.0%) based on 445 subjects reporting such reactions of a total of 1084 subjects. For post-injection systemic reactions, these rates were 1215/3762, i.e., 32.3% (95% CI: 30.8%, 33.8%) for HEPLISAV, and 405/1084, i.e., 37.4% (95% CI: 34.5%, 40.3%) for Engerix-B.

Table 4.2.1 and Table 4.2.2 provide further details about the post-injection local and systemic reactions by treatment groups. From Table 4.2.1, HEPLISAV appeared to have either higher injection-site reaction rates, such as for redness (3.7%, 95% CI: 3.1%, 4.4%) compared to Engerix-B (1.1%, 95% CI: 0.6%, 1.9%), or the rates were comparable, for example for Pain and Swelling. With regard to the post-injection systemic reactions, the rates were comparable across the treatment groups (Table 4.2.2).

Table 4.2.1: Overview of Post-Injection Local Reactions by Treatment, Age 18-70 years, Pivotal Safety Populations

	HEPLISAV (N=3777)	Engerix-B (N=1087)
N	3762	1084
Pain, n(%), 95% CI	1567 (41.7), (40.0, 43.2)	439 (40.5), (37.6, 43.5)
Redness, n(%), 95% CI	141 (3.7), (3.1, 4.4)	12 (1.1), (0.6, 1.9)
Swelling, n(%), 95% CI	90 (2.4), (1.9, 2.9)	14 (1.3), (0.7, 2.2)

Adapted from Table 2.7.4-12,Table 2.7.4-13 & Table 2.7.4-15, Summary of Clinical Safety, pp. 59, 60, 63.

Table 4.2.2: Overview of Post-Injection Systemic Reactions by Treatment, Age 18-70 years, Pivotal Safety Populations

	HEPLISAV (N=3777)	Engerix-B (N=1087)
N	3762	1084
Fatigue, n(%), 95% CI	805 (21.4), (20.1, 22.7)	272 (25.1), (22.5, 27.8)
Headache, n(%), 95% CI	755 (20.1), (18.8, 21.4)	274 (25.3), (22.7, 28.0)
Malaise, n(%), 95% CI	520 (13.8), (12.7, 15.0)	173 (16.0), (13.8, 18.3)
Severe Fever (39°C-40°C), n/N (%), 95% CI	9/3733 (0.2), (0.1, 0.5)	10/1076 (0.9), (0.4, 1.7)

Adapted from Table 2.7.4-12,Table 2.7.4-13 & Table 2.7.4-15, Summary of Clinical Safety, pp. 59, 60, 63.

4.3 OVERVIEW OF ADVERSE EVENTS

4.3.1 Deaths. The summary of major categories of adverse events by treatment group in subjects 18 years or older is presented in Table 4.3.1. Two deaths were reported, one under each treatment. The sponsor, however, did not consider them as related to the treatment. Further details about these deaths are provided in Table 4.3.2.

Table 4.3.1: Summary of Adverse Events by Treatment Group, Age 18-70, All Pivotal Safety Population

Number (%) of Subjects With:	HEPLISAV (N = 3777)	Engerix-B (N = 1087)
Any AE	2089 (55.3)	631 (58.0)
Any Related AE	234 (6.2)	65 (6.0)
Any SAE	104 (2.8)	36 (3.3)
Any Related SAE	1 (0.0)	1 (0.1)
Any AESI	8 (0.2)	4 (0.4)
Any AESI + New-Onset AIAE	10 (0.3)	4 (0.4)
Discontinuation of treatment due to AE	19 (0.5)	4 (0.4)
Discontinuation of treatment due to Related AE	6 (0.2)	1 (0.1)
Death	1 (0.0)	1 (0.1)

Adapted from Table 2.7.4-9, STN 125428, Summary of Clinical Safety, pp. 55.
AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event.

Table 4.3.2: Deaths During the Clinical Development of HEPLISAV (All Subjects)

	Subj ID	Age	Sex	MedDRA Preferred Term	Days since last active dose	Relationship to treatment
HBV-16/ **HEPLISAV**	22-003	45	M	Pulmonary embolism	(b) (6)	Not related
HBV-16/ **Engerix-B**	92-638	64	M	Myocardial infarction	(b) (6)	Not related

Adapted from Table 2.7.4-24, STN 125428, Summary of Clinical Safety, pp. 82

4.3.2 AE/SAE/AESI. The pivotal studies reported 2089 adverse events in a total of 3777 vaccinees receiving HEPISAV, and as such an AE rate of 55.3% (95% CI: 53.7%, 56.9%) in the HEPLISAV arm. This can be compared to 58.0% (95% CI: 55.0%, 61.0%) based on 631 AEs among 1087 vaccinees in the Engerix-B arm. The rates for serious adverse events (SAEs) were 2.8% (95% CI: 2.2%, 3.3%) and 3.3% (95% CI: 2.3%, 4.6%) in the HEPLISAV and Engerix-B arms, respectively. In addition, several adverse events of special interest (AESI) were reported, with 8 subjects being from the HEPLISAV arm and 4 from the Engerix-B arm. The corresponding AESI rates were 0.2% (95% CI: 0.09%, 0.42%) and 0.4% (95% CI: 0.10%, 0.94) for HEPLISAV and Engerix-B, respectively.

4.3.3 Autoimmune AE

A detailed presentation of the AESI events is provided in Table 4.3.3. The narrative shows one case of Guillain-Barre Syndrome, one case of Wegener's Granulomatosis,

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both in the HEPLISAV arm. In the Engerix-B arm as well, one case of ANCA positive vasculitis was present. Please refer to the medical/epidemiological reviews for consideration of these AESIs.

Table 4.3.3: Adverse Events of Special Interest by Treatment Group, Pivotal Trials

Pivotal Trial/Arm	Subj ID[a]	Age	Sex	MeDRA Preferred Term	Days since last active dose	SAE?	Severity	Outcome	Relationship to Treatment as identified by sponsor
HBV-10/Heplisav	08-038	41	F	Basedow's Disease	43	No	3	Ongoing	Probably Not Related[b]
HBV-10/Heplisav	10-060	52	F	Systemic Lupus Erythematosus	84	No	0	Resolved	Not Related
HBV-10/Heplisav	11-168	36	F	Guillain-Barre Syndrome	110	Yes	3	Resolved	Probably Not Related[b]
HBV-10/Heplisav	24-057	54	F	Wegener's Granulomatosis	72	Yes	3	Ongoing	Possibly Related
HBV-10/Heplisav	25-141	42	F	Rheumatoid Arthritis	239	No	1	Resolved	Not Related
HBV-16/Heplisav	28-615	62	M	Erythema Nodosum	19	No	2	Resolved	Possibly Related
HBV-16/Heplisav	30-352	59	M	VIIth Nerve Paralysis	270	No	1	Resolved	Not Related
HBV-16/Heplisav	41-624	69	M	Vitiligo	1	No	1	Ongoing	Possibly Related
HBV-10/Engerix-B	06-083*	44	F	ANCA Positive Vasculitis	126	Yes	3	Resolved	Not Related
HBV-10/Engerix-B	06-083	44	F	Mixed Connective Tissue Disease	316	No	1	Ongoing	Not Related
HBV-10/Engerix-B	06-083	44	F	Scleroderm	126	No	1	Ongoing	Not Related
HBV-10/Engerix-B	06-360	34	M	VIIth Nerve Paralysis	121	No	2	Resolved	Not Related
HBV-10/Engerix-B	11-153	30	F	Basedow's Disease	77	No	2	Ongoing	Not Related
HBV-10/Engerix-B	12-119	46	M	Raynaud's Phenomenon	32	No	1	Ongoing	Not Related

Adapted from Table 2.7.4–33, STN 125428, Summary of Clinical Safety, pp. 103.
[a] Subject has no associated safety narrative in the CSR
[b] The assessment of "Probably Not Related" used in HBV-10 was considered equivalent to "Not Related" for analysis purposes.
* The subject had three AEs
Note: Severity: 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening or disabling, 5 = Death.

4.4 CONCLUSIONS

1. Two deaths were reported from the combined safety population (N=4880) of the pivotal phase III trials. These deaths were considered by the study investigator as not related to the treatments.

2. The post-injection site reaction, such as redness, seemed to have occurred with a higher rate in the HEPLISAV arm (3.7%, 95% CI: 3.1%-4.4%) compared to Engerix-B (1.1%, 95% CI: 0.6%-1.9%), but the incidence was infrequent with rates ≤ 3.7%.

3. The study reported 8 adverse events of special interest from the HEPLISAV arm and 4 from the Engerix-B arm. These AESIs included potential autoimmune cases, particularly in the HEPLISAV arm.
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5 REVIEWER'S OVERALL SUMMARY AND CONCLUSIONS

Efficacy

1. Based on the two pivotal studies, the BLA demonstrated that the primary immunogenicity endpoint of seroprotection with HEPLISAV met the non-inferiority criterion when compared with the licensed vaccine Engerix-B. With the observed SPRs in the HEPLISAV and Engerix-B arms being, respectively, 95.1% (95% CI: 93.9%, 96.1%) and 81.1% (95% CI: 77.5%, 84.4%), the 95% CI lower limit of the observed difference (HEPLISAV – Engerix-B) was +10.6% in study DV2-HBV-10 and far exceeded the pre-specified non-inferiority margin of -10%. In study DV2-HBV-16, the point estimate of the SPR difference was 19.6% with 95% CI: (14.7%, 24.7%) and, again, the lower bound of the difference far exceeded the -10% margin. All together, these results establish the non-inferiority of SPR with HEPLISAV. These results were closely reproduced in the reviewer's analyses (Table 2.3.1 and Table 3.3.1).

2. The applicant acknowledged that the three consistency lots did not meet the clinical lot consistency criterion based on the pre-planned Week 8 of immunogenicity measurements. But based on the post-hoc shift of the time point to Week 12 for immunogenicity measurements, the lots were considered to have met the criterion (Table 3.4.2). For each pairwise comparison between lots, a 95% CI on the ratio of GMC was contained within the limits (2/3, 3/2), the bounds that were pre-specified for lot consistency evaluation. Based on the reviewer's analysis, the lots were found consistent by the Z_{min} statistic also, a method that tested for overall consistency of the three lots. Satisfying the consistency criterion, the observed value of the Z_{min} statistic (1.93) was larger than its critical value (1.51) in the per-protocol population, and as well in the MITT population with the Z_{min} value (2.12) exceeding its critical value (1.52).

Although the 12-week time point for lot consistency assessment was chosen post hoc, this time point was the same one pre-specified for the primary endpoint analysis and was around the time that the immune responses peaked. Also, all other analyses at multiple time points post vaccination corroborated the consistency of the lots.

3. The BLA, overall, indicates comparable immunogenicities between the old lot TDG006 and the combined three consistency lots of HEPLISAV, in terms of GMC ratios (Table 3.5.1). In the per-protocol population, the GMCs at Week 8 for the combined new lots and old lot were, respectively, 41.5 (95% CI: 36.1, 47.6) and 36.5 (95% CI: 28.9, 46.2), yielding a GMC ratio of 1.14 (95% CI: 0.86, 1.49). For the same population at Week 12, the corresponding results were 93.0 (95% CI: 82.9, 104.2), 81.0 (95% CI: 67.2, 98.0), and 1.15 (95% CI: 0.92, 1.43). The GMC ratios excluded both a 2/3-fold decrease and a 3/2-fold increase, supporting bridging of the immunogenicity results at both time points of Week 8 and Week 12 in the per-protocol population. At these same time points and in the MITT population, the respective GMC ratios and confidence bounds were 1.21 (0.95, 1.55) and 1.20 (95%

CI: 0.98, 1.47), showing the GMC ratio 95% CIs did not have marked departure from the interval (2/3, 3/2) used for bridging.

4. Based on the secondary analyses, HEPLISAV's increased SPR, and a faster rise and higher level of GMC, compared to Engerix-B, appear to have persisted over the study courses of both pivotal trials and across the major demographic characteristics (Tables: 2.3.2 – 2.3.4; Tables 3.3.3 - 3.3.4; and Table 3.3.6).

Safety

Based on safety data in the two pivotal trials in this BLA, no concern about the general safety profile, in terms of the reported post-injection local and systemic reactions and general AEs, arose. Two deaths were reported but were considered by the study investigator(s) as unrelated to treatment. Additionally, the applicant identified 8 adverse events of special interest (AESIs) in the HEPLISAV group and 4 in the Engerix-B group. These included potential autoimmune cases (Table 4.3.3), particularly in the HEPLISAV arm. The statistical reviewer defers to the medical reviewers for assessment of these ARSIs. Note also that these studies, even combined, were not powered for rare events.

Recommendations

1. The BLA provided data supporting the non-inferiority of HEPLISAV vaccine to Engerix-B in terms of seroprotection rates.

2. Although the pre-specified Week 8 lot consistency analysis did not demonstrate consistency, the post-hoc Week 12 analysis did meet the lot consistency criterion. This finding was corroborated by additional lot consistency analyses of data from multiple time points post vaccination. In hindsight, the Week 12 time point likely should have been pre-specified for the analysis, since this time point was pre-specified for the primary analyses. It happened that Week 12 was also around the time that immune responses peaked.

3. No marked difference in general safety profile between study arms was discerned, but potential autoimmune cases were identified by the applicant. The studies, however, were not powered for rare event detection. Please refer to the medical reviews for assessment of these AEs.