HEPLISAV-B®, a 2-Dose Hepatitis B Vaccine Using a Toll-like Receptor 9 Adjuvant, Is Well Tolerated and Induces Higher Rates of Seroprotection than Engerix-B in Persons with Diabetes Aged 60 Years or Older

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BACKGROUND

- Adult patients with diabetes mellitus (DM) have a greater risk of contracting hepatitis B virus (HBV) than the general population, including those aged ≥ 60 years[1–3]
  - When infected, patients with DM have more severe HBV-related morbidity and accelerated progression[3–5]
- The CDC recommends HBV vaccination of all adults with DM who are aged ≥ 60 years at the discretion of the treating physician[3]
  - 87% of individuals with DM who are aged ≥ 60 years remain unvaccinated[6]
- HEPLISAV-B® (Hepatitis B Vaccine [Recombinant], Adjuvanted) is a 2-dose HBV vaccine using a cytosine phosphoguanine (CpG) adjuvant targeting Toll-like receptor 9 that has demonstrated higher seroprotection rates than a 3-dose vaccine, particularly in populations known to be hyporesponsive (US data)[7,8]

OBJECTIVE

- To assess the safety and efficacy of HEPLISAV-B in patients with type 2 DM aged ≥ 60 years

METHODS

Participants

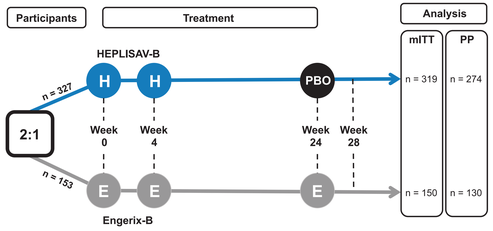
- Adults aged 60 to 70 years with a clinical diagnosis of type 2 DM who are taking insulin and/or a hypoglycemic agent
  - Participants were excluded if they had a history of HBV or human immunodeficiency virus (HIV) infection or autoimmune disorder; were seropositive for hepatitis B surface antigen (HBsAg), antibody against hepatitis B surface antigen (anti-HBs), antibody against hepatitis B core antigen (anti-HBc), or antibody against HIV; or previously received any hepatitis B vaccine, DNA plasmid, or oligonucleotide injection

Study Design and Vaccine Administration

- This was a post hoc analysis of data collected during a large phase 3, observer-blinded, randomized, active-controlled, multicenter trial of the safety and immunogenicity of HEPLISAV-B in adults with and without type 2 DM (NCT02117934)
- Participants were randomized 2:1 to receive either 2 doses of HEPLISAV-B or 3 doses of Engerix-B® (HBsAg-Eng) **(Figure 1)**
  - HEPLISAV-B (20 µg of subtype *adw* recombinant HBsAg and 3 mg of a proprietary phosphorothioate oligodeoxynucleotide adjuvant, known as "1018", per 0.5-mL dose), was administered intramuscularly (IM) into the deltoid muscle at 0 and 4 weeks, followed by placebo at 24 weeks to maintain blinding
  - Engerix-B (20-µg HBsAg adsorbed on 500-µg aluminum hydroxide per 1.0-mL dose) was injected IM at 0, 4, and 24 weeks

Figure 1. Study Design

Post Hoc Analysis: Participants with Type 2 Diabetes Aged ≥ 60 Years*



*Predefined subgroups include sex, smoking status, and body mass index.
H = HEPLISAV-B; E = Engerix-B; mITT = modified intent-to-treat population; PBO = placebo; PP = per-protocol population.

Immunogenicity Assessments

- Blood samples for anti-HBs quantification were collected before study drug injection at week 24 and week 28
- Seroprotection was defined as anti-HBs serum concentration ≥ 10 mIU/mL
  - Seroprotection rate (SPR) induced by HEPLISAV-B at week 28 was compared with the SPR induced by Engerix-B at week 28 (primary immunogenicity endpoint for the phase 3 study) among all participants and by subgroups including sex, body mass index (BMI), and smoking status
  - Anti-HBs serum geometric mean concentrations (GMCs) at week 24 and week 28 were calculated
  - A reverse cumulative frequency plot was used to assess and compare the distribution of anti-HBs concentrations in response to HEPLISAV-B and Engerix-B at week 28

Safety Assessments

- Adverse events (AEs) were assessed for all participants who received ≥ 1 injection of study drug
- The proportion of participants with new-onset (reported from first injection [week 0] to week 56), treatment-emergent medically attended AEs (MAEs), immune-mediated AEs of special interest, and deaths were recorded

METHODS

Statistical Analysis

- Modified intent-to-treat (mITT) analysis included participants who received ≥ 1 injection and had ≥ 1 immunogenicity evaluation
- Participants who had no major deviations from the study protocol, received all injections, and had blood drawn for anti-HBs levels at week 28 were included in the per-protocol (PP) analysis
- The 95% confidence intervals (CIs) for the SPRs of HEPLISAV-B and Engerix-B were calculated using the 2-sided Clopper-Pearson method. For the difference in the SPRs between HEPLISAV-B and Engerix-B, the 95% CIs were calculated using the Miettinen and Nurminen method without stratification
- GMCs, GMC ratios, and the associated CIs were calculated using *t* test based on $\log_{10}$-transformation

RESULTS

Participants

- 480 participants were included in this post hoc analysis with 327 participants receiving HEPLISAV-B and 153 participants receiving Engerix-B
  - mITT analysis: 319 participants in the HEPLISAV-B group and 150 participants in the Engerix-B group
  - PP analysis: 274 participants in the HEPLISAV-B group and 130 in the Engerix-B group
- Demographics and baseline characteristics were similar between groups **(Table 1)**

Table 1. Demographics and Baseline Characteristics (Safety Population)

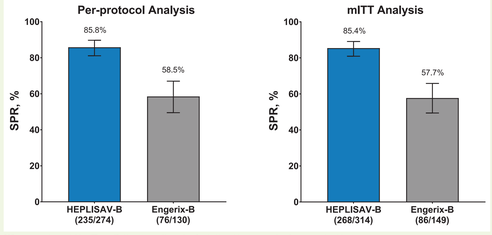
Parameter	HEPLISAV-B (2 dose) (n = 327)	Engerix-B (3 dose) (n = 153)
Age, years		
Mean (SD)	64.5 (2.91)	64.6 (2.86)
Median (range)	64.0 (60.0 – 70.0)	65.0 (60.0 – 70.0)
Sex, n (%)		
Male	208 (63.6)	89 (58.2)
Female	119 (36.4)	64 (41.8)
Weight, kg		
Mean (SD)	100.4 (22.25)	101.1 (21.63)
Median (range)	98.5 (47.2 – 180.0)	101.0 (53.6 – 171.6)
BMI, kg/m^2		
Mean (SD)	33.9 (7.11)	34.4 (6.68)
Median (range)	32.9 (12.9 – 58.8)	33.3 (21.1 – 54.2)
BMI stratum, kg/m^2 (%)		
< 30	99 (30.3)	44 (28.8)
≥ 30	228 (69.7)	109 (71.2)
Smoking status, n (%)		
Smoker	59 (18.0)	24 (15.7)
Non-smoker	268 (82.0)	129 (84.3)

BMI = body mass index.

Immunogenicity by Seroprotection Rates

- At week 28, in the PP analysis, SPR in the HEPLISAV-B group was significantly higher than the SPR in the Engerix-B group for all patients **(Figure 2)** and in each subgroup **(Table 2, Figure 3)**
- Similarly, in the mITT analysis, the SPR at week 28 was significantly higher for HEPLISAV-B than for Engerix-B, with a treatment difference of 27.6% (95% CI: 18.9% – 36.5%) **(Figure 2)**
- HEPLISAV-B induced significantly higher SPR in the PP analysis at week 24 than Engerix-B at week 28, with a treatment difference of 29.7% (95% CI: 20.5% – 39.1%); similar results were found in the mITT analysis
  - In each subgroup, the SPR at week 24 in the HEPLISAV-B group was markedly higher than at week 28 in the Engerix-B group

Figure 2. HEPLISAV-B Induced Significantly Higher SPR at Week 28 Compared With Engerix-B



SPR = seroprotection rate (n/N); mITT = modified intent to treat; N = number of evaluable participants; n = number of seroprotected participants.

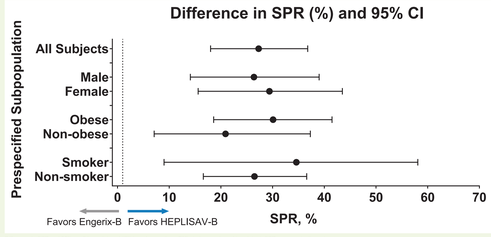
RESULTS

Table 2. SPR at Week 28 for HEPLISAV-B and Engerix-B (PP Analysis)

Prespecified Subpopulation	HEPLISAV-B (2 dose) (n = 274) n/N	HEPLISAV-B (2 dose) (n = 274) SPR, %	Engerix-B (3 dose) (n = 130) n/N	Engerix-B (3 dose) (n = 130) SPR, %	Difference in SPR (95% CI)
All Participants	235/274	85.8	76/130	58.5	27.3 (18.0 – 36.8)
Sex					
Male	146/174	83.9	42/73	57.5	26.4 (14.1 – 39.0)
Female	89/100	89.0	34/57	59.6	29.4 (15.6 – 43.5)
BMI Stratum, kg/m^2					
Obese, ≥ 30	159/192	82.8	48/91	52.7	30.1 (18.6 – 41.5)
Non-obese, < 30	76/82	92.7	28/39	71.8	20.9 (7.1 – 37.3)
Smoking Status, n (%)					
Smoker	40/49	81.6	8/17	47.1	34.6 (9.0 – 58.1)
Non-smoker	195/225	86.7	68/113	60.2	26.5 (16.6 – 36.6)

PP = Per-protocol; SPR = seroprotection rate.

Figure 3. At Week 28 HEPLISAV-B Induced Significantly Higher Seroprotection Rates Than Engerix-B (Per-protocol Analysis)



Difference in SPR and 95% confidence interval (CI) by subgroup (sex, BMI stratum, and smoking status). SPR = seroprotection rate.

Immunogenicity by Geometric Mean Concentration

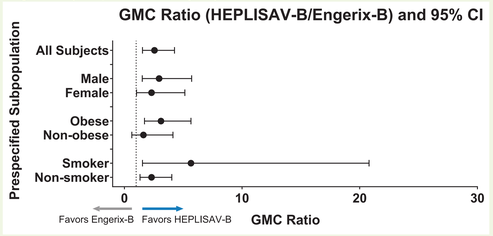
- At week 28, in the PP analysis, GMC in the HEPLISAV-B group was significantly higher than the GMC in the Engerix-B group for all patients and in each subgroup **(Table 3; Figure 4)**
- In the mITT analysis, the GMC at week 28 was 126.7 mIU/mL in the HEPLISAV-B group and 44.1 mIU/mL in the Engerix-B group, with a GMC ratio of 2.9 (95% CI: 1.8 – 4.6)
- HEPLISAV-B induced significantly higher GMC (137.3 mIU/mL) in the PP analysis at week 24 than Engerix-B at week 28, with a GMC ratio of 2.7 (95% CI: 1.6 – 4.4), similar results were found in the mITT analysis
  - In each subgroup, the GMC at week 24 in the HEPLISAV-B group was markedly higher than the GMC at week 28 in the Engerix-B group

Table 3. GMC at Week 28 for HEPLISAV-B and Engerix-B (PP Analysis)

Prespecified Subpopulation	HEPLISAV-B (2 dose) (n = 274) N	HEPLISAV-B (2 dose) (n = 274) GMC, mIU/mL (95% CI)	Engerix-B (3 dose) (n = 130) N	Engerix-B (3 dose) (n = 130) GMC, mIU/mL (95% CI)	GMC Ratio (95% CI)
All Participants	274	131.9 (102.7 – 169.3)	130	51.6 (30.5 – 87.1)	2.6 (1.5 – 4.3)
Sex					
Male	174	110.8 (80.5 – 152.5)	73	37.6 (18.8 – 75.1)	2.9 (1.5 – 5.7)
Female	100	178.5 (119.6 – 266.4)	57	77.4 (34.3 – 174.2)	2.3 (1.0 – 5.1)
BMI Stratum, kg/m^2					
Obese, ≥ 30	192	107.4 (79.7 – 144.7)	91	34.5 (18.8 – 63.2)	3.1 (1.7 – 5.7)
Non-obese, < 30	82	213.2 (135.8 – 334.8)	39	131.9 (48.3 – 360.1)	1.6 (0.6 – 4.1)
Smoking Status, n (%)					
Smoker	49	100.1 (53.8 – 186.4)	17	17.7 (4.4 – 71.1)	5.7 (1.5 – 20.8)
Non-smoker	225	140.0 (106.4 – 184.2)	113	60.6 (34.3 – 106.8)	2.3 (1.3 – 4.0)

GMC = geometric mean concentration; PP = Per-protocol.

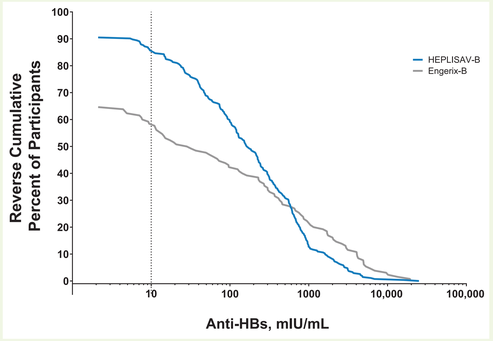
Figure 4. At Week 28 HEPLISAV-B Induced Significantly Higher GMC Than Engerix-B (Per-protocol Analysis)



GMC ratio and 95% confidence interval (CI) by subgroup (sex, BMI stratum, and smoking status). GMC = geometric mean concentration.

- In the PP analysis, the reverse cumulative frequency curves for HEPLISAV-B and Engerix-B had relatively different slopes, showing a more consistent immune response with HEPLISAV-B **(Figure 5)**
  - The slope of the HEPLISAV-B curve was steeper than the Engerix-B curve, indicating the antibody response to HEPLISAV-B was less variable than the response to Engerix-B
  - The shallow slope of the Engerix-B curve indicates larger variance in the antibody response to Engerix-B compared with HEPLISAV-B

Figure 5. Reverse Cumulative Frequency Plot of Anti-HBs Level By Group at Week 28



Anti-HBs = antibody against hepatitis B surface antigen.

Safety

- In the HEPLISAV-B group:
  - 210 (64.2%) participants reported an MAE, of these 77 (23.5%) participants experienced a grade 3 or 4 MAE
  - 1 (0.3%) participant experienced an AE of special interest related to the study treatment (polymyalgia rheumatica, a musculoskeletal and connective tissue disorder). This individual is receiving ongoing treatment and monitoring
  - 3 deaths (due to hepatic cirrhosis, acute respiratory distress syndrome, and cardiac arrest) occurred, but are not considered related to treatment
- In the Engerix-B group:
  - 85 (55.6%) participants experienced MAEs, of these 34 (22.2%) participants reported a grade 3 or 4 MAE
  - 1 death (due to cardiorespiratory arrest) occurred, but was not considered related to treatment
  - The most commonly reported MAEs are reported in **Table 4**

Table 4. Most Common (≥ 2% in Either Treatment Group) Treatment-emergent Medically Attended Adverse Events

Preferred Term	HEPLISAV-B (2 dose) (n = 327) Patients, n (%)	Engerix-B (3 dose) (n = 153) Patients, n (%)
Upper respiratory tract infection	18 (5.5)	3 (2.0)
Back pain	13 (4.0)	7 (4.6)
Bronchitis	12 (3.7)	7 (4.6)
Urinary tract infection	12 (3.7)	4 (2.6)
Hypertension	12 (3.7)	2 (1.3)
Osteoarthritis	11 (3.4)	5 (3.3)
Sinusitis	8 (2.4)	6 (3.9)
Type 2 diabetes mellitus*	7 (2.1)	8 (5.2)
Cellulitis	7 (2.1)	0
Arthralgia	5 (1.5)	4 (2.6)
Rotator cuff syndrome	5 (1.5)	3 (2.0)
Cough	5 (1.5)	4 (2.6)
Chronic obstructive pulmonary disease	4 (1.2)	3 (2.0)
Constipation	3 (0.9)	3 (2.0)
Diarrhea	2 (0.6)	4 (2.6)
Pneumonia	2 (0.6)	3 (2.0)
Foot fracture	2 (0.6)	3 (2.0)
Musculoskeletal pain	2 (0.6)	3 (2.0)
Gastric ulcer	0	3 (2.0)

*Denotes a worsening of Type 2 diabetes mellitus.

CONCLUSIONS

- Adult patients with diabetes have a greater risk of contracting hepatitis B virus (HBV)
- Objectives were to assess the safety and efficacy of HEPLISAV-B in patients with Type 2 diabetes mellitus aged ≥ 60 years
- 2-dose HEPLISAV-B vaccine provided:
  - Significantly higher rates of seroprotection against HBV than 3-dose vaccine (Engerix-B)
  - Had a similar safety profile in patients with diabetes aged ≥ 60 years, regardless of subgroup (smoking status, body mass index, and sex)

DISCLOSURES

RNH and RSJ are full-time employees of Dynavax Technologies and may hold stock and/or stock options.

Dynavax Technologies participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving of this poster for submission. All authors had access to the data; participated in the development, review, and approval of the poster; and agreed to submit this poster to the American Diabetes Association's 78th Scientific Session for consideration as an oral presentation or poster. Medical writing assistance, funded by Dynavax Technologies, was provided by Caroline Walsh Cazares, PhD, of JB Ashtin.

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