Hepatitis B vaccine side-by-side comparison

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Executive Summary

In 2021, the Advisory Committee on Immunization Practices (ACIP) voted to recommend universal hepatitis B (HepB) vaccination for all adults aged 19 to 59 years and in adults aged 60 years and older with risk factors. There are currently 4 FDA-approved HepB vaccines for use in adult immunization. These include 2 first-generation, aluminum-adjuvanted, single-antigen vaccines – Recombivax HB and Engerix-B – and 2 novel vaccines – Heplisav and PreHevbrio. Heplisav is a single-antigen vaccine that contains the novel adjuvant CpG 1018 and is given as a 2-dose series. PreHevbrio, like first-generation HepB vaccines, is aluminum-adjuvanted and is given as a 3-dose series but contains 3 hepatitis surface antigens (vs. just 1 surface antigen). In young, responsive populations, Heplisav and PreHevbrio are noninferior to aluminum-adjuvanted, single-antigen HepB vaccines for achievement of seroprotection, but are associated with higher antibody titers at comparative time points. It is unknown if higher antibody titers prolong durability of response. In historically hyporesponsive populations, the impact of age, smoking, diabetes mellitus, male gender, and obesity are less pronounced in Heplisav and PreHevbrio recipients than in recipients of aluminum-adjuvanted, single-antigen HepB vaccines. In pivotal trials, both newer vaccines achieved significantly higher seroprotection rates (SPRs) in hyporesponsive populations compared with aluminum-adjuvanted, single-antigen HepB vaccines. There are no head-to-head comparisons between Heplisav and PreHevbrio, so it is unknown if immunogenicity differs between the newer vaccines. Compared with an aluminum-adjuvanted, single-antigen HepB vaccine, symptoms of local and systemic reactogenicity occurred at a similar rate with Heplisav, but at a significantly higher rate with PreHevbrio. Results from a single observational cohort study refute findings from the pivotal HBV-23 trial that suggested a potential cardiac safety signal with Heplisav. Other potential safety signals that occurred during Heplisav pivotal trials, including an imbalance between vaccine groups in the occurrence of autoimmune disorders and herpes zoster reactivation, are currently under investigation in post licensure safety studies.

As a 2-dose series completed within 4 weeks, Heplisav has a convenience advantage compared with 3-dose HepB vaccines. Rapid induction of protective antibody levels may be an important consideration in situations where rapid protection is required (eg, high-risk patients or travelers) or when subsequent doses cannot be guaranteed. Real-world evidence suggests that Heplisav is associated with higher HepB vaccine series completion rates compared with 3-dose HepB vaccine series, but completion rates are still suboptimal even with a 2-dose series.

In conclusion, Heplisav and PreHevbrio appear to be more immunogenic than first-generation, aluminum-adjuvanted, single-antigen HepB vaccines and may be an attractive alternative for use in historically hyporesponsive populations. Though SPR is a validated serologic correlate of protection, significantly higher SPRs do not equate to clinical significance or superiority for prevention of breakthrough HBV infections. While protection with the new vaccines is expected to be durable, the duration of protection is unknown and will require more years of clinical use to determine.

SUMMARY POINTS

- There are 4 FDA-approved HepB vaccines approved for use in adults, including 2 first-generation, aluminum-adjuvanted, single-antigen vaccines – Recombivax HB and Engerix-B and 2 novel vaccines – Heplisav and PreHevbrio.
- All 4 HepB vaccines are ACIP recommended for use in adults.
- Heplisav is a single-antigen vaccine that contains the novel adjuvant CpG 1018 and is given as a 2-dose series.
- PreHevbrio is an aluminum-adjuvanted, tri-antigen HepB vaccine that is given as a 3-dose series.
- In historically hyporesponsive populations, Heplisav and PreHevbrio achieve significantly higher SPRs compared with first-generation vaccines. The difference in effect size is less pronounced between novel and first-generation vaccines in historically responsive populations.
- In trials, Heplisav was well tolerated, but potential cardiovascular and autoimmune safety signals have been investigated in post licensure studies.
- In trials, PreHevbrio was associated with a greater incidence of local and systemic reactogenicities vs. first-generation vaccines.
- As a 2-dose series, Heplisav has a convenience advantage compared with 3-dose HepB vaccines.

Hepatitis B vaccine side-by-side comparison

	Brand name			
	Heplisav-B	**Engerix-B**	**Recombivax HB**	**PreHevbrio**
Manufacturer	Dynavax	GlaxoSmithKline	Merck	VBI Vaccines
Approval date	2017	1989	1986	2021
Product description				
No. of surface antigens	1 (s)	1 (s)	1 (s)	3 (s, pre-S1, pre-S2)
Adjuvant	CpG 1018	Aluminum hydroxide	Amphorous aluminum hydroxyphosphate sulfate	Aluminum hydroxide
Derivation source	Yeast (*Hansenula polymorpha*)	Yeast (*Saccharomyces cerevisiae*)	Yeast (*Saccharomyces cerevisiae*)	Mammalian (CHO)
Indications and usage				
Indication	Prevention of infection caused by all known subtypes of HBV			
Approved population	≥ 18 y	≥ Birth	≥ Birth	≥ 18 y
Dosage and administration, adults aged ≥ 18 y[a]				
Route of administration	IM	IM	IM	IM
Dose of HBsAg (volume)	20 mcg (0.5 mL)	• 18-19 y: 10 mcg (0.5 mL) • ≥ 20 y: 20 mcg (1 mL) • HD and other immunocompromised adults ≥ 20 y: 40 mcg (2-mL dose or as two 1-mL doses)	• 18-19 y: 5 mcg (0.5 mL) • ≥ 20 y: 10 mcg (1 mL) • HD and other immunocompromised adults ≥ 20 y: 40 mcg (1 mL)	10 mcg (1 mL)
No. of doses in series	2	3 (non-HD) or 4 (HD)	3	3
Administration schedule	2 doses at 0, 1 mo	• ≥ 18 y: 3 doses at 0, 1, and 6 mos • HD or immunocompromised: 4 doses at 0, 1, 2, and 6 mos	3 doses at 0, 1, and 6 mos	3 doses at 0, 1, and 6 mos

	Brand name			
	Heplisav-B	**Engerix-B**	**Recombivax HB**	**PreHevbrio**
Dosage and administration, adolescents, and pediatrics < 18 y[b]				
Route of administration	Not approved in < 18 y	IM	IM	Not approved in < 18 y
Dose of HBsAg (volume)		• Birth-17 y: 10 mcg (0.5 mL) • HD and other immunocompromised < 20 y: 10 mcg (0.5 mL)	• Birth-10 y: 5 mcg (0.5 mL) • 11-15 y: 10 mcg (1 mL) • 11-17 y: 5 mcg (0.5 mL) • HD and other immunocompromised < 20 y: 5 mcg (0.5 mL)	
No. of doses in series		3	2 (10 mcg, 11-15 y) or 3 (5 mcg, Birth-17 y)	
Administration schedule		**ACIP routine series** • 3-dose series at age 0, 1-2, 6-18 mos. If not started at birth, begin series as soon as feasible. • 4 doses are permitted when a combination vaccine containing HepB is used after the birth dose. • Minimum intervals: dose 1 to 2: 4 wks; dose 2 to 3: 8 wks; and dose 1 to 3: 16 wks **ACIP catch-up vaccination** • 3 dose series at 0, 1-2, 6 mos • 2 doses at 0 and 4-6 mos for adolescents aged 11-15 y (adult formulation of Recombivax HB only)		
Dosage form and strength	Solution for IM injection	Suspension for IM injection • Pediatric/adolescent formulation: 10 mcg (0.5 mL) • Adult formulation: 20 mcg (1 mL)	Suspension for IM injection • Pediatric/adolescent formulation: 5 mcg (0.5 mL) • Adult formulation: 10 mcg (1 mL) • Dialysis formulation: 40 mcg (1 mL)	Suspension for IM injection
Contraindications	• Severe allergic reaction, such as anaphylaxis, after a previous dose of any HBV vaccination • Severe allergic reaction to any component of the vaccine, including yeast			• Severe allergic reactions after a previous dose of any HBV vaccination

	Brand name			
	Heplisav-B	**Engerix-B**	**Recombivax HB**	**PreHevbrio**
				• Severe allergic reaction to any component of the vaccine
Warnings and precautions	• Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions. • Immunocompromised persons, including those on immunosuppressant therapy, may have a diminished immune response. • HBV vaccine may not prevent infection in individuals who have an unrecognized infection at time of vaccination.			
	--	• Syncope can occur in association with injectable vaccines. • Defer vaccination for infants with a birth weight < 2,000 g if mother is HBsAg negative at birth. Vaccination may occur at chronological age 1 mo or at hospital discharge. • Infants born weighing < 2,000 g to HBsAg-positive mothers or those whose HBsAg status cannot be determined within 12 h of birth should receive vaccine + HBIG within 12 h of birth. • The birth dose in infants weighing < 2,000 g does not count as the first dose. • Postpone HepB vaccination in persons with moderate or severe acute febrile illness unless they are at immediate risk of HBV infection. • Defer vaccination for infants with a birth weight < 2,000 g if mother is HBsAg negative at birth. Vaccination may occur at chronological age 1 month or at hospital discharge. • Infants born weighing < 2,000 g to HBsAg-positive mothers or those whose HBsAg status cannot be determined within 12 h of birth should receive vaccine + HBIG within 12 h of birth.		--
Adverse reactions	• Local: Injection site • Systemic: Fatigue (11-17%) and headache (8-17%)	Most common are injection-site soreness (22%) and fatigue (14%)	• Infants and children (up to 10 y, >1% of injections): Irritability, fever, diarrhea, fatigue/weakness, diminished appetite, and rhinitis. • In adults, injection site and systemic adverse reactions reported in 17% and 15% of injections, respectively.	• Local: Injection site pain (45-64 y: 42.2-48.8%; ≥ 65 y: 26.7-34.8%) and tenderness (45-64 y: 43.2-50.5%; ≥ 65 y: 30.2-32.8%) • Systemic, ≥ 65 y: Headache (7.3-12.2%), fatigue (11.5-14.5%), and myalgia (11.5-16.6%)

	Brand name			
	Heplisav-B	**Engerix-B**	**Recombivax HB**	**PreHevbrio**
Interactions				
Drug	No data to assess the concomitant use with immune globulin. If given together, use different syringes at different injection sites.	• May be administered concomitantly with immune globulin. • Do not mix with any other vaccine or product in the same syringe or vial.	• May be administered concomitantly with immune globulin. • Do not mix with any other vaccine or product in the same syringe or vial.	No data to assess the concomitant use with immune globulin. If given together, use different syringes at different injection sites.
Laboratory	HBsAg derived from HBV has been transiently detected in blood samples following vaccination. Serum HBsAg may not have diagnostic value within 28 d after receipt of HBV.			
Special Populations				
Pregnancy or lactation	If pregnant women require HepB vaccination, ACIP recommends Engerix-B, Recombivax HB, or Twinrix.			
	• No adequate or well-controlled studies in pregnancy • Unknown if excreted in human milk • Use alternative HepB vaccine	• No adequate or well-controlled studies • Unknown if excreted in human milk	• No adequate or well-controlled studies • Available post-approval data do not suggest an increased risk of miscarriage or major birth defects. • Unknown if excreted in human milk	• No adequate or well-controlled studies in pregnancy • Unknown if excreted in human milk • Use alternative HepB vaccine
Hemodialysis	Safety and effectiveness not established	Approved for use	Approved for use	Safety and effectiveness not established
Clinical pharmacology	Anti-HBs ≥ 10 mIU/mL are recognized as conferring protection against infection.			
	A portion of the HBV gene coding for the s antigen is cloned into yeast and the vaccine is produced from cultures of the recombinant yeast strain. The antigen induces an antibody response to HBV.			S, pre-S2, and pre-S1 HBsAg are co-purified from genetically modified CHO cells. The antigens induce an antibody response to HBV.

	Brand name			
	Heplisav-B	**Engerix-B**	**Recombivax HB**	**PreHevbrio**
How supplied				
SDV, expressed as HBsAg content (volume)	--	20 mcg (1 mL)	• Pediatric/adolescent formulation: 5 mcg (0.5 mL) • Adult formulation: 10 mcg (1 mL) • Dialysis formulation: 40 mcg (1 mL)	10 mcg (1 mL)
Pre-filled syringe, expressed as HBsAg content (volume)	20 mcg (0.5 mL)	• Pediatric/adolescent formulation: 10 mcg TIP-LOK • Adult formulation: 20 mcg TIP-LOK	• Pediatric/adolescent formulation: 5 mcg • Adult formulation: 10 mcg	--
Latex	No	Yes - tip caps of prefilled syringes contain natural rubber latex.	Yes - vial stopper, syringe plunger stopper, and tip cap contain natural rubber latex.	No
Combination product	No	• Twinrix (≥ 18 y): HepA-HepB combination vaccine • Pediarix (6 wk – 6 y): Diphtheria, tetanus, pertussis, HepB, and poliomyelitis combination vaccine	No	No
Storage and handling	Store at 2-8°C	Store at 2-8°C	• Protect from light • Store at 2-8°C • Stable from 0-25°C for 72 h	• Protect from light • Store at 2-8°C
Quick reference coding guide				
CPT Drug Code(s)	90739	90744, 90746, 90747	90746, 90743, 90740, 90744	90759
CPT Administration Code(s)	90471	90460, 90471, 90472	90460, 90471, 90472	90471
HCPCS	G0010	G0010	G0010	G0010
Comparative effectiveness in hyporesponsive populations, antibody response only				
Obesity	Heplisav > Engerix (Appendix 1)	N/A	N/A	PreHevbrio > Engerix (Appendix 1)

	Brand name			
	Heplisav-B	**Engerix-B**	**Recombivax HB**	**PreHevbrio**
Diabetes	• Heplisav > Engerix (Appendix 1) • **CKD and T2DM**, subgroup analysis of phase 3 trial of vaccine naïve (Heplisav 3 doses or Engerix 4 double doses). Heplisav > Engerix for SPR (*P* < .05).[c]	N/A	N/A	N/A
Chronic liver disease	**Heterogeneous CLD**, retrospective cohort. Heplisav > Engerix for SPR (*P* = .03).[d]	N/A	N/A	**Liver transplant**, case series of patients receiving lamivudine prophylaxis. SP after 2 courses of 3 double doses, achieved in 10/20 patients (50%).[e]
Chronic kidney disease	• **ESKD on dialysis**, phase 1 single-arm trial (4 dose series given at 0, 4, 8, and 16 wks). SP achieved in 67/75 (89.3%) of patients.[f] • **ESKD on dialysis**, retrospective cohort of vaccine naïve (Heplisav 2 dose or Engerix 4 double dose series), non-responders (repeat Heplisav 2 dose or Engerix 4 double dose series), or those in need of booster dose (single dose). In vaccine naïve, Engerix > Heplisav for SPR (*P* < .001). SPRs not different between Engerix and Heplisav in non-responders or boosted.[g] • **CKD** (GFR ≤ 45 mL/mL, including ESKD on dialysis) phase 3 trial of vaccine naïve (Heplisav 3 doses or Engerix 4 double doses). Heplisav > Engerix for SPR (*P* < .05).[h]	N/A	N/A	• **ESKD**, case series of non-responders. Seroprotection achieved in 25/29 patients (86%)[i] • **ESKD**, vaccine naïve and vaccine non-responders. SPR not different between PreHevbrio and Engerix (*P* = .73).[j]

	Brand name			
	Heplisav-B	**Engerix-B**	**Recombivax HB**	**PreHevbrio**
Non-responders	**Non-responders** (<10 mIU/mL anti-HB antibodies) after 3 or 4-6 doses of alum-based HepB vaccine. In 3-dose cohort, Heplisav = Engerix for SPR. In 4-6 dose cohort, Heplisav > Engerix for anti-HBs ≥ 100 mIU/mL.[k]	N/A	N/A	**Non-responders** (<10 mIU/mL anti-HB antibodies) after ≥ 4 injections of yeast-derived HBV vaccine: PreHevbrio > Engerix for SPR ($P < .001$).[l]
Other	**HIV**, case series of those receiving primary vaccination and non-responders. SP achieved in 52/64 patients (81%).[m]	N/A	N/A	• **IBD patients** treated with immunosuppressive therapy: NS difference, Engerix B.[n] • **HIV**, case series of vaccine naïve. SP achieved in 26/31 (84%).[o]

Clinical studies

Heplisav

- **HBV-10 trial. *Vaccine*. 2012;30(15):2556-2563.**[p] In a randomized, double-blind, active-controlled, multicenter phase 3 trial, 2,415 HBV infection and immunization naïve adults aged 18 to 55 y were randomized to receive 2 doses of Heplisav at 0 and 4 wks (n = 1809) or 3 doses of Engerix at 0, 4, and 24 wks (n = 606). Notable exclusion criteria included autoimmune disease, clinically significant illness, and pregnancy. The mean age of participants in both groups was 39 y. For the primary immunogenicity outcome of SPR (percentage of patients that achieved anti-HBs ≥ 10 mIU/mL) measured 8 wks (study week 12) and 4 wks (study week 28) after the last dose of Heplisav and Engerix, respectively. Heplisav was noninferior and superior to Engerix with SPRs of 95.1% and 81.1%, respectively (difference in SPRs: 13.9%; 95% CI, 10.6%-17.6%). Heplisav was superior to Engerix for proportion of participants seroprotected at all assessed serology timepoints (study weeks 4, 8, 12, 24, and 28) and for GMC at all assessed timepoints except for study week 28. In both the younger (18-39 y) and the older (40-55 y) cohorts, Heplisav was superior to Engerix for achievement of SPR at all assessed timepoints. Pain at the injection site after any dose was more frequently reported with Heplisav (35.3%-38.6% vs. 21.6%-33.7% for Engerix), but there was no difference in the occurrence of systemic AEs between vaccine groups. There were no significant changes from baseline in ANA and anti-ds-DNA – markers of autoimmunity – in either vaccine group. One patient in each vaccine group developed an autoimmune disorder.
- **HBV-16 trial. *Vaccine.* 2013;31(46):5300-5305**.[q] In a randomized, double-blind, active-controlled, multicenter phase 3 trial, 1,482 HBV infection and immunization naïve adults aged 40 to 70 y were randomized to receive 2 doses of Heplisav at 0 and 4 wks (n = 1,123) or 3 doses of Engerix at 0, 4, and 24 wks (n = 359). Notable exclusion criteria included autoimmune disease, clinically significant illness, or pregnancy. For the primary immunogenicity outcome of SPR (percentage of patients that achieved anti-HBs ≥ 10 mIU/mL) at 8 wks after the last dose of vaccine, Heplisav was noninferior and superior to Engerix with SPRs of 90% and 70.5% in the per-protocol population, respectively (difference in SPRs: 19.5%; 95% CI, 14.7%-24.7%). Treatment group SPR curves separated at week 4 and the separation was maintained through the end of the study, 48 wks after the last dose of Heplisav and 24 wks after the last dose of Engerix (SPR of 91.9% vs. 59%), respectively; difference in SPR: 32.9% (95% CI, 27.6%-38.3%). There were no differences in the rate of occurrence of the most commonly reported local (injection site pain, redness, swelling) and systemic (fever, malaise, headache) AEs. Three adjudicated autoimmune events occurred in the Heplisav group (hypothyroidism, vitiligo) vs. none in the Engerix group.
- **HBV-23 trial - efficacy. *Vaccine*. 2018;36(5):668-674.**[r] In a randomized, double-blind, active-controlled, multicenter phase 3 trial, 8,374 HBV infection and immunization naïve adults aged 18 to 70 y were randomized to receive 2 doses of Heplisav at 0 and 4 wks (n = 5,592) or 3 doses of Engerix at 0, 4, and 24 wks (n = 2,782). Notable exclusion criteria included pregnancy, HIV, or an autoimmune condition. At baseline, the mean age of participants was 50.4 y, 49% were female, and 13.7% had diabetes. The primary immunogenicity outcome of SPR (proportion of patients who achieved anti-HBs ≥ 10 mIU/mL) at study week 28 was assessed in the

cohort of patients with T2DM (n = 961). In this cohort, the SPR at the primary assessment point was 90% (576/640) and 65.1% (209/321) in the Heplisav and Engerix per-protocol populations, respectively (SPR difference of 24.9%; 95% CI, 19.3%-30.7%); Heplisav met prospectively defined criteria for noninferiority and superiority. In a secondary analysis conducted in the overall per-protocol population (n = 6,826), the SPR in the Heplisav group at week 24 was 95.2% (4837/5080) as compared with a SPR of 80.7% (2094/2595) in the Engerix group at week 28 (SPR difference of 14.5%; 95% CI, 12.9%-16.2%). Heplisav achieved significantly higher SPRs in all subpopulations with the greatest differences between vaccine groups reported in the following subpopulations: smokers, persons with obesity, persons with T2DM, and aged 60 to 70 y.

- ***Vaccine.* 2013;31(46):5306-5313.**[h] In a randomized, double-blind, active-controlled, multicenter phase 3 trial, 521 HBV infection and immunization naïve adults aged 18 to 75 y with an estimated GFR ≤ 45 mL/min/1.73m^2 including ESKD patients on dialysis were randomized to receive 3 single doses (total dose: 60 mcg) of Heplisav at 0, 4, and 24 wks or 4 double doses (total dose: 160 mcg) of Engerix at 0, 4, 8, and 24 wks. Notable exclusion criteria included pregnancy, autoimmune disease, or HIV. For the primary immunogenicity outcome of SPR (proportion of patients who achieved anti-HBs ≥ 10 mIU/mL) in the modified intent-to-treat population measured at study week 28 (4 wks after last vaccine dose), Heplisav met the predefined criteria for noninferiority and superiority (SPR of 89.9% (204/227) vs. SPR of 81.8% (198/242) for Engerix; difference: 8% (95% CI, 1.7%-14.3%)). At week 28, more participants in the Heplisav group achieved anti-HBs ≥ 100 mIU/mL (73.6% vs. 63.2% for Engerix) and Heplisav group had a 3-fold higher GMC. Between group differences persisted through week 52. While local reactions occurred more frequently in the Engerix group, the frequencies of systemic AEs and development of autoantibodies were similar between groups. There was a slight imbalance between groups in deaths (7(2.8%) vs 3(1.1%) for Heplisav and Engerix, respectively), but no death was directly attributable to the vaccine.

PreHevbrio

- **PROTECT trial. *Lancet Infect Dis*. 2021;21(9):1271-1281.**[s] In a randomized, double-blind, multicenter phase 3 trial, 1,607 HBV infection and immunization naïve adults aged ≥ 18 y in stable health were randomized to receive 3 doses of PreHevbrio (n = 796) or Engerix (n = 811) at 0, 4, and 24 wks. Notable exclusion criteria included autoimmune disease, pregnancy, and HIV. At baseline, the mean age of participants was 56.6 y, 62% were female, and 7.8% had diabetes. PreHevbrio met both co-primary endpoints of the study, including demonstrating noninferiority for SPR (proportion of patients attaining anti-HBs ≥ 10 mIU/mL) in adults aged ≥ 18 y and superiority for SPR in adults aged ≥ 45 y. In adults aged ≥ 18 y, SPRs at week 28 were 91.4% (656/718) and 76.5% (553/723) in the PreHevbrio and Engerix groups, respectively (SPR difference: 14.9%; 95% CI, 11.2%-18.6%) and in adults aged ≥ 45 y, the corresponding values were 89.4% and 73.1%, respectively (SPR difference: 16.4%; 95% CI, 12.2%-20.7%). At all additional assessed timepoints (weeks 4, 8, 24, 48), PreHevbrio induced higher SPRs vs Engerix in all analyzed age cohorts, including 18-44 y, 45-64 y, and ≥ 65 y. In an exploratory analysis, 2 doses of PreHevbrio did not achieve noninferiority to 3 doses of Engerix for SPR. Higher rates of local (71.9% vs. 46.7%) and systemic (55.9% vs. 48.8%) reactogenicities were reported in the PreHevbrio group compared with the Engerix group, largely due to higher rates of injection site pain, tenderness, and myalgia. There were no reported safety signals.
- **CONSTANT trial. *JAMA Netw Open.* 2021;4(10):e2128652.**[t] In a randomized, double-blind, multicenter phase 3 trial, 2,838 HBV infection and immunization naïve, generally healthy adults aged 18 to 45 y were randomized to receive 3 doses of PreHevbrio (n = 2,126) or Engerix (n = 712) at 0, 4, and 24 wks. Notable exclusion criteria included autoimmune disease, pregnancy, and HIV. At baseline, the mean age of participants was 33.5 y, 57.8% were female, and 61.6% were non-smokers. The primary endpoint – lot-to-lot consistency among 3 PreHevbrio lots – was achieved. For the secondary immunogenicity endpoint of SPR (proportion of patients attaining anti-HBs ≥ 10 mIU/mL) at week 28 (4 wks after the third injection) in the per-protocol population, PreHevbrio was noninferior to Engerix with SPRs of 99.3% and 94.8%, respectively (difference: 4.5%; 95% CI, 2.9%-6.6%). In an exploratory analysis, the SPR after 2 doses of PreHevbrio was similar to the SPR after 3 doses of Engerix (90.4% vs. 94.8%, respectively; difference: -4.3%; 95% CI, -6.5% to -1.9%). PreHevbrio was associated with higher GMCs of anti-HBs at each measured timepoint, with GMC ratios (PreHevbrio/Engerix) of 7.9, 3.5, and 4.4 at study weeks 24, 28, and 48, respectively. The incidence of solicited local and systemic AEs was higher with PreHevbrio (local: 85% vs. 65.9% for Engerix; systemic: 68% vs. 60.1% for Engerix). No vaccine-related serious AEs were reported.

Summary of Evidence

Introduction: HBV is a virus in the Hepadnaviridae family and is a cause of viral hepatitis. HBV is transmitted by mucosal or parenteral exposure to body fluids from a person with acute or chronic HBV infection. Acute infection occurs within the first 6 months following exposure to HBV. An incubation period of around 60 to 90 days generally precedes the onset of clinical signs and symptoms. Symptoms range from asymptomatic to severe illness requiring hospitalization, with 1 to 2% of adults progressing to fulminant hepatitis. Infants and children are more likely to be asymptomatic compared with adults; approximately 50% of adults have symptoms following acute HBV infection. However, most adults can clear the virus from their bodies without treatment and do not progress to chronic HBV infection. Chronic HBV is a life-long infection, and the likelihood of progressing to chronic HBV varies by age. Infants and children are more likely to develop chronic HBV infection compared with adults. As

many as 90% of infants and up to 50% of children 5 years of age or younger infected with HBV will develop chronic infection. In adults, approximately 5% will develop chronic infection. Persons with chronic infection are often asymptomatic. However, chronic infection is also responsible for most of the HBV-related morbidity and mortality, such as chronic hepatitis, hepatocellular carcinoma, cirrhosis, and liver failure. Premature death due to chronic HBV infection occurs in 25% of persons infected as children and 15% of persons infected as adults.[u,v]

Approximately 257 million people worldwide are infected with HBV. The prevalence of infection varies by geographic location. HBV infection is a disease of low endemicity in the US and Western European countries, while other parts of the world such as Southeast Asia and Africa have a higher prevalence, with up to 15% of the population having chronic HBV infection. Risk factors for exposure to HBV include sexual exposure, percutaneous exposure, household contact that is HBsAg-positive, ESKD, diabetes, HCV or CLD, HIV, international travel to regions with high endemic HBV infection, and incarceration. In the US, chronic infection is present in 0.1% to 0.5% of the total population. Despite a lower prevalence, this still amounts to approximately 850,000 to 2.2 million people in the US who are living with chronic HBV.[u,v]

Vaccines are a fundamental component of decreasing the morbidity and mortality attributed to HBV infection. Following the introduction of HepB vaccines, the incidence of acute HBV infection decreased by approximately 90% in the US. Prior to HepB vaccines, the overall incidence rate of acute infection was about 9.6 cases per 100,000 population; in 2018 the incidence rate was 1 case per 100,000 population. The first HepB vaccine was licensed in the US in 1981 and was a plasma-derived vaccine. Recombinant vaccines eventually replaced plasma-derived vaccines in 1986. The first recombinant vaccine was Recombivax HB, followed by Engerix-B, which was approved in 1989. Engerix-B and Recombivax HB were the primary, stand-alone, HepB vaccines until 2017 when Heplisav-B, a novel, adjuvanted recombinant vaccine was approved.[u,v] Recently, a fourth HepB vaccine was approved in November 2021 called PreHevbrio. PreHevBrio is unique because it is the first 3-antigen vaccine. Recombivax, Engerix, and Heplisav all contain 1 antigen while PreHevBrio also contains the pre-S1 and pre-S2 antigens. The focus of the discussion is on the newer HepB vaccines, Heplisav and PreHevbrio.

Heplisav: *Overview*: Heplisav, approved for the prevention of infection caused by all known subtypes of HBV in patients aged 18 years and older, contains 20 mcg of yeast-derived recombinant HBsAg and 3000 mcg of synthetic immunostimulatory cytidine-phospho-guanosine oligodeoxynucleotide (CpG 1018) – a novel adjuvant – per 0.5 mL and is given as a 2-dose series at 0 and 4 weeks.[w] CpG-1018 is a Toll-like 9 receptor (TLR9) agonist that replaces the aluminum adjuvant found in other HepB vaccines. In general, TLR agonists function as a link between the innate and adaptive immune systems. The binding of bacterial or viral DNA to TLR9 induces an immune response characterized by dendritic cell activation, cytokine secretion, B-cell proliferation, and antibody production. It is thought that CpG-1018 drives the adaptive immune response toward a T-helper cell 1 phenotype.[x]

Efficacy: During its initial phase 3 development program, 2 trials – HBV-10[p] and HBV-16[q] – were conducted to demonstrate 2 doses of Heplisav were noninferior to 3 doses of Engerix. After receipt of the first non-approval letter, an additional phase 3 trial, HBV-23[r] was conducted to increase the size of the safety database. While HBV-23 generated additional immunogenicity data, the FDA only used data from HBV-10 and -16 trials to render its efficacy decision. All phase 3 trials were randomized, double-blind, active-controlled trials designed to primarily evaluate the noninferiority and secondarily the superiority of 2 doses of Heplisav to 3 doses of Engerix for the surrogate endpoint of SPR, defined as the proportion of participants with an anti-HBsAg level ≥ 10 mIU/mL at assessed timepoints. Prospectively defined criterion for noninferiority was a lower limit of the 95% CI for the difference in SPR between Heplisav and Engerix > -10% and for superiority, the lower limit of the 95% CI for the difference in SPR between Heplisav and Engerix > 0%.[p-r] Trials enrolled slightly different patient populations and SPRs were assessed at different timepoints. Of note, SPR peaks at 20 weeks (trial week 24) and 4 weeks (trial week 28) after the second dose of Heplisav and third dose of Engerix, respectively.

Trials HBV-10 and -16 enrolled generally healthy adults without HIV or autoimmune disorders. While participants enrolled in HBV-10 were younger (mean age of 39.9 y vs. 54.4 y for HBV-16), both trials enrolled populations that historically have an adequate response to aluminum-adjuvanted HepB vaccines. For the primary immunogenicity endpoint of SPR post-dose 2 for Heplisav vs. SPR post-dose 3 for Engerix, Heplisav was noninferior and superior to Engerix with SPRs of 95.1% (trial week 12) and 90% (trial week 12) in HBV-10 and -16, respectively (vs. 81.1% (trial week 28) and 70.5% (trial week 32) for Engerix in HBV-10 and -16, respectively). In both studies, the SPR curves of vaccine groups separated at week 4, corresponding to a substantial increase in GMC antibody titers that occurred after dose 2 in the Heplisav arm, but not until after dose 3 in the Engerix arm.[p,q] Trial HBV-23[r] enrolled adults aged 18 to 70 y. In comparison to HBV-10 and -16 trials, HBV-23 enrolled a greater number of participants with baseline characteristics such as T2DM, smoking, and obesity that are historically associated with hyporesponsiveness to aluminum-adjuvanted HepB vaccines. The primary immunogenicity analysis was conducted in the T2DM cohort and secondarily in the overall population. In the T2DM cohort and the overall population, Heplisav met the criteria for noninferiority and superiority for peak SPR after dose 2 compared with peak SPR after dose 3 with Engerix (90% vs.

65.1%, respectively for diabetes cohort and 95.2% vs. 80.7% for overall population, respectively).[r] Results from HBV-23[r] and a post-hoc analysis of HBV-10 and -16 trials[y] demonstrated that the largest differences in effect size between Heplisav and Engerix occurred in historically hyporesponsive populations (See Appendix 1 for SPRs in selected subpopulations).

***Safety*:** Heplisav experienced 2 safety rejections prior to its approval. During its initial review in 2012, a VRBPAC voiced concerns that the size of the safety database was inadequate to detect a safety signal with the novel adjuvant. To address this concern, HBV-23 was conducted to increase the size of the safety database, but a potential cardiovascular safety signal occurred in HBV-23 that was not present in other trials.[z] In pivotal trials, there were no differences between vaccine groups in the occurrence of local or systemic treatment-related AEs with both vaccine groups experiencing local events such as injection site pain, redness, and swelling and systemic events such as fever, malaise, and headache.[p-r] Concerns about potential cardiovascular and autoimmunity safety signals delayed approval of Heplisav until 2017.[z]

Because CpG-1018 is immunostimulatory, common markers of autoimmunity were monitored in HBV-10 and -16. Results showed that rates of development of common autoantibodies including ANA (Heplisav: 5.5%; Engerix: 5.1%) and anti-ds-DNA (Heplisav: 1.2%; Engerix: 1.0%) were similar between vaccine groups.[aa] Additionally, a subset of patients in HBV-23 was tested for the development of antiphospholipid antibodies. The development of new onset antibodies was similar except for a transient increase in beta 2 glycoprotein 1 IgM in the Heplisav group during week 8 that was not associated with thrombotic or thromboembolic events.[aa] The applicant reviewed the frequency of new onset immune-mediated disorders in pivotal trials and concluded that there was no imbalance between vaccine groups (10 vs. 3 events with Heplisav vs. Engerix, respectively); however, immune-mediated events were not prospectively evaluated and adjudicated in HPV-10.[aa] The Center for Biologics Evaluation and Research noted during its review that AEs of special interest that were adjudicated by an expert panel as potential immune-mediated events in trials HBV-16 and -23 were almost exclusively reported with Heplisav (15 subjects (0.20%) vs. 1 subject (0.03%) for Engerix). Additionally, the CBER reviewer noted that 3 systemic granulomatous diseases (granulomatosis with polyangiitis, Tolosa-Hunt Syndrome, and granulomatous dermatitis) were identified in the Heplisav groups during the pivotal trials.[z] Given the rarity of these disorders, the opinion of the CBER reviewer was that it was not a chance finding that 3 rare events occurred in a safety database of <10,000 Heplisav recipients. An imbalance of herpes zoster was also noted in pivotal trials. Due to the overall small number of immune-mediated events and differences in surveillance methods during clinical trials, causality between Heplisav and immune-mediated events was unable to be determined and the applicant agreed to conduct a post-marketing observational study to evaluate the incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis. The final report was due in February 2022.[z]

A blinded post-hoc analysis of major cardiovascular adverse events in pivotal trials was conducted by external consultants. A numeric imbalance in the occurrence of adjudicated AMI events was observed in HBV-23. No imbalance was observed in HBV-10 or -16 likely due to the healthier population enrolled in these 2 trials. In HBV-23, 14 AMI events occurred in the Heplisav group (0.25%) vs. 1 event in the Engerix group (0.04%).[aa] All subjects who reported an AMI had at least 1 cardiovascular risk factor.[z] Based on adjudicated events, the relative risk of non-fatal AMI and composite 3-point major adverse cardiovascular endpoint was 6.97 (95% CI, 0.92-52.97) and 2.32 (95% CI, 0.96-5.60), respectively.[aa] While the occurrence of death from cardiovascular cause was not imbalanced between vaccine groups, more patients in the Heplisav group were adjudicated as having an unknown cause of death (7 (0.13%) vs. 0 for Engerix). Two of three experts consulted by CBER to review the findings opined it was important to conduct a prospective study to determine if the imbalance in AMI represented a true safety signal.[z] The members of the 2017 VRBPAC felt that the findings were likely spurious and voted 12 to 1 (with 3 abstentions) that the available data support the safety of Heplisav. The committee recommended a post-marketing study to evaluate if a causal association exists.[z]

Results from the real-world, post-marketing cardiovascular safety study that was required for vaccine licensure were recently published.[bb] Briefly, the observational study compared the occurrence of confirmed type 1 AMI among 69,625 non-dialysis patients who received at least 1 dose of Heplisav or Engerix as a part of a routine ambulatory care visit and had at least 1 year of follow-up after the initial dose. The confirmed rates for occurrence of type 1 AMI were 1.67 and 1.86 per 1000 person-years in those receiving at least 1 dose of Heplisav and Engerix, respectively. The upper bound of the 97.5% CI for the adjusted hazard ratio was below the noninferiority margin, suggesting that Heplisav was not associated with an increased risk of AMI in this cohort.[bb] Although the study was observational, it employed a nonrandomized cluster design to minimize selection bias and used inverse probability of treatment weighing to adjust for known confounders that were measured. While it is likely that the findings in the HBV- 23 trial occurred due to chance alone, some of the baseline characteristics of the enrolled patient populations differed between studies including ethnicity (HBV 23 – majority Caucasian; real-world safety study – plurality Hispanic), obesity (HBV- 23: 45%; real-world safety study: 24.3%), and diabetes (HBV-23: 13.6%; real-world safety study: 58.9%). Additionally, less than half of participants in the real-world study received a second dose of Heplisav during the follow-up period.[cc]

In HBV-23, the occurrence of cardiovascular events was clustered within 2 to 3 months of any dose and during the latter 6 months of the trial.[r] It is unknown what, if any effect, differences in cumulative dose may have had on the occurrence of events.

PreHevbrio: *Overview*: PreHevbrio was approved in 2021 and is indicated in adults aged 18 years and older for the prevention of infection caused by all known subtypes of HBV. Each 1 mL of PreHevbrio contains 10 mcg of mammalian-derived recombinant surface antigens adsorbed on aluminum hydroxide as an adjuvant and is given as a 3-dose series at 0, 4, and 24 weeks.[dd] Unlike yeast-derived HepB vaccines that only contain the small, non-glycosylated S antigen, PreHevbrio contains all 3 surface antigens of the HBV envelope, including the small s, pre-S1, and pre-S2 and resembles naturally occurring HBV particles in terms of protein composition and glycosylation patterns. The highly immunogenic epitopes present in the pre-S1 and pre-S2 antigens may enhance immunogenicity and overcome non-responsiveness to the s antigen.[ee]

Efficacy: The US phase 3 development program included 2 trials – CONSTANT[t] and PROTECT[s] – and was designed to primarily demonstrate the noninferiority and secondarily the superiority of 3 doses of PreHevbrio to 3 doses of Engerix for the surrogate endpoint of SPR, defined as the proportion of participants with an anti-HBsAg level ≥ 10 mIU/mL measured at 4 weeks after dose 3. Prospectively defined criterion for noninferiority was a lower limit of the 95% CI for the difference in SPR between Heplisav and Engerix > -5% and for clinical superiority (PROTECT trial only), the lower limit of the 95% CI for the difference in SPR between PreHevbrio and Engerix > 5%. In exploratory analyses, the noninferiority of 2 doses of PreHevbrio to 3 doses of Engerix was also examined.

Both phase 3 trials were randomized, double-blind, active-controlled trials. The CONSTANT trial enrolled participants aged 18 to 45 years old (mean age 33.5 y)[t] while participants in stable health aged 18 years or older were enrolled in the PROTECT trial (mean age: 56.6 y).[s] The majority of trial participants were non-smokers and non-obese.[s,t] Not unexpectedly, in the young, healthy population evaluated in the CONSTANT trial, SPRs were high in the PreHevbrio and Engerix groups at 99.3% and 94.8%, respectively.[t] Although the SPR was numerically higher in the PreHevbrio group, the difference between groups was not clinically important. In the older population evaluated in the PROTECT trial, PreHevbrio met the predefined criteria for clinical superiority in the overall cohort and in those aged 45 years and older with differences in SPRs between vaccine groups (95% CI) of 14.9% (11.2%-18.6%) and 16.4% (12.2%-20.7%), respectively at 4 weeks after dose 3.[s] In exploratory analyses, 2 doses of PreHevbrio were inferior to 3 doses of Engerix; however, in cohorts 45 years and younger, SPR was high after 2 doses of PreHevbrio (90.4% and 87.2% in CONSTANT and PROTECT, respectively vs. 94.8% and 91.1% after 3 doses of Engerix, respectively).[s,t] In a single-arm phase 4 trial, 98.8% of participants (mean age: 26.2 y) achieved SP 2 months after the second dose of PreHevbrio.[ff] These results suggest that in responsive populations, a high percentage of patients may achieve SP after 2 doses of PreHevbrio, which is likely clinically important given the low adherence to 3-dose regimens. In younger populations, there was an approximately 7-fold difference between PreHevbrio and Engerix in GMC titers after dose 2 that declined to a 3.5-fold difference after dose 3.[t] The clinical significance of these higher titers is unclear and further study will be required to determine if higher titers confer more durable protection.

In addition to FDA approval, PreHevbrio is currently approved for use in Israel and Hong Kong. As such, results from other phase 3 studies are published. In general, results from these additional studies support those of the US phase 3 development program, namely that PreHevbrio achieves numerically higher SPRs in older patient populations vs. Engerix[gg] and achieves SPRs that are noninferior to those of Engerix in younger populations.[hh,ii]

Safety: In the CONSTANT and PROTECT trials, PreHevbrio was associated with higher rates of local and systemic reactogenicities compared with Engerix. Differences between the vaccines were largely driven by a higher occurrence of injection site pain, tenderness, and myalgias with PreHevbrio.[s,t] No signal or clear pattern of unsolicited AEs emerged in phase 3 trials.[s,t,gg-ii]

Convenience Factors: Multiple published studies show that adherence to multi-dose HepB vaccines is low and that completion rates are suboptimal.[jj-mm] Suboptimal completion rates may leave patients unprotected. Heplisav's novel 2-dose administration schedule may improve adherence and might be advantageous for populations less likely to complete a 3-dose series. Results from a recent cohort study of 10,888 patients who initiated an HepB vaccine series demonstrated that those who initiated a 2-dose series were 77% (aRR: 1.77; 95% CI, 1.68-1.87) and 96% (aRR: 1.92; 95% CI, 1.84-2.01) more likely to complete the series within 3 months of the recommended schedule and within 1 year of the first dose, respectively than those who initiated a 3-dose series. Although adherence was significantly improved with the 2-dose series, it was still low with just 44.7% of the 2-dose series cohort completing the series within 3 months of the recommended schedule and 60.5% completing the series within 1 year after the first dose.[nn] While the 2-dose series significantly increased completion rates, these results suggest that a 2-dose series does not fully overcome barriers to optimal adherence and completion.

Special populations: Risk factors for non-response to HBV vaccines include advanced age, immune compromising condition, male sex, *DRB1* and *DQB1* human leukocyte antigen class II alleles, diabetes mellitus, obesity, smoking, and cirrhosis.[oo,pp] Phase 3 development programs for Heplisav and PreHevbrio excluded patients with immune compromising conditions (eg, ESKD and HIV), but did include patients with other risk factors for hyporesponsiveness. Results from HBV-23[r] and PROTECT[s] trials demonstrated that the impact of age, smoking, diabetes mellitus, male gender, and obesity are less pronounced in Heplisav and PreHevbrio recipients than in recipients of aluminum-adjuvanted, single-antigen HepB vaccines. Due to the exclusion of ESKD patients from pivotal trials, the optimal dosing for newer HBV vaccines is unknown and current guidelines recommend using first-generation HepB vaccines.[a] Similarly, pregnant patients were excluded from pivotal trials and if the need arises to give a HepB vaccine during pregnancy, first-generation, aluminum-adjuvanted, single-antigen HepB vaccines should be given.[a]

Guidelines: In November 2021, the ACIP voted 15 to 0 to recommend universal HepB vaccination for all adults ages 19 to 59 years old in the US. Adults aged 60 years and older are recommended to follow risk-based guidelines to determine if they should receive the vaccine. Except for pregnancy and ESKD, ACIP does not prefer one brand of HepB vaccine to another in adults and if necessary, different brands may be used to complete the vaccine series.[a] Heplisav and PreHevbrio were added to the ACIP list of recommended adult HepB vaccines in 2018 and 2022, respectively. Heplisav and PreHevbrio are not approved and not recommended in pediatric populations. It is unlikely Heplisav or PreHevbrio will have clinically meaningful use in pediatrics because combination vaccination is the preferred method of vaccine administration in children[b] and current aluminum-adjuvanted, single-antigen HepB vaccines elicit high immune responses in pediatrics.

Conclusions: In 2021, ACIP voted to recommend universal HepB vaccination for all adults aged 19 to 59 years and in adults aged 60 years and older with risk factors. This recommendation has the potential to double the annual HepB vaccine market. There are currently 4 FDA-approved HepB vaccines for use in adult immunization. These include 2 first-generation, aluminum-adjuvanted vaccines – Recombivax HB and Engerix-B – and 2 novel vaccines – Heplisav and PreHevbrio. Heplisav is a single-antigen vaccine that contains the novel adjuvant CpG 1018 and is given as a 2-dose series. PreHevbrio, like first-generation HepB vaccines, is aluminum-adjuvanted and is given as a 3-dose series but contains 3 surface antigens (vs. just 1). In young, responsive populations, Heplisav and PreHevbrio are noninferior to aluminum-adjuvanted, single-antigen HepB vaccines for SPR, but are associated with higher antibody titers at comparative time points. It is unknown if higher antibody titers prolong durability of response. In historically hyporesponsive populations, the impact of age, smoking, diabetes mellitus, male gender, and obesity appear less pronounced in Heplisav and PreHevbrio recipients than in recipients of aluminum-adjuvanted, single-antigen HepB vaccines. In pivotal trials, both newer vaccines achieved significantly higher SPRs in hyporesponsive populations compared with aluminum-adjuvanted, single-antigen HepB vaccines. There are no head-to-head comparisons between Heplisav and PreHevbrio, so it is unknown if immunogenicity differs between the newer vaccines. Compared with an aluminum-adjuvanted, single-antigen HepB vaccine, symptoms of local and systemic reactogenicity occurred at a similar rate with Heplisav, but at a significantly higher rate with PreHevbrio. Results from a single observational cohort study refute findings from the pivotal HBV-23 trial that suggested a potential cardiac safety signal with Heplisav. Other potential safety signals that occurred during Heplisav pivotal trials, including an imbalance between vaccine groups in the occurrence of autoimmune disorders and herpes zoster reactivation, are currently under investigation in post licensure safety studies. As a 2-dose series completed within 4 weeks, Heplisav has a convenience advantage compared with 3-dose HepB vaccines. Rapid induction of protective antibody levels may be an important consideration in situations where rapid protection is required (eg, high-risk patients or travelers) or when subsequent doses cannot be guaranteed. Real-world evidence suggests that Heplisav is associated with higher HepB vaccine series completion rates compared with 3-dose HepB vaccine series, but completion rates are still suboptimal even with a 2-dose series. PreHevbrio achieves significantly higher antibody titers compared with a single-antigen HepB vaccine after dose 2 and for a significant proportion of younger, responsive patients this translates to achievement of SPR with just 2 doses of PreHevbrio. Despite this finding, PreHevbrio should still be given as a 3-dose series because 2 doses of PreHevbrio were inferior to 3 doses of Engerix in pivotal trials.

In conclusion, Heplisav and PreHevbrio appear to be more immunogenic than first-generation, aluminum-adjuvanted, single-antigen HepB vaccines and may be an attractive alternative for use in historically hyporesponsive populations. Though SPR is a validated serologic correlate of protection, significantly higher SPRs do not necessarily equate to clinical significance or superiority for prevention of breakthrough HBV infections. While protection with the new vaccines is expected to be durable, the duration of protection is unknown and will require more years of clinical use to determine. While Heplisav and PreHevbrio offer enhanced immunogenicity, the biggest barrier to protection against HBV remains adherence.

Abbreviations: ACIP = Advisory Committee on Immunization Practices; AE = adverse events; AMI = acute myocardial infarction; ANA = antinuclear antibodies; anti-ds-DNA = anti-double-stranded DNA; anti-HBs = hepatitis B surface antibody; aRR = adjusted relative risk; CBER = Center for Biologics Evaluation and Research; CHO = Chinese Hamster Ovary; CI = confidence interval; CKD = chronic kidney disease; CLD = chronic liver disease; ESKD = end stage kidney disease; FDA = Food and Drug Administration; GFR = glomerular filtration rate; GMC = geometric mean concentration; IBD = inflammatory bowel disease; IM =

intramuscular; HBIG = hepatitis B immunoglobulin; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; SDV = single-dose vial; SP = seroprotection; SPR = seroprotection rate; T2DM = type 2 diabetes mellitus; VRBPAC = Vaccines and Related Biological Products Advisory Committee

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Appendix 1. Seroprotection rates for subpopulations

Subpopulation		SPR% (n/N)		Difference in SPRs (%) (95% CI)
		Comparator (measured timepoint)	HBsAg-Eng (measured timepoint)	
Subpopulation analysis of HBV-23 (Heplisav vs. Engerix)				
Age	18-29 y	100 (wk 28) (174)	93.9 (wk 28) (99)	6.1 (2.8-12.6)
	30-39 y	98.9 (wk 28) (632)	92.0 (wk 28) (326)	6.9 (4.2-10.4)
	40-49 y	97.2 (wk 28) (974)	84.2 (wk 28) (518)	13.1 (9.9-16.6)
	50-59 y	95.2 (wk 28) (1439)	79.7 (wk 28) (758)	15.5 (12.6-18.7)
	60-70 y	91.6 (wk 28) (1157)	72.6 (wk 28) (588)	19.0 (15.2-23)
Gender	Female	96.4 (wk 28) (2173)	83.3 (wk 28) (1139)	12.6 (10.4-15)
	Male	94.5 (wk 28) (2203)	78.8 (wk 28) (1150)	15.7 (13.2-18.3)
Diabetes	Yes	90 (wk 28) (640)	65.1 (wk 28) (321)	24.9 (19.3-30.7)
	No	96.2 (wk 28) (3762)	83.9 (wk 28) (1968)	12.3 (10.6-14.1)
Obesity	Yes	94.7 (wk 28) (2165)	75.4 (wk 28) (1076)	19.4 (16.7-22.2)
	No	96.1 (wk 28) (2208)	86.6 (wk 28) (1212)	9.6 (7.6-11.7)
Smoker	Yes	95.9 (wk 28)	78.6 (wk 28)	17.3 (14.2-20.6)

		(1371)	(711)	
	No	95.2 (wk 28) (3005)	82.4 (wk 28) (1578)	12.8 (10.8-14.8)
Subpopulation analysis of HBV-10 and HBV-16 (Heplisav vs. Engerix)				
Age	18-29 y	99.7 (wk 24) 307/308	92.9 (wk 28) 91/98	6.8 (2.5-14.3)
	30-39 y	99.6 (wk 24) 479/481	86.7 (wk 28) 143/165	12.9 (8.1-19.3)
	40-49 y	97.2 (wk 24) 1200/1234	74.3 (wk 28) 284/382	22.9 (18.5-27.7)
	50-59 y	95.3 (wk 24) 1023/1073	72.5 (wk 28) 200/276	22.9 (17.6-28.7)
	60-70 y	91.6 (wk 24) 481/525	67.7 (wk 28) 86/127	23.9 (15.6-33.1)
Gender	Female	96.6 (wk 24) 1845/1909 (week 24)	79.3 (wk 28) 448/565	17.4 (14.1-21.0)
	Male	96.1 (wk 24) 1644/1711	73.7 (wk 28) 356/483	22.4 (18.5-26.6)
BMI ≥ 30 kg/m^2		95 (wk 24) 1205/1268	68.3 (wk 28) 243/356	27 (22.2-32.1)
Current Smoker		97.2 (wk 24) 991/1020	69 (wk 28) 220/319	28.2 (23.2-33.5)
Subpopulation analysis of PROTECT (PreHevbrio vs. Engerix)				
Age	18-39 y	100 (wk 28) (71)	93.1 (wk 28) (72)	6.9 (1.6-15.3)
	40-49 y	98.7 (wk 28) (158)	89.5 (wk 28) (143)	9.2 (4.4-15.5)
	50-59 y	92.8 (wk 28)	78.1 (wk 28)	14.8 (7.2-22.5)

		(153)	(164)	
	60-69 y	89.1 (wk 28) (221)	72.1 (wk 28) (229)	17.1 (9.9-24.3)
	≥ 70 y	78.3 (wk 28) (115)	56.5 (wk 28) (115)	21.7 (9.7-33.2)
Gender	Female	94.3 (wk 28) (436)	80.6 (wk 28) (454)	13.7 (9.5-18)
	Male	86.9 (wk 28) (282)	69.5 (wk 28) (269)	17.4 (10.6-24.2)
BMI	> 30 kg/m^2	89.2 (wk 28) (269)	68.1 (wk 28) (254)	21.1 (14.3-28)
	≤ 30 kg/m^2	92.7 (wk 28) (449)	81 (wk 28) (469)	11.6 (7.4-16)
Smoking status	Current smoker	85.9 (wk 28) (92)	70.5 (wk 28) (95)	15.3 (3.5-27)
	Non-smoker	93.4 (wk 28) (439)	77.4 (wk 28) (430)	16 (11.4-20.6)

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