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Immunogenicity and safety of a 2-dose hepatitis B vaccine, HBsAg/CpG 1018, in persons with diabetes mellitus aged 60–70 years

Randall N. Hyer *, Robert S. Janssen

Dynavax Technologies Corporation, 2929 Seventh Street, Suite 100, Berkeley, CA 94710, United States

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ABSTRACT

Background: Hepatitis B virus (HBV) remains a major public health issue, although it is a vaccine-preventable disease. Adults with diabetes are at greater risk of contracting HBV than the general population. Commonly used 3-dose HBV vaccines have reduced immunogenicity in older individuals and in those with diabetes mellitus.

Methods: In this post hoc analysis of a phase 3 clinical trial, participants with type 2 diabetes mellitus aged 60–70 years received either 2-dose HBsAg/CpG 1018 (HEPLISAV-B®, n = 327) at 0 and 4 weeks and placebo at 24 weeks or 3-dose HBsAg/alum (Engerix-B®, n = 153) at 0, 4, and 24 weeks. Immunogenicity, including seroprotection rate (SPR) at week 28, and safety were assessed by subgroup (sex, body mass index, and smoking status). SPR was defined as antibody against hepatitis B surface antigen serum concentration ≥10 mIU/mL.

Results: The SPR at week 28 was significantly higher with HBsAg/CpG 1018 (85.8% [235/274]) than with HBsAg/alum (58.5% [76/130]) in the per-protocol analysis, for an overall difference of 27.3% (95% CI, 18.0–36.8). SPRs with HBsAg/CpG 1018 were consistently markedly higher compared with HBsAg/alum, regardless of sex, body mass index, or smoking status. Adverse events and deaths were comparable between groups.

Conclusions: Two-dose HBsAg/CpG 1018 provides a higher level of seroprotection against HBV than does a 3-dose vaccine (HBsAg/alum) with a similar safety profile in patients aged 60–70 years with type 2 diabetes mellitus.

Study identifier: NCT02117934.

1. Introduction

Hepatitis B virus (HBV) is highly transmissible and causes a serious and potentially life-threatening liver infection. The World Health Organization estimates that 257 million people are seropositive for hepatitis B surface antigen (HBsAg), a marker of active HBV infection, and roughly 887,000 people died from hepatitis B complications in 2015 alone [1]. In the United States, it is estimated that 850,000 to 2.2 million people are living with chronic HBV infection, and despite the availability of prophylactic HBV vaccines, the rate of HBV infection is increasing, with the majority of new infections occurring in adults [2,3].

Adults with diabetes mellitus (DM) are at a greater risk of contracting HBV than the general population [2,4,5], including those aged 60 years or older [6,7]. Non-institutionalized persons with diagnosed DM have a 60% higher prevalence rate of HBV infection than those without DM (National Health and Nutrition Examination Survey) [6]. Patients with DM have more severe HBV-related morbidity, including increased risk of liver cirrhosis and hepatocellular carcinoma, and accelerated disease progression and death compared to those without DM [8,9]. HBV infection outbreaks occur among elderly patients with DM in institutional healthcare settings, such as assisted-living facilities and nursing homes, where breaches of infection control practices associated with sharing of blood glucose monitors and other diabetes related–care equipment have been documented [10–12].

The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommends HBV vaccination of unvaccinated adults with DM aged 19–59 years, and

Abbreviations: AE, adverse event; BMI, body mass index; DM, diabetes mellitus; GMC, geometric mean concentration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; MAE, medically attended adverse event; mITT, modified intent-to-treat; PP, per protocol; SPR, seroprotection rate.

* Corresponding author.
E-mail addresses: rhyer@dynavax.com (R.N. Hyer), rjanssen@dynavax.com (R.S. Janssen).

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unvaccinated adults with DM who are aged 60 years or older may be administered the HBV vaccination at the discretion of the treating physician [7]. However, because of ongoing challenges of vaccinating at-risk adults [13,14], low rates of adherence to Advisory Committee on Immunization Practices guidelines for HBV immunization and vaccine coverage in people with DM persist [15]. Nearly 90% of individuals with DM who are aged 60 years or older remain unvaccinated for HBV [16]. Compounding these challenges, seroprotection rates (SPRs) after hepatitis B vaccination steadily decrease with increasing age [10–12].

HBsAg/CpG 1018 (HEPLISAV-B®, Dynavax Technologies Corporation, Berkeley, California, USA) is the only 2-dose HBV vaccine approved for adults by the US Food and Drug Administration. HBsAg/CpG 1018 is administered over 4 weeks. It provides a markedly higher level of seroprotection, particularly in historically hyporesponsive populations—including older adults, men, people with obesity, adults with diabetes, and smokers—than the most commonly used 3-dose vaccine (HBsAg/alum, Engerix-B®, GlaxoSmithKline Biologicals, Rixensart, Belgium), which is administered over 24 weeks [17–21]. For example, in a recent study of adults with type 2 DM, 90% of participants were seroprotected after completing 2-dose HBsAg/CpG 1018 compared with 65.1% of participants who completed 3-dose HBsAg/alum (95% CI: 19.3%, 30.7%) [21]. We assessed the safety and efficacy of HBsAg/CpG 1018 among adults with type 2 DM who are aged 60–70 years compared with HBsAg/alum. This subpopulation of adults is characteristically hyporesponsive to 3-dose alum-adjuvanted HBsAg/alum, with reduced rates of seroprotection against HBV [22,23].

2. Methods

2.1. Study design

This study 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 HBsAg/CpG 1018 in adults with and without type 2 DM (NCT02117934) [21,24]. The overall study included 5592 adults randomized to receive 2-dose HBsAg/CpG 1018 and 2782 adults randomized to receive 3-dose HBsAg/alum. The study was conducted in accord with the Good Clinical Practice Guideline as defined by the International Conference on Harmonisation guidelines and with applicable local, legal, and regulatory requirements. The study protocol (DV2-HBV-23) and informed consent documents were approved by a central institutional review board (Sterling IRB, Atlanta, Georgia, USA).

2.2. Participants

Participants included in this analysis were adults with a clinical diagnosis of type 2 DM who were taking insulin and/or a hypoglycemic agent and who were aged 60 to 70 years (Fig. 1). We excluded participants if they had a history of HBV or human immunodeficiency virus (HIV) infection or an autoimmune disorder; were seropositive for HBsAg, antibody against hepatitis B surface antigen (anti-HBs), antibody against hepatitis B core antigen (anti-HBc), or antibody against HIV (anti-HIV); or previously received any hepatitis B vaccine, DNA plasmid, or oligonucleotide injection. Participants provided written informed consent prior to enrollment.

2.3. Study vaccine administration

Participants in the overall phase 3 study were randomized in a 2:1 ratio to receive either 2-dose HBsAg/CpG 1018 (Lot #1017098, manufactured by Rentschler Biotechnologie GMbH, Laupheim, Germany) or 3-dose HBsAg/alum (Lot #592D3, manufactured by GlaxoSmithKline Biologics, Philadelphia, PA, USA). Randomization was stratified by site, age group (18–39, 40–70 years), and type 2 DM status. HBsAg/CpG 1018 (20 μg of subtype *adw* recombinant HBsAg and 3 mg of a proprietary phosphorothioate oligodeoxynucleotide adjuvant, known as CpG-1018, per 0.5-mL dose) was administered intramuscularly into the deltoid muscle at 0 and 4 weeks, followed by placebo at 24 weeks to maintain blinding. HBsAg/alum (20 μg HBsAg adsorbed on 500 μg aluminum hydroxide per 1.0-mL dose) was injected intramuscularly into the deltoid muscle at 0, 4, and 24 weeks.

2.4. Outcomes

2.4.1. Immunogenicity

The primary immunogenicity end point for the phase 3 study was at week 28 in participants with DM. Seroprotection was defined as anti-HBs serum concentration ≥10 mIU/mL. The SPR induced by HBsAg/CpG 1018 at week 28 was compared with the SPR induced by HBsAg/alum at week 28 among participants who were aged 60–70 years and by subgroups, including sex, body mass index (BMI), and smoking status. In previous phase 3 trials, the SPR for HBsAg/CpG 1018 peaked at week 24 and SPR for HBsAg/alum peaked at week 28. Therefore, the SPRs as well as the anti-HBs serum geometric mean concentrations (GMCs) induced by HBsAg/CpG 1018 at week 24 and by HBsAg/alum at week 28 were also compared. A reverse cumulative frequency plot [25] was used to summarize, assess, and compare the distribution of anti-HBs concentrations in response to HBsAg/CpG 1018 and HBsAg/alum at week 28.

2.4.2. Safety

Adverse events (AEs) were assessed for all participants in the cohort aged 60 to 70 years with type 2 DM who received at least 1 injection of study vaccine. The proportion of participants with new-onset (reported from the time of first injection [week 0] to week 56), treatment-emergent medically attended AEs (MAEs), including cardiovascular events, immune-mediated AEs of special interest, and deaths were recorded.

2.5. Statistical analysis

The modified intent-to-treat (mITT) analysis was comprised of enrolled participants with type 2 DM aged 60–70 years who received at least 1 injection and underwent at least 1 immunogenicity evaluation. Participants in the cohort aged 60–70 years with type 2 DM who did not deviate 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.

For SPRs and their 95% confidence intervals (CIs), the 2-sided Clopper-Pearson method and the Miettinen and Nurminen method without stratification were used respectively. For GMCs, the 95% CI for HBsAg/CpG 1018 and HBsAg/alum were calculated using the 2-sided Clopper-Pearson method. For the HBsAg/CpG 1018 to HBsAg/alum GMC ratio, 95% CIs were calculated using the Miettinen and Nurminen method without stratification.

3. Results

3.1. Participants

A total of 480 participants were included in this post hoc analysis, with 327 participants receiving HBsAg/CpG 1018 and 153 participants receiving HBsAg/alum (Fig. 1). In the mITT analysis, 319

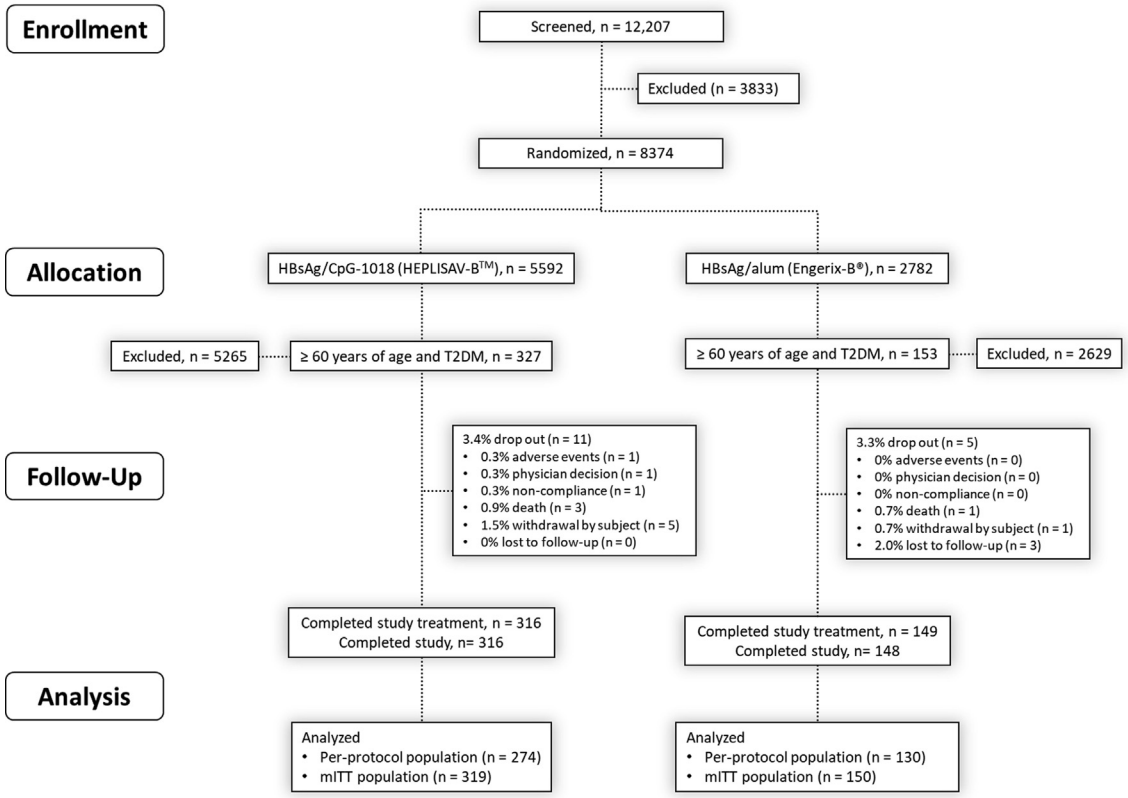

Fig. 1. Disposition of patients. mITT, modified intent-to-treat; T2DM, type 2 diabetes mellitus.

participants were in the HBsAg/CpG 1018 group and 150 participants were in the HBsAg/alum group, whereas in the PP analysis, 274 participants were in the HBsAg/CpG 1018 group and 130 participants were in the HBsAg/alum group. Demographic and baseline characteristics were similar between groups (Table 1). The mean age of participants was 64.5 years (range: 60–70 years), and most were obese, with a BMI $\geq$ 30 kg/m^2.

3.2. Immunogenicity by seroprotection rates

At week 28, in the PP analysis, the SPR in the HBsAg/CpG 1018 group (85.5% [235/274]) was significantly higher than the SPR in the HBsAg/alum group (58.5% [76/130]), with a treatment effect difference of 27.3% (95% CI, 18.0–36.8%) (Fig. 2A). Similarly, in the mITT analysis, the SPR at week 28 was significantly higher for HBsAg/CpG 1018 than for HBsAg/alum, with a treatment effect difference of 27.6% (95% CI, 18.9–36.5%) (Fig. 2B). In each subgroup (sex, BMI stratum, and smoking status), the SPR at week 28 was markedly higher in participants who received HBsAg/CpG 1018 than in those who received HBsAg/alum (Fig. 3).

3.3. Immunogenicity by geometric mean concentration

In the PP analysis, the GMC at week 28 was 131.9 mIU/mL in the HBsAg/CpG 1018 group and 51.6 mIU/mL in the HBsAg/alum group, with a GMC ratio of 2.6 (95% CI, 1.5–4.3; Fig. 4). In each subgroup (sex, BMI stratum, and smoking status), the GMC at week 28 in the HBsAg/CpG 1018 group was markedly higher than the GMC in the HBsAg/alum group (Fig. 4). In the mITT analysis, the GMC at week 28 was 126.7 mIU/mL in the HBsAg/CpG 1018 group and 44.1 mIU/mL in the HBsAg/alum group, with a GMC ratio of 2.9 (95% CI, 1.8–4.6).

The reverse cumulative frequency curves for HBsAg/CpG 1018 and HBsAg/alum had distinctly different shapes (Fig. 5). The slope of the HBsAg/CpG 1018 curve was steeper than the HBsAg/alum curve, indicating that the antibody response to HBsAg/CpG 1018 was less variable than the response to HBsAg/alum. The shallow slope of the HBsAg/alum curve indicates a larger variance in the antibody response to HBsAg/alum compared with HBsAg/CpG-1018.

3.4. Safety

The overall safety of HBsAg/CpG 1018 was comparable to that of HBsAg/alum. A total of 210 (64.2%) participants in the HBsAg/CpG 1018 group reported an MAE with 77 (23.5%) participants who experienced a grade 3 or 4 MAE. The most commonly reported MAEs in the HBsAg/CpG 1018 group were upper respiratory tract infection, back pain, bronchitis, urinary tract infection, and hypertension (Table 2). In the HBsAg/alum group, 85 (55.6%) participants experienced MAEs, 34 (22.2%) of whom reported a grade 3 or 4 MAE. The most commonly reported MAEs in the HBsAg/alum group were type 2 DM, back pain, bronchitis, sinusitis, and osteoarthritis. Two participants (0.6%) in the HBsAg/CpG 1018 group and 5 participants (3.3%) in the HBsAg/alum group reported an MAE that was related to the study treatment. No MAEs related to the study treatment were cardiovascular events. No serious AEs related to the study treatment were reported in either group.

In the HBsAg/CpG 1018 group, 1 (0.3%) participant experienced an immune-mediated AE of special interest related to the study treatment. This participant was diagnosed with polymyalgia rheumatica and, to date, is receiving ongoing treatment and monitoring. No immune-mediated AEs of special interest were reported in the HBsAg/alum group. There were 3 deaths (due to hepatic

Table 1
Demographics and baseline characteristics (safety population).

Parameter	HBsAg/CpG-1018 (n = 327)	HBsAg/alum (n = 153)	Total (n = 480)
Age, years			
Mean (SD)	64.5 (2.91)	64.6 (2.86)	64.5 (2.89)
Median (range)	64.0 (60.0–70.0)	65.0 (60.0–70.0)	65.0 (60.0–70.0)
Sex, n (%)			
Male	208 (63.6)	89 (58.2)	297 (61.9)
Female	119 (36.4)	64 (41.8)	183 (38.1)
Weight, kg			
Mean (SD)	100.4 (22.25)	101.1 (21.63)	100.6 (22.04)
Median (range)	98.5 (47.2–180.0)	101.0 (53.6–171.6)	99.0 (47.2–180.0)
Body mass index, kg/m^2			
Mean (SD)	33.9 (7.11)	34.4 (6.68)	34.1 (6.97)
Median (range)	32.9 (12.9–58.8)	33.3 (21.1–54.2)	33.1 (12.9–58.8)
Body mass index stratum, kg/m^2 (no. [%])			
<30	99 (30.3)	44 (28.8)	143 (29.8)
≥30	228 (69.7)	109 (71.2)	337 (70.2)
Smoking status, n (%)			
Smoker	59 (18.0)	24 (15.7)	83 (17.3)
Nonsmoker	268 (82.0)	129 (84.3)	397 (82.7)
HbA1c at week 0, n (%)			
<6.5	87 (26.6)	42 (27.5)	129 (26.9)
6/5–9.0	203 (62.1)	83 (54.2)	286 (59.6)
>9.0	31 (9.5)	19 (12.4)	50 (10.4)
Number of diabetes complications, n (%)			
0	32 (9.8)	21 (13.7)	53 (11.0)
1	145 (44.3)	68 (44.4)	213 (44.4)
2	82 (25.1)	39 (25.5)	121 (25.2)
3+	68 (20.8)	25 (16.3)	93 (19.4)
Duration of diabetes, n (%)			
<5 years	90 (27.5)	46 (30.1)	136 (28.3)
5+ years	237 (72.5)	106 (69.3)	343 (71.5)
Unknown	0	1 (0.7)	1 (0.2)

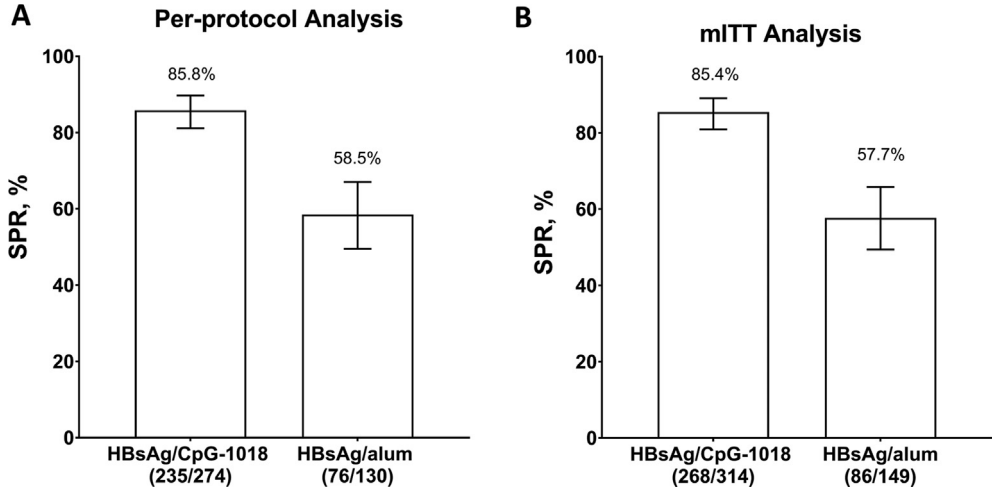

Fig. 2. HBsAg/CpG 1018 induced a significantly higher seroprotection rate (SPR) at week 28 compared with HBsAg/alum. A-Per-protocol analysis (number of seroprotected participants/number of evaluable participants). B-Modified intent-to-treat (mITT) analysis (number of seroprotected participants/number of evaluable participants).

cirrhosis, acute respiratory distress syndrome, and cardiac arrest) in the HBsAg/CpG 1018 group not considered related to treatment and 1 death (due to cardiorespiratory arrest) in the HBsAg/alum group not considered related to treatment.

4. Discussion

Findings from this analysis demonstrated that HBsAg/CpG 1018 induced markedly higher levels of seroprotection against HBV than did HBsAg/alum in participants with type 2 DM who were aged 60–70 years. Invariably, SPRs achieved in participants with type 2 DM who were aged 60–70 years and older were significantly higher in the HBsAg/CpG 1018 group compared with the HBsAg/alum group, regardless of sex, BMI, or smoking status subgroup. The safety profile of the 2-dose HBsAg/CpG 1018 vaccine is similar to that of a commonly used 3-dose vaccine. The immunogenicity and safety findings of this post hoc analysis are consistent with results from the overall phase 3 study

A SPR at week 28 for HBsAg/CpG-1018 and HBsAg/alum (Per-protocol Analysis)

	HBsAg/CpG-1018 (2 Doses)		HBsAg/alum (3 Doses)		
Prespecified Subpopulation	**n/N**	**SPR (%)**	**n/N**	**SPR (%)**	**Difference in SPR (95% CI)**
All Subjects	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					
Non-obese, < 30	76/82	92.7	28/39	71.8	20.9 (7.1 – 37.3)
Obese, ≥ 30	159/192	82.8	48/91	52.7	30.1 (18.6 – 41.5)
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)

B

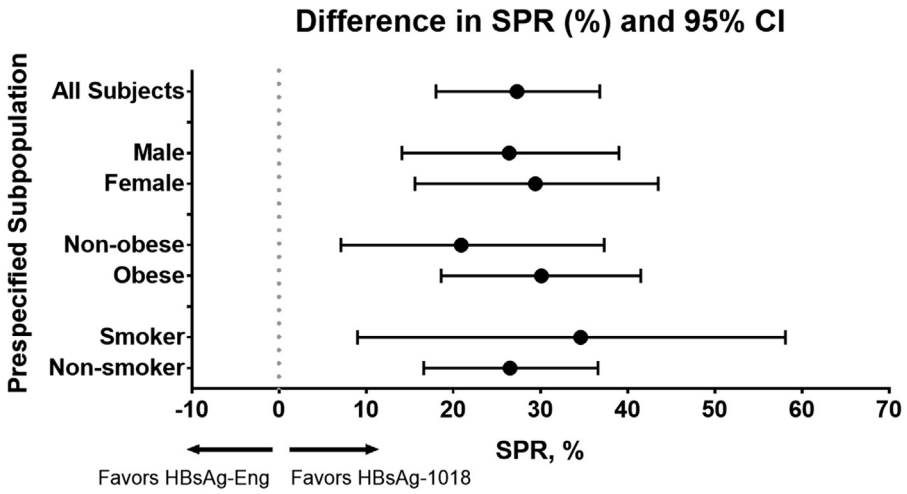

Fig. 3. At week 28, HBsAg/CpG 1018 induced significantly higher seroprotection rates (SPRs) than HBsAg/alum (per-protocol analysis). A-SPR at week 28 for HBsAg/CpG 1018 and HBsAg/alum. B-Difference in SPR and 95% confidence interval (CI) by subgroup (sex, body mass index [BMI] stratum, and smoking status). N, number of evaluable participants; n, number of seroprotected participants.

population and several previous phase 3 studies of HBsAg/CpG [19–21,23].

Although hepatitis B is a vaccine-preventable disease, HBV infection remains a major global public health issue. Both the World Health Organization and the National Academies of Sciences, Engineering, and Medicine have declared hepatitis a major public health problem and have called for its elimination by 2030 [26,27]. Vaccination is a proven tool in populations in whom the current vaccines work well, such as children and healthy young adults. Despite effective childhood vaccination programs, the prevalence of hepatitis B in the United States is increasing, with the majority of new infections occurring in adults [2,3]. Many adults, including older persons with diabetes, do not achieve seroprotection with 3-dose vaccines [10–12]. A prospective, controlled study of 3-dose recombinant hepatitis B vaccine immunogenicity and safety found only 58.2% of participants with DM aged ≥60 years achieved seroprotection compared with 70.2% of age matched non-diabetic controls.[22] Notably, results from a Vaccine Safety Datalink study showed that only half of adults receive all 3 doses, and it has been demonstrated that the third dose is essential for reliable seroprotection [17,18,28,29]. For instance, in a randomized, observer-blinded study, just 32.4% of healthy adults who received HBsAg/alum were seroprotected at 24 weeks after the second dose, whereas 81.1% were seroprotected 4 weeks after the third dose [30]. The prevalence of DM is steadily increasing [31,32] and the proportion of the world's population aged 65 years and older is growing at an unprecedented rate [33]. Given that DM is most prevalent in adults aged 65 years and older [34], we have a dual challenge for this population who is at increasing risk for HBV infection and disease and who do not respond well to traditional 3-dose, alum-adjuvanted vaccines. Improved HBV vaccines that demonstrated higher and earlier seroprotection in older adults with DM may help address this growing public health problem.

In the United States, people with DM are at greater risk of contracting HBV [4], with the odds of a person with diabetes aged ≥60 years developing acute HBV being 1.5 times higher than age-matched controls without diabetes [7]. In 2011, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommended that unvaccinated adults with DM aged 19–59 years receive the HBV vaccine and unvaccinated adults with DM aged 60 years and older may be vaccinated for hepatitis B at the discretion of the treating physician [7]. Yet, findings from multiple studies have shown that adherence to this national guideline remains low due in part to low vaccination coverage [15]

A **GMC at week 28 for HBsAg/CpG-1018 and HBsAg/alum (Per-protocol Analysis)**

Prespecified Subpopulation	HBsAg/CpG-1018 (2 Doses) N	HBsAg/CpG-1018 (2 Doses) GMC (95% CI)	HBsAg/alum (3 Doses) N	HBsAg/alum (3 Doses) GMC (95% CI)	GMC Ratio (95% CI)
All Subjects	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/m²					
Non-obese, < 30	82	213.2 (135.8 – 334.8)	39	131.9 (48.3 – 360.1)	1.6 (0.6 – 4.1)
Obese, ≥ 30	192	107.4 (79.7 – 144.7)	91	34.4 (18.8 – 63.2)	3.1 (1.7 – 5.6)
Smoking status, n (%)					
Smoker	49	100.1 (53.8 – 186.4)	17	17.7 (4.4 – 71.1)	5.6 (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)

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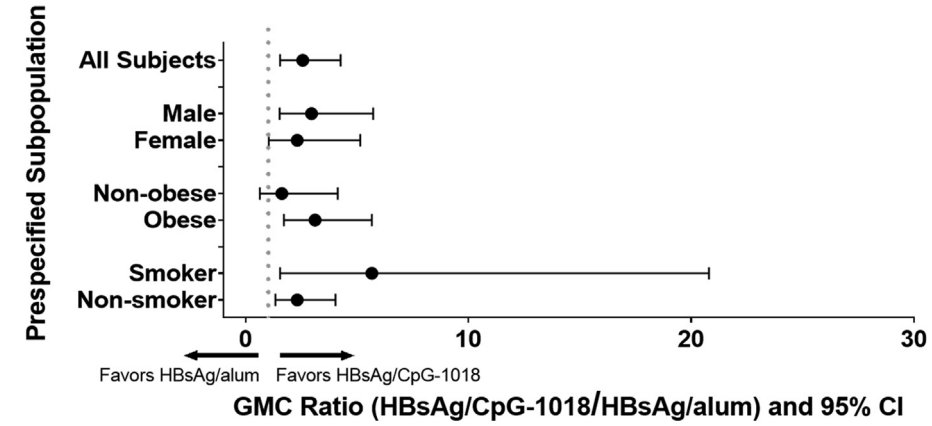

Fig. 4. At week 28, HBsAg/CpG 1018 induced a significantly higher geometric mean concentration (GMC) than HBsAg/alum (per-protocol analysis). A-GMC at week 28 for HBsAg/CpG 1018 and HBsAg/alum. B-GMC ratio and 95% confidence interval (CI) by subgroup (sex, body mass index [BMI] stratum, and smoking status). N, number of evaluable participants; n, number of seroprotected participants.

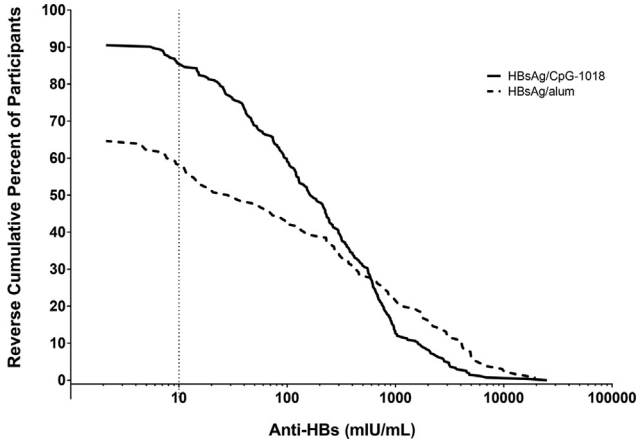

Fig. 5. Reverse cumulative frequency plot of hepatitis B surface antigen (anti-HBs) level by group at week 28.

and low vaccine series completion rates. A claims-based study of US hepatitis vaccination series completion rates from 2007 to 2015 demonstrated that the 3-dose hepatitis B series completion rate ranged from 39.6% to 48.9% in the commercial/Medicare enrol-

Table 2
Most common (≥2% in either treatment group) treatment-emergent medically attended adverse events.

MedDRA Preferred Term	Patients, n (%) HBsAg/CpG-1018 (n = 327)	Patients, n (%) HBsAg/alum (n = 153)
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[a]	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)

[a] Denotes a worsening of type 2 diabetes mellitus. MedDRA, Medical Dictionary for Regulatory Activities.

lee cohort [35]. Most individuals with DM aged 60 years and older are not vaccinated and remain unprotected against HBV [16]. The exact reasons for this low vaccination coverage and completion rates are not clear, though the immunogenicity and safety data presented here would support new prevention options for policymakers.

This exploratory post hoc subgroup analysis has inherent constraints, including overemphasizing the differences between the 2 treatment groups and limited generalizability due to the stringent enrollment criteria [36]. Another limitation is the relatively homogeneous population with respect to race and ethnicity. Future studies would be warranted to determine the immunogenicity and safety of HBsAg/CpG in participants of American Indian/Alaskan Native, non-Hispanic black, and Hispanic backgrounds with the highest rates of diagnosed diabetes according to the National Diabetes Statistics Report, 2017 [34]. Even though the sample size in this post hoc analysis was relatively small, this study was the largest to date in patients with type 2 DM aged 60–70 years.

To further foster the global endeavor of eliminating viral hepatitis by 2030, many European health agencies have begun implementing hepatitis prevention measures to reduce infection incidence in key risk groups [37]. At present, these initiatives do not include vaccination of people with DM, although HBV outbreaks due to capillary blood sampling have been reported not only in the United States, but in countries in the European Union as well [7,38]. Unlike the Centers for Disease Control and Prevention and American Diabetes Association, the World Health Organization Regional Office for Europe, European Association for the Study of Diabetes, and the European Center for Disease Control do not provide guidance on vaccination of patients with DM. In several countries in the European Union, there are currently no recommendations for HBV vaccination of people with DM [39,40]. With HBV outbreaks in people with DM similar to those in the United States, European healthcare providers and policymakers may need to consider strategies to protect people with diabetes against hepatitis B and, if desired, create a framework to provide HBV vaccination to these patients.

Our findings suggest careful consideration of the potential benefits of administering the 2-dose HBsAg/CpG 1018 vaccine to protect against HBV in patients with type 2 DM who are aged 60–70 years and to other traditionally hyporesponsive and at-risk individuals including men, people with obesity, and smokers. Future studies are needed to determine the potential benefits of administering the 2-dose HBsAg/CpG 1018 vaccine to patients with type 2 DM who are aged >70 years.

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Declaration of Competing Interest

The authors are full-time employees of Dynavax Technologies and own stock or stock options.

Author contributions

Both authors designed the analysis; interpreted the data; critically reviewed the manuscript during development; approved the final version for submission; and accept responsibility for the accuracy of the data, their analysis, and this report.

Data sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All authors attest they meet the ICMJE criteria for authorship.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.08.005.

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