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Long-term immunogenicity and safety of the hepatitis B vaccine HepB-CpG (HEPLISAV-B) compared with HepB-Eng (Engerix-B) in adults with chronic kidney disease

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ABSTRACT

Background: Hepatitis B virus (HBV) infection remains a significant global burden, especially for patients with chronic kidney disease (CKD) receiving hemodialysis. Three doses of HepB–CpG (HEPLISAV-B® vaccine) induced a superior immune response compared with 4 double doses of HepB–Eng (Engerix-B®) in a phase 3 trial (HBV-17) in adults with CKD. Here we report the long-term immunogenicity and safety of HepB-CpG and HepB–Eng in eligible participants of HBV-17 who enrolled in this optional 34-month follow-up trial (HBV-19).

Methods: HBV-19 is a multicenter, open-label, phase 3b trial of adults with CKD who previously received a complete series of HepB-CpG or HepB-Eng in the HBV-17 trial. Participants were assigned to seroprotection categories at enrollment on the basis of their antibody response to hepatitis B surface antigen (anti-HBs) in HBV-17. The objective was to evaluate the durability of seroprotection (defined as an anti-HBs concentration $\geq$ 10 mIU/mL) induced by HepB-CpG and HepB-Eng. Participants whose anti-HBs concentration was below 10 mIU/mL received additional HepB-CpG or HepB-Eng doses.

Results: 147 participants were enrolled; 66.7 % were men, median age was 65.0 years, and 83.7 % were white. The durability of seroprotection in participants with CKD was similar in those who received HepB-CpG and those who received HepB-Eng. Antibody concentrations $\geq$ 100 mIU/mL persisted for longer in HepB-CpG than HepB-Eng recipients, among those with anti-HBs $\geq$ 100 mIU/mL post vaccination. The geometric mean anti-HBs concentration in the HepB-CpG group was significantly higher than in the HepB-Eng group over time ($P \leq 0.0001$). The safety profiles were similar between the vaccine groups.

Conclusions: Due to the higher antibody levels induced by HepB-CpG in participants with CKD, seroprotection against HBV may be expected to persist longer than that induced by HepB-Eng. ClinicalTrials.gov: NCT01282762.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; AE, adverse event; AESI, adverse event of special interest; Anti-HBs, hepatitis B surface antigen antibodies; CKD, chronic kidney disease; CI, confidence intervals; GFR, glomerular filtration rate; GMC, geometric mean concentration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; mITT, modified intention-to-treat; SAE, serious adverse event; SPR, seroprotection rate.

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1. Introduction

Hepatitis B virus (HBV) infection remains a major global public health problem, including in patients with chronic kidney disease (CKD) receiving hemodialysis. CKD patients are at increased risk of exposure to HBV in the hemodialysis setting, where they receive a treatment procedure with high-volume blood access and where equipment and supplies are reused for multiple patients. In addition, when infected, patients with CKD have a high risk of developing chronic HBV infection and its sequelae, including cirrhosis and hepatocellular carcinoma [1].

Vaccination is an important tool in preventing the transmission of HBV in the dialysis setting [2,3] but seroprotection rates (SPRs: proportion of persons with anti–hepatitis B antibodies [anti-HBs] $\geq$ 10 mIU/mL) are reduced in patients with CKD and on dialysis compared with healthy adults post vaccination [4–8]. Some studies have demonstrated higher response rates in CKD patients prior to becoming dialysis-dependent [1,4]. The Advisory Committee on Immunization Practices (ACIP) recommends that predialysis patients receive the standard hepatitis B vaccine regimen for healthy adults, 10 μg or 20 μg of hepatitis B surface antigen (HBsAg) in a 3-dose regimen [5], although higher doses may induce higher rates of seroprotection [6].

The ACIP recommends dialysis patients be vaccinated with 40 μg of HBsAg in a 3- or 4-dose regimen. If a patient receiving hemodialysis has a hepatitis B surface antibodies (anti-HBs) concentration $\geq$ 10 mIU/mL after the primary series, and subsequently the antibody level declines to < 10 mIU/mL, administration of a booster dose is recommended. If the anti-HBs concentration is < 10 mIU/mL after the primary series, the ACIP recommends an additional 3 doses of vaccine [1].

An important question in the dialysis setting is: How long will seroprotection last before a booster dose is needed [7]? Unlike healthy individuals, patients with CKD have impaired anamnestic responses and therefore depend on maintenance of a seroprotective anti-HBs concentration for reliable protection against infection [8]. Long-term maintenance of an anti–HBs $\geq$ 10 mIU/mL is necessary because breakthrough infections have occurred in patients with CKD with concentrations < 10 mIU/mL [3,9].

The duration of protection against HBV depends on the peak post-vaccination antibody level [10,11]. Some authors have proposed that an anti–HBs level $\geq$ 100 mIU/mL is desirable in CKD patients because it correlates better with a longer duration of protection than lower levels of antibody [12–14]. In fact, in Germany, the Standing Committee on Vaccination recommends all patients on hemodialysis receive a booster injection of hepatitis B vaccine when their anti-HBs concentration decreases below 100 mIU/mL [15].

Results of a phase 3 trial in participants with CKD (HBV-17) demonstrated that 3 doses of HepB-CpG (referred to in other publications as HBsAg-1018 or HEPLISAV-B®, Dynavax Technologies Corporation, Emeryville, California, USA [18]), which uses a Toll-like-receptor 9 agonist adjuvant (CpG 1018 adjuvant), met the primary endpoint of noninferiority and secondary endpoint of superiority to 4 double doses of HepB-Eng (referred to in other publications as HBsAg-Eng or Engerix-B®, GlaxoSmithKline Biologicals, Rixensart, Belgium [19]) and induced a superior peak geometric mean concentration (GMC) compared with HepB-Eng with a similar safety profile [16]. HepB-CpG induced significantly higher immune responses than HepB-Eng in participants with additional factors that make them less likely to respond to hepatitis B vaccines such as diabetes [17]. Here, we present long-term immunogenicity and safety data in a follow-up to the initial trial.

2. Materials and methods

2.1. Study design and participants

This trial (HBV-19) was an open-label, long-term follow-up trial of adult participants with CKD who previously received a complete series of either HepB-CpG or HepB-Eng in trial HBV-17. The methods for HBV-17 have been previously published [16].

Participants enrolled in HBV-17 were aged 18 to 75 years with CKD (defined by an estimated glomerular filtration rate [modification of diet in renal disease formula] $\leq$ 45 mL/min/1.73 m^2); had no prior history of hepatitis B vaccination; were clinically stable; were serum negative for HBsAg, anti-HBs, antibody against hepatitis B core antigen, hepatitis C virus, and HIV; did not have an autoimmune disease; and were not scheduled to undergo a kidney transplant within the next 12 months. In HBV-17, participants were randomized to receive single doses of HepB-CpG administered at weeks 0, 4, and 24 or double doses of HepB-Eng administered at weeks 0, 4, 8, and 24, consisting of two 1.0 mL injections of 20 μg HBsAg for a total of 40 μg HBsAg. Matching placebos were used in the HepB-CpG group for blinding purposes.

Enrollment in HBV-19 was offered to everyone who had participated in HBV-17 and completed the study. Eligible participants received a full vaccine regimen in HBV-17; were clinically stable; and were willing to provide informed consent. Those who received commercially available hepatitis B vaccine after HBV-17, or who had a known history of autoimmune disease were not eligible. Eligible participants were assigned to a seroprotection category at enrollment based on their previous immunologic response: 1) anti-HBs $\geq$ 10 mIU/mL at enrollment; 2) anti-HBs < 10 mIU/mL at enrollment after having responded to the vaccine in HBV-17; or 3) anti-HBs < 10 mIU/mL at enrollment after failing to respond to the vaccine in HBV-17.

The trial was conducted at 27 sites (18 in the United States, 2 in Canada, and 7 in Germany) from November 2011 to October 2013; was approved by the appropriate institutional review boards in each country; and was conducted according to the Declaration of Helsinki and Good Clinical Practices. Written informed consent was obtained prior to enrollment.

2.2. Study vaccines and administration

HepB-CpG was composed of 20 μg recombinant HBsAg, subtype *adw* and 3000 μg CpG 1018 adjuvant (lots TDG010, TDG013). Participants who had responded to HepB-CpG in HBV-17 received a single booster injection (0.5 mL) in the deltoid muscle if their anti-HBs levels were < 10 mIU/mL at any time during HBV-19. Participants in the HepB-CpG group who failed to respond in HBV-17 (anti-HBs < 10 mIU/mL) received a single dose of HepB-CpG administered by injection (0.5 mL) in the deltoid muscle at weeks 0, 4, and 24.

HepB-Eng was composed of 20 μg recombinant HBsAg combined with 500 μg alum adjuvant (lots AHBVB910AA and AHBVC111AA [US], AHBVB925AB [Canada], and AHBVB988AB and AHBVC016AC [Germany]). Participants who had responded to HepB-Eng in HBV-17 received a double dose of booster injections (1.0 mL per injection; 2 injections indicated for adults on hemodialysis) in the deltoid muscle if their anti-HBs levels were < 10 mIU/mL at any time during HBV-19. Participants who failed to respond in HBV-17 (anti-HBs < 10 mIU/mL) received a double dose of HepB-Eng in the deltoid muscle at study weeks 0, 4, and 24.

2.3. Study procedures

Demographic information, medical history, medication history, and smoking history were collected and laboratory testing for

anti-HBs was conducted during the screening visit. At regularly scheduled visits, participants underwent clinical safety evaluations and had blood drawn for measurement of anti-HBs levels.

2.4. Safety assessments

The safety and tolerability assessments included monitoring and recording of local and systemic post-injection reactions, adverse events, autoimmune adverse events, and serious adverse events (SAEs). Diary cards solicited information about the presence and severity of local post-injection reactions (redness, swelling, pain at or near the injection site); systemic post-injection reactions (malaise, headache, myalgia, fatigue) and oral temperature for 7 days after study injection.

Participants who did not receive vaccine during the study (ie, their anti-HBs level was always $\geq$ 10 mIU/mL), were assessed only for immune-mediated adverse events of special interest (AESIs). Participants who received a booster dose of vaccine during the study were assessed for adverse events for 4 weeks after the injection and for AESIs for the duration of the study. Participants who received a full vaccine series during the study were assessed for adverse events for 28 weeks after the first injection and for immune-mediated AESIs for the duration of the study. An independent safety evaluation and adjudication committee adjudicated whether suspected autoimmune adverse events were autoimmune and related to study vaccine in a blinded fashion.

2.5. Immunogenicity assessments

Anti-HBs serum concentrations were measured using the Ortho Vitros® enhanced chemiluminescence immunoassay (Ortho Clinical Diagnostics, Rochester, NY). Seroprotection was defined as anti-HBs serum concentration $\geq$ 10 mIU/mL.

2.6. Statistical methods

The primary objective of the trial was to evaluate the durability of seroprotection induced by HepB-CpG and HepB-Eng as measured by the SPR. SPRs were calculated with associated exact binomial 95 % confidence intervals (CIs) using the Clopper-Pearson method [20]. All time-to-event analyses, such as durability of seroprotection and anti-HBs concentration $\geq$ 100 mIU/mL, were analyzed by vaccination group (HepB-CpG and HepB-Eng) using the Kaplan-Meier method [21]. Anti-HBs concentrations were summarized using geometric means. The antibody decay curve over time was estimated by vaccination group for participants who were seroprotected in HBV-17 and enrolled in HBV-19. To estimate the antibody decay curve over time, a mixed-linear model appropriate for repeated measure was fitted to $\log_{10}$ transformed anti-HBs concentrations, starting from the time of peak concentration for each participant [22]. The model included vaccination group, days, and $\log_{10}$ transformed days as fixed effects and participants as a random effect. The estimated model then was raised to the 10th power to obtain the estimated decay function.

Immunogenicity analyses used the modified intent-to-treat (mITT) analysis population comprising all participants who had an immunogenicity evaluation. The safety population included participants who received study vaccine in HBV-17 or HBV-19 and who had a post-injection safety evaluation. For analyses of reactogenicity, the safety population included participants who received study vaccine in HBV-19 and turned in diary cards. One participant assigned to the HepB-Eng group erroneously received HepB-CpG and was excluded from the immunogenicity analysis and included in the HepB-CpG group for safety analyses.

All statistical tests were performed at the 2-sided 0.05 level of significance. No imputations were made for missing immunogenicity data. All data analyses were performed using SAS® version 9.2 or later (SAS Institute, Cary, NC).

3. Results

3.1. Study participants

In this follow-up study, 147 participants were enrolled: 72 in the HepB-CpG group and 75 in the HepB-Eng group. At enrollment, 105 participants were followed for durability of seroprotection (HepB–CpG: n = 54; HepB-Eng: n = 51), 16 of whom received at least one booster dose of vaccine (n = 8 for each vaccine group), 23 participants who were seroprotected in the primary study but not at enrollment in the follow-up study were assigned to receive a booster dose of vaccine (HepB-CpG: n = 10; HepB–Eng: n = 13), and 19 participants who were not seroprotected in the primary study were assigned to receive a second vaccine series (HepB-CpG: n = 8; HepB-Eng: n = 11).

Of the 39 participants who did not complete the study, 13 were lost to follow-up and 13 withdrew consent (Table 1). Three participants died during the study. The median follow-up was 1026 days (33.7 months) after the first visit in HBV-17 for the HepB-CpG group and 1045 days (34.3 months) for the HepB-Eng group.

The majority of participants were men (66.7 %; Table 2); median age was 65.0 years; and 83.7 % of participants were white. Over half the participants were obese and over half had type 2 diabetes mellitus. In general, the baseline characteristics of the participants in HBV-19 were similar to those of the overall population in HBV-17, with the following exceptions: a lower proportion of participants had diabetes or were obese than in HBV-17; a higher proportion had a glomerular filtration rate (GFR) $\geq$ 31 mL/min/1.73 m^2 than in HBV-17. In general, in HBV-19, the demographic and baseline characteristics were similar between vaccination groups, except a higher proportion of participants with diabetes and a lower proportion of participants with a low GFR (<15 mL/min/1.73 m^2) were in the HepB-CpG group than in the HepB-Eng group.

Participants in the HepB-CpG group who enrolled in HBV-19 had an SPR that was 3.8 % lower than the total HepB-CpG population in HBV-17 (Table 3), while HepB-Eng participants in HBV-19 had an SPR 3.5 % higher than in the total HepB-Eng population in HBV-17. Thus, the difference in SPRs between vaccine groups was lower in HBV-19 than in HBV-17, with a difference of 0.8 % in HBV-19 and 8.0 % in HBV-17. The proportion of participants with anti-HBs $\geq$ 100 mIU/mL in the HepB-CpG group was the same in HBV-19 participants as compared with the total HepB-CpG population in HBV-17. However, the proportion of participants with anti-HBs $\geq$ 100 mIU/mL in the HepB-Eng group was higher in HBV-19 than in the total HepB-Eng population in HBV-17, resulting in a smaller difference in the proportion of participants with anti-HBs $\geq$ 100 mIU/mL between vaccine groups in HBV-19 (2.9 %) than in HBV-17 (10.3 %).

Table 1
Disposition (mITT population).

	HepB-CpG (n = 72)	HepB-Eng (n = 75)	Total (N = 147)
Completed, n (%)	53 (73.6)	55 (73.3)	108 (73.5)
Discontinued, n (%)	19 (26.4)	20 (26.7)	39 (26.5)
Consent withdrawn	6 (8.3)	7 (9.3)	13 (8.8)
Lost to Follow-up	8 (11.1)	5 (6.7)	13 (8.8)
Death	1 (1.4)	2 (2.7)	3 (2.0)
Other	4 (5.6)	6 (8.0)	10 (6.8)

Abbreviations: mITT = modified intention-to-treat.

Table 2
Demographic and baseline characteristics for trial HBV-17 and trial HBV-19 (mITT populations).

Characteristic	Trial HBV-17			Trial HBV-19		
	HepB-CpG (n = 247)	HepB-Eng (n = 260)	Total (N = 507)	HepB-CpG (n = 72)	HepB-Eng (n = 75)	Total (N = 147)
Sex, n (%)						
Male	157 (63.6)	157 (60.4)	314 (61.9)	50 (69.4)	48 (64.0)	98 (66.7)
Female	90 (36.4)	103 (39.6)	193 (38.1)	22 (30.6)	27 (36.0)	49 (33.3)
Age (years)[a]						
Mean (SD)	61.4 (9.03)	61.3 (9.73)	61.3 (9.38)	62.8 (10.24)	61.0 (11.30)	61.9 (10.79)
Median	64.0	63.0	63.0	66.5	64.0	65.0
Min, Max	34.0, 75.0	22.0, 75.0	22.0, 75.0	36.0, 77.0	24.0, 76.0	24.0, 77.0
BMI (kg/m^2)						
N	247	260	507	71	75	146
Mean (SD)	34.1 (8.51)	32.2 (6.93)	33.1 (7.79)	32.6 (7.90)	31.4 (6.64)	32.0 (7.28)
Median	32.5	31.5	32.0	30.7	30.7	30.7
Min, Max	16.9, 72.6	18.2, 53.2	16.9, 72.6	19.9, 51.9	19.9, 51.4	19.9, 51.9
BMI stratum, n (%)						
<30 kg/m^2	96 (38.9)	106 (40.8)	202 (39.8)	32 (44.4)	36 (48.0)	68 (46.3)
≥30 kg/m^2	151 (61.1)	154 (59.2)	305 (60.2)	39 (54.2)	39 (52.0)	78 (53.1)
Unknown				1 (1.4)		1 (0.7)
Race, n (%)						
White	197 (79.8)	202 (77.7)	399 (78.7)	60 (83.3)	63 (84.0)	123 (83.7)
Black or African American	44 (17.8)	46 (17.7)	90 (17.8)	9 (12.5)	9 (12.0)	18 (12.2)
Asian	3 (1.2)	5 (1.9)	8 (1.6)	2 (2.8)	3 (4.0)	5 (3.4)
American Indian or Alaska Native	0 (0)	1 (0.4)	1 (0.2)	0	0	0
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.4)	1 (0.2)	0	0	0
Other	3 (1.2)	5 (1.9)	8 (1.6)	1 (1.4)	0	1 (0.7)
Ethnicity, n (%)						
Hispanic	63 (25.5)	71 (27.3)	134 (26.4)	15 (20.8)	15 (20.0)	30 (20.4)
Non-Hispanic	184 (74.5)	189 (72.7)	373 (73.6)	57 (79.2)	60 (80.0)	117 (79.6)
Smoking Status, n (%)						
Yes	34 (13.8)	43 (16.5)	77 (15.2)	6 (8.3)	8 (10.7)	14 (9.5)
No	213 (86.2)	217 (83.5)	430 (84.8)	66 (91.7)	67 (89.3)	133 (90.5)
Type 2 Diabetes Status, n (%)						
Yes	168 (68.0)	160 (61.5)	328 (64.7)	43 (59.7)	39 (52.0)	82 (55.8)
No	79 (32.0)	100 (38.5)	179 (35.3)	29 (40.3)	36 (48.0)	65 (44.2)
Dialysis, n (%)						
Yes	34 (13.8)	40 (15.4)	74 (14.6)	9 (12.5)	10 (13.3)	19 (12.9)
No	213 (86.2)	220 (84.6)	433 (85.4)	63 (87.5)	65 (86.7)	128 (87.1)
Glomerular Filtration Rate (mL/min/1.73 m^2)[b]*, n (%)*						
≤15	39 (15.8)	54 (20.8)	93 (18.3)	10 (13.9)	14 (18.7)	24 (16.3)
16–30	97 (39.3)	96 (36.9)	193 (38.1)	24 (33.3)	25 (33.3)	49 (33.3)
≥31	111 (44.9)	110 (42.3)	221 (43.6)	38 (52.8)	36 (48.0)	74 (50.3)

Abbreviations: BMI = body mass index; Max = maximum; Min = minimum; mITT = modified intent-to-treat; SD = standard deviation.
[a] Age at trial enrollment.
[b] Measured at HBV-17 screening.

Table 3
Peak seroprotection rates in HBV-17 among all participants in trial HBV-17 and trial HBV-19 (mITT population).

	HBV-17 Participants			HBV-19 Participants[a]		
	HepB-CpG (n = 227)	HepB-Eng (n = 242)		HepB-CpG (n = 72)	HepB-Eng (n = 75)	
HBV-17 Week 28	**SPR (%) (95 % CI)**	**SPR (%) (95 % CI)**	**Difference (95 % CI)**	**SPR (%) (95 % CI)**	**SPR (%) (95 % CI)**	**Difference (95 % CI)**
	89.9 (85.2, 93.5)	81.8 (76.4, 86.5)	8.0 (1.3, 14.8)	86.1 (75.9, 93.1)	85.3 (75.3, 92.4)	0.8 (-10.9, 12.5)
	Anti-HBs ≥100 mIU/mL (%) (95 % CI)	**Anti-HBs ≥100 mIU/mL (%) (95 % CI)**	**Difference (95 % CI)**	**Anti-HBs ≥100 mIU/mL (%) (95 % CI)**	**Anti-HBs ≥100 mIU/mL (%) (95 % CI)**	**Difference (95 % CI)**
	73.6 (67.3, 79.2)	63.2 (56.8, 69.3)	10.3 (1.9, 18.8)	73.6 (61.9, 83.3)	70.7 (59.0, 80.6)	2.9 (-11.6, 17.5)
	GMC (mIU/mL) (95 % CI)	**GMC (mIU/mL) (95 % CI)**	**Ratio of GMCs**	**GMC (mIU/mL) (95 % CI)**	**GMC (mIU/mL) (95 % CI)**	**Ratio of GMCs**
	587.1 (386.7, 891.4)	156.5 (103.6, 236.3)	3.68 (2.04, 6.61)	663.0 (292.9, 1500.6)	248.9 (125.0, 495.9)	2.7 (0.9, 7.7)

Abbreviations: anti-HBs = antibody to hepatitis B surface antigen; CI = confidence interval; GMC = geometric mean concentration of anti-HBs; mITT = modified intent-to-treat; SPR = seroprotection rate (proportion with anti-HBs ≥ 10 mIU/mL).
[a] Trial results from HBV-17 in HBV-19 participants.

The peak GMC at week 28 in HBV-17 was lower in both vaccine groups than the peak GMC at week 28 for the total populations in HBV-19, but the difference was greater in the HepB-Eng group. Thus, the ratio of GMCs was lower in those who participated in HBV-19 than those who participated in HBV-17 (Table 3).

3.2. Immunogenicity

3.2.1. Primary Objective

Among participants who were seroprotected in HBV-17, the durability of seroprotection over time was similar between

HepB-CpG and HepB-Eng recipients. Of the 62 HepB-CpG recipients who were seroprotected at week 28 in HBV-17, 48 (77.4 %) maintained seroprotection through study termination (median follow-up of 33.7 months from the enrollment of HBV-17). Of the 64 HepB-Eng recipients who were seroprotected at week 28 in HBV-17, 45 (70.3 %) maintained seroprotection through study termination (median follow-up of 34.3 months from the enrollment of HBV-17).

The time to loss of seroprotection from week 28 in HBV-17 was similar between the 2 vaccine groups (Fig. 1; P = 0.4723). As greater than 70 % of participants retained seroprotection over the course of the trial, the median time to loss of seroprotection was not estimable. The time to loss of seroprotection at the 25th percentile was 791 days (26.0 months) for HepB-CpG recipients and 581 days (19.1 months) for HepB-Eng recipients.

3.2.2. Secondary Objectives

Among participants with anti-HBs $\geq$ 100 mIU/mL at week 28 in HBV-17, the persistence of an antibody concentration $\geq$ 100 mIU/mL was longer in HepB-CpG recipients than in HepB-Eng recipients. Of the 53 HepB-CpG recipients who had anti-HBs $\geq$ 100 mIU/mL in HBV-17, 31 (58.5 %) maintained concentrations $\geq$ 100 mIU/mL through study termination. The persistence of anti-HBs concentrations $\geq$ 100 mIU/mL in HBV-19 participants from week 28 in HBV-17 was significantly longer in the HepB-CpG group than in the HepB-Eng group (Fig. 2; P = 0.0076). The median time to loss of an anti-HBs concentration $\geq$ 100 mIU/mL was 1143 days (37.6 months) for HepB-CpG recipients and 530 days (17.4 months) for HepB-Eng recipients.

The rate of decrease in anti-HBs concentrations was similar between participants who received HepB-CpG and those who received HepB-Eng (Fig. 3). The mean anti-HBs concentration in the HepB-CpG group was significantly higher than in the HepB-Eng group over time (Fig. 3C; $P \leq 0.0001$).

3.3. Safety

3.3.1. Exposure

Overall, 24 participants in the HepB-CpG group and 32 participants in the HepB-Eng group received additional vaccine doses beyond that received in HPV-17 (more than 3 and 4 doses, respectively; Table 4). Participants in the HepB-CpG group received 3 to 6 cumulative doses and participants in the HepB-Eng group received 2 to 8 cumulative double doses. The highest exposure was in participants assigned to receive a second vaccine series. For participants not seroprotected during HBV-17 in the HepB-CpG group, 5 participants (6.8 %) received a second series of 3 doses. For participants not seroprotected during HBV-17 in the HepB-Eng group, 6 participants (8.1 %) received a second series of 3 double doses, and 4 participants (5.4 %) received a second series of 3 double doses and a single booster dose.

3.3.2. Post-injection Reactions

A lower proportion of HepB-CpG recipients than HepB-Eng recipients reported local reactions and a higher proportion of HepB-CpG recipients than HepB-Eng recipients reported systemic reactions within 7 days following administration of 1 or more doses of vaccine (Table 5). All reactions were mild to moderate severity except for 1 HepB-CpG recipient who reported severe malaise; among HepB-Eng recipients, 1 reported severe pain and 1 reported severe myalgia. The frequency of post-injection reactions decreased as the number of doses increased. Overall, post-injection reactions were similar between the two groups.

3.3.3. Adverse Events

Adverse events were similar between the vaccine groups (Table 5). Participants in the HepB-CpG and HepB-Eng groups reported adverse events (16.7 % and 18.8 %, respectively) or SAEs (4.2 % and 3.1 %, respectively). One adverse event of gastroenteritis lasting for 4 days was considered by the investigator to be related to HepB-CpG. One HepB-CpG recipient reported SAEs of hypercalcemia, traumatic pneumothorax, and multi-organ failure; and 1 HepB-Eng group recipient reported SAEs of plasmacytoma, amyloidosis, and epidermolysis. None of the SAEs was considered by the investigator to be related to study vaccine. No participant discontinued vaccine because of an AE and there were no immune-related AESIs. Three participants died during the study of conditions typical for this participant population. One participant in the HepB-CpG group died from multi-organ failure 163 days after administration of the last study injection. Two additional deaths occurred outside the adverse events collection period: 1 participant in the HepB-CpG group experienced a fatal cardiac arrest

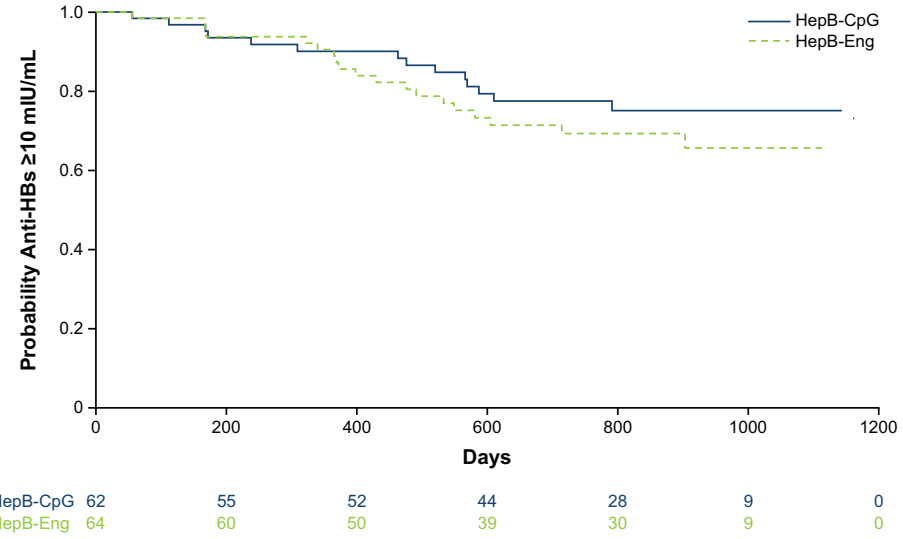

Fig. 1. Kaplan-Meier analysis of persistence of anti-HBs concentrations $\geq$ 10 mIU/mL in HBV-19 participants who had anti-HBs concentrations $\geq$ 10 mIU/mL at week 28 in HBV-17 (mITT population). Number of participants at risk are shown for each group. Abbreviations: anti-HBs = antibody to hepatitis B surface antigen; mITT = modified intention-to-treat. Logrank P = 0.4723.

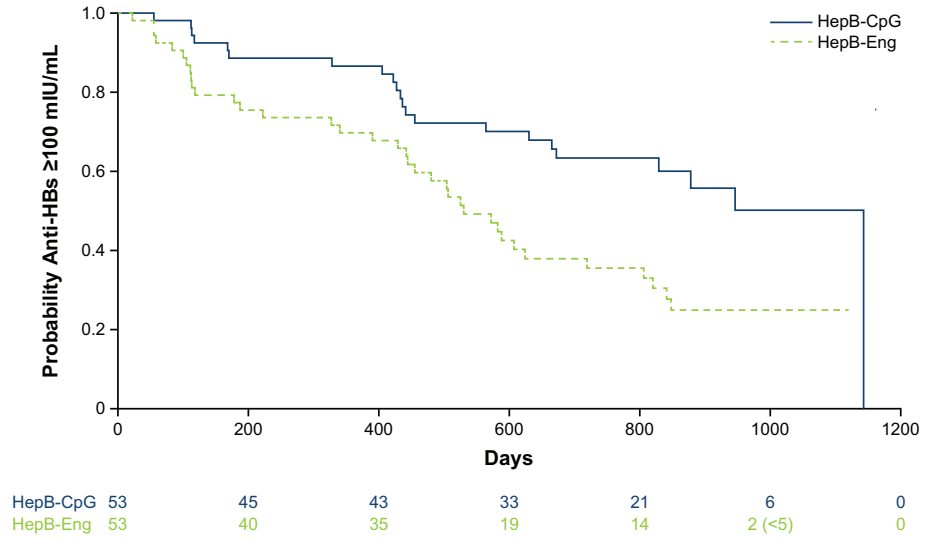

Fig. 2. Kaplan-Meier analysis of persistence of anti-HBs concentrations ≥ 100 mIU/mL in HBV-19 participants who had anti-HBs concentrations ≥ 100 mIU/mL at week 28 in HBV-17 (mITT population). Number of participants at risk are shown for each group. Abbreviations: anti-HBs = antibody to hepatitis B surface antigen; mITT = modified intention-to-treat. Logrank P = 0.0076.

495 days after administration of the last study injection, and 1 participant in the HepB-Eng group experienced a fatal event of hyperkalemia 584 days after administration of the last study injection. No death was considered to be related to study vaccine by investigators.

4. Discussion

This 34-month follow-up to the phase 3 study HBV-17 was designed to assess the long-term persistence of antibodies against HBsAg induced by HepB-CpG compared with HepB-Eng in participants with CKD. In HBV-17, a significantly higher proportion of CKD participants in the HepB-CpG group were seroprotected and had anti-HBs ≥ 100 mIU/mL than in the HepB-Eng group. In addition, the GMC of antibodies to HBsAg induced by HepB-CpG was significantly higher than the GMC of antibodies to HBsAg induced by HepB-Eng.

While enrollment in HBV-19 was offered to all HBV-17 participants, only 29 % of the mITT population enrolled in the follow-up study, with similar proportions in the 2 vaccine groups. The participants in HBV-19 were not truly representative of the participants in HBV–17; the HepB-Eng group in HBV-19 had higher immune responses than in all HepB-Eng recipients in HBV-17. Thus, the difference in immune responses between vaccine groups in those who participated in HBV-19 was smaller than in the randomized study HBV-17.

Although the difference between vaccine groups was smaller than in HBV-17, the persistence of antibodies to HBsAg was longer in those who received HepB-CpG than in those who received HepB-Eng. Because more than 70 % of participants who entered the HBV-19 trial had anti-HBs ≥ 100 mIU/mL, it is not surprising that the median duration of seroprotection (anti-HBs ≥ 10 mIU/mL) was not estimable in this study over a median follow-up of 29 months. Twenty-five percent of HepB-CpG recipients lost seroprotection over a median of 26 months and 25 % of HepB-Eng recipients lost seroprotection over a median of 19 months. The median time to an anti-HBs level < 100 mIU/mL was significantly longer in the HepB-CpG group than the HepB-Eng group (38 months versus 17 months) as would be expected because of the higher peak GMC in the HepB-CpG group. Additionally, anti-HBs levels persisted significantly longer in the HepB-CpG group than in the HepB-Eng group with similar rates of antibody decay. These results suggest that antibodies to HBsAg induced by HepB-CpG are similar to those induced by HepB-Eng.

An important challenge in the prevention of hepatitis B is long-term protection of patients with CKD. Not only do patients with CKD require higher doses of HBsAg in the vaccine than healthy adults, anti-HBs concentrations decrease more rapidly for CKD patients than healthy adults. In studies of patients with CKD, 7 % to 50 % lose seroprotection with hepatitis B vaccines within a year [9,23–25]; in 1 study, the median time to loss of seroprotection was 29 months in participants who received HepB-Eng [25]. However, comparisons across studies are challenging because different populations have been studied, different antibody concentration cutoffs have been used, loss to follow-up was high, and different analyses have been presented. In a randomized study of 105 hemodialysis participants comparing intradermal versus intramuscular (IM) administration of HepB-Eng, the mean time to loss of seroprotection was 23.6 months in participants who received IM injections [23]. In a single arm study of HepB-Eng in 60 hemodialysis participants, 59 % of participants remained seroprotected up to 3 years after initiation of the vaccine series [9]. In an observational study of 13,661 HepB-Eng participants at Fresenius Medical Care Centers in the United States, 23 % of dialysis participants lost seroprotection in a year [26].

Overall, 24 participants in the HepB-CpG group and 32 participants in the HepB-Eng group received a second vaccine series or a booster dose in this study. HepB-CpG was well tolerated in these participants who had previously received a primary 3-dose series of vaccine in HBV-17. In this study, adverse events, SAEs, and deaths were similar between the vaccine groups and no new-onset autoimmune conditions were reported.

The primary limitation of this study was that a relatively small proportion of eligible participants enrolled in HBV-19 and they were not truly representative of the overall population in the randomized phase 3 HBV-17 study. The immune responses of HepB-CpG recipients were more similar to those in HBV-17 than the HepB-Eng recipients. Regardless, as in HBV-17, the GMC in the HepB-CpG group was higher than in the HepB-Eng group resulting in a significantly longer persistence of antibodies in HepB-CpG recipients than in HepB-Eng recipients. However, toward the end of the 3-year follow up, <5 HepB-Eng recipients were at risk for

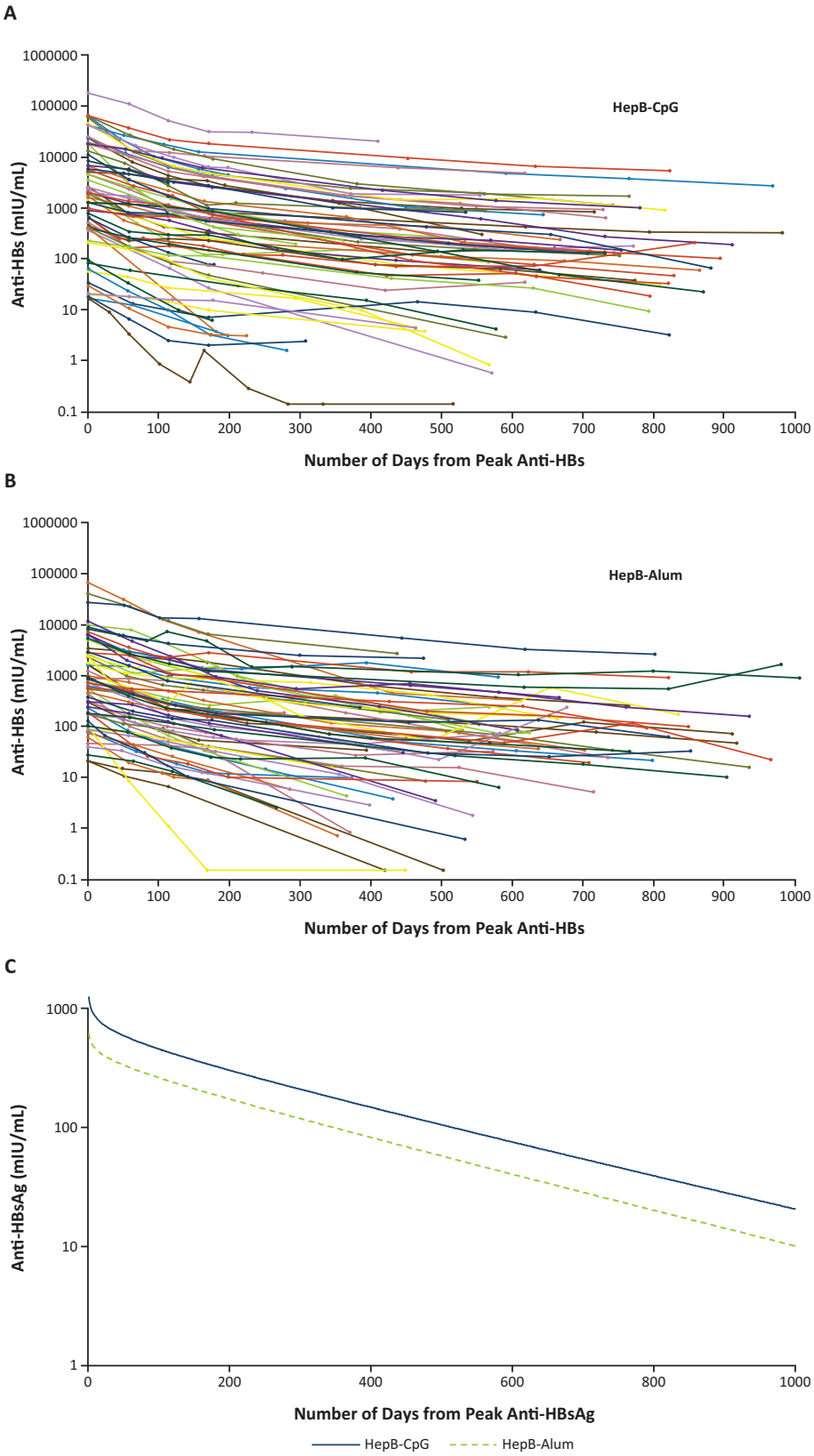

Fig. 3. A) Change of anti-HBs concentration over time in participants who received HepB-CpG. B) Change of anti-HBs concentration over time in participants who received HepB-Eng. C) Anti-HBs decay curve by vaccine group: model based on HBV-19 mITT population with anti-HBs concentrations ≥ 10 mIU/mL during HBV-17 (mITT population). Abbreviations: anti-HBs = antibody to hepatitis B surface antigen; mITT = modified intention-to-treat. $P < 0.0001$.

losing an anti-HBs level ≥ 100 mIU/mL, making the subsequent evaluation of this endpoint unreliable. An additional limitation was that 25 % of participants did not complete the full 3-year follow-up from the beginning of HBV-17. This is a challenge in HBV vaccine studies in participants with late-stage CKD [25]. While approximately half of participants had a GFR < 30 mL/mi

Table 4
Cumulative vaccine exposure in trial HBV-17 and trial HBV-19 by vaccination group (safety population).

Number (%) of Participants Receiving Doses	HepB-CpG (n = 73)	HepB-Eng (n = 74)	Total (N = 147)
2 Doses	0	1 (1.4)	1 (0.7)
3 Doses	49 (67.1)	0	49 (33.3)
4 Doses	11 (15.1)	41 (55.4)	52 (35.4)
5 Doses[a]	6 (8.2)	19 (25.7)	25 (17.0)
6 Doses	7 (9.6)	3 (4.1)	10 (6.8)
7 Doses	0	6 (8.1)	6 (4.1)
8 Doses	0	4 (5.4)	4 (2.7)

[a] Includes 1 participant in the HepB-CpG group who received 4 double doses of HepB-Eng in HBV-17 and 1 dose of HepB-CpG in HBV-19.

n/1.73 m^2, a small number of participants in each arm were undergoing dialysis, which limits conclusions for durability of HepB-CpG and HepB-Eng in this important subgroup of participants with CKD. Finally, the numbers of participants who received a booster dose of study vaccine or a second series of vaccine was too small to allow meaningful comparisons.

In conclusion, use of HepB-CpG may reduce the need for a second vaccine series due to lack of seroprotection and likely reduce the need for subsequent booster doses of vaccine, while also maintaining a safety profile that is similar to HepB-Eng. High antibody levels induced by HepB-CpG in participants with CKD may be expected to persist longer than those induced by HepB-Eng.

Author Disclosures

This study was funded by Dynavax Technologies Corporation. M.G. received speaker's honoraria from Astellas, Daiichi Sankyo, Novartis, Sanofi, Vifor, and GlaxoSmithKline unrelated to the topic of this work. F.X. is a consultant for and R.S.J. is an employee of Dynavax Technologies Corporation. No other conflicts were reported.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.G. received speaker's honoraria from Astellas, Daiichi Sankyo, Novartis, Sanofi, Vifor, and GlaxoSmithKline unrelated to the topic of this work. F.X. is a consultant for and R.S.J. is an employee of Dynavax Technologies Corporation. No other conflicts were reported.

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Table 5
Safety events by trial HBV-19 vaccination group (safety population).

	HepB-CpG (N = 24)	HepB-Eng (N = 32)
Post-injection reaction[a]	n = 23	n = 30
Any, n (%)	7 (30.4)	6 (20.0)
Severe, n (%)	1 (4.3)	1 (3.3)
Local reactions		
Total, n (%)	2 (8.7)	4 (13.3)
Severe	0	1 (3.3)
Injection site redness		
Total, n (%)	1 (4.3)	1 (3.4)
Severe (>100 mm)	0	0
Injection site swelling		
Total, n (%)	1 (4.3)	1 (3.4)
Severe (>100 mm)	0	0
Injection site pain		
Total, n (%)	2 (8.7)	4 (13.8)
Severe	0	1 (3.3)
Systemic reactions		
Total, n (%)	7 (30.4)	4 (13.3)
Severe	1 (4.3)	1 (3.3)
Fever (elevated body temperature), N		
Total, n (%)	0	0
Severe (39 °C or higher)	0	0
Malaise		
Total, n (%)	3 (13.0)	1 (3.3)
Severe	1 (9.1)	0
Headache		
Total, n (%)	2 (8.7)	2 (6.7)
Severe	0	0
Myalgia		
Total, n (%)	4 (17.4)	2 (6.7)
Severe	0	1 (33.3)
Fatigue		
Total, n (%)	4 (17.4)	2 (6.7)
Severe	0	0
Any AE, [b]n (%)	4 (16.7)	6 (18.8)
Any related AE, n (%)	1 (4.2)	0
Any SAE, [b]n (%)	1 (4.2)	1 (3.1)
Any related SAE, n (%)	0	0
Any AE leading to discontinuation of study medication, n (%)	0	0
	N = 73	N = 74
Any new onset immune-mediated AESI,[c] n (%)	0	0
Death, n (%)	2 (2.7)	1 (1.4)

AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event.

[a] Reactogenicity within 7 days post-injection include active injections only and are presented as percentages due to the different denominators. Percentages are based on the number of participants (n) providing data for each category. Two participants in each vaccination group did not provide oral temperature data. If a participant had the same type of reaction more than once across the study period, only the most severe reaction within that type was counted. Local reactions include redness ≥ 25 mm, swelling ≥ 25 mm, and pain. Local pain, malaise, headache, myalgia, and fatigue were graded as severe if they were significant and prevented daily activity.

[b] AEs were captured at each examination on an AE case report form.

[c] Protocol-defined AESIs included neuroinflammatory disorders, musculoskeletal disorders, gastrointestinal disorders, metabolic diseases, skin disorders, and others.

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