VBI VACCINES

ACTIVATING THE POWER WITHIN

Safety & Immunogenicity of a 3-Antigen Hepatitis B Vaccine, PreHevbrio™ *[Hepatitis B Vaccine (Recombinant)]*

ACIP Committee Presentation

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About VBI Vaccines

VBI Vaccines is a global biotechnology company driven by immunology in the pursuit of powerful prevention and treatment of disease

Our product...

PreHevbrio™
Hepatitis B Vaccine (Recombinant)

Approved by the FDA on November 30, 2021

Our pipeline...

... includes lead prophylactic and therapeutic candidates that target:

- Hepatitis B
- Glioblastoma (GBM)
- COVID-19
- Cytomegalovirus (CMV)

Our locations...

Rehovot, Israel
Manufacturing Facility
Fully-owned GMP manufacturing facility for the production of HBV program

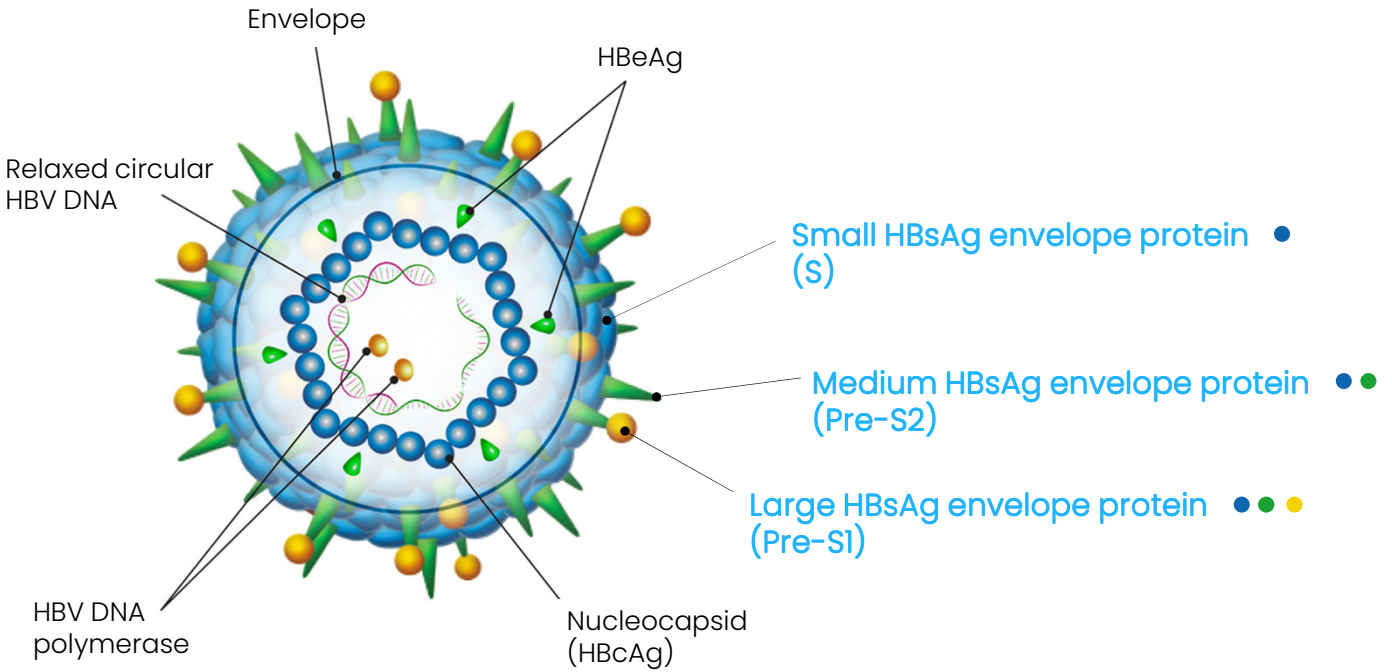
Ottawa, Canada
Research Operations
R&D headquarters and facility

Cambridge, MA, USA
Corporate Headquarters
Central location in biotechnology hub

Introduction to VBI's 3-Antigen HBV Vaccine – PreHevbio™

Hepatitis B Virus (HBV) Structure

HBV genome encodes for three distinct surface antigen, all of which are present on the surface of a wildtype virus – pre-S1, pre-S2, and S antigens

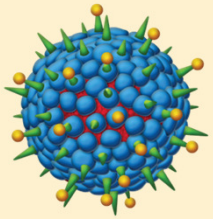
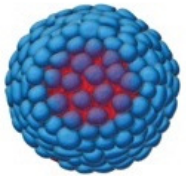
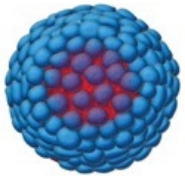
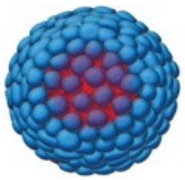


The pre-S1 and pre-S2 regions of the hepatitis B virus contain hepatocyte receptor binding sites

References:
Shouval et al. Improved immunogenicity in mice of mammalian cell-derived recombinant hepatitis B vaccine containing pre-S1 and pre-S2 antigens as compared with conventional yeast-derived vaccines. *Vaccine*. 1994, Vol 12, Num 15; 1453-1459

Scientifically Differentiated from Other HBV Vaccines

PreHevbrio™ expresses the three hepatitis B surface antigens – pre-S1, pre-S2, and S – and is manufactured in mammalian cells (vs. yeast)

	PreHevbrio™	Engerix-B®[1] *Hepatitis B Vaccine (Recombinant)*	Recombivax HB® *Hepatitis B Vaccine (Recombinant)*	Heplisav-B® *Hepatitis B Vaccine (Recombinant), Adjuvanted*
				
Viral antigens mimicked:				
S Antigen	✓	✓	✓	✓
Pre-S2 Antigen	✓			
Pre-S1 Antigen	✓			
Derivation:	Mammalian (CHO) Cell	rDNA yeast	rDNA yeast	rDNA yeast
Adjuvant:	500µg Aluminum hydroxide	500µg Aluminum hydroxide	500µg Aluminum hydroxide	3000µg CpG 1018
Dose of HBs Antigens:	10µg	20µg	10µg or 40µg (HD)	20µg

Note: Head-to-head studies of the 3-antigen HBV vaccine vs. Recombivax HB or Heplisav-B have not been conducted – safety and efficacy cannot be compared across these products

[1]Also included in Twinrix® [Hepatitis A & Hepatitis B (Recombinant) Vaccine]

Importance of Scientific Differentiation

Native Conformation Elicits Efficient Immunogenicity

- Benefit of Mammalian glycosylation
- CHO-derived HBsAg folded to its native conformation[1]
- Major part of yeast-derived antigen misfolded or unfolded, resulting in unnatural conformation[1]

Strong Humoral and Cellular Responses with Pre-S1 & Pre-S2 Antigens

- Pre-S1 & pre-S2 regions significantly more immunogenic at T and B cell levels than S[2]
- Pre-S1 & pre-S2 antigens can overcome non-responsiveness to S antigen, through expanded T cell epitopes and distinct regulation pathways[2]
- Response to pre-S antigens seen with more rapid onset and pronounced antibody response to S antigen[3,4]

Pre-S1 & Pre-S2 Antigens Increase Breadth of HBV Protection

- High titers of anti-HBs required to prevent infection with non-vaccine genotype HBV[6]
- While overall effect of vaccine escape mutants is likely low, emergence of drug resistant mutants with alterations in "a" determinant of S protein is of some concern[3]
- Pre-S1 and pre-S2 epitopes may help reduce emergence of vaccine escape mutants[7] and may reduce risk of HBV infection caused by escape mutants[8]

References:

[1]Gerlich W. Prophylactic vaccination against hepatitis B: achievements, challenges and perspective. *Med Microbiol Immunol* (2015) 204:39-55;
[2]Milich D, et al. Enhanced immunogenicity of the pre-S region of Hepatitis B surface antigen. *Science.* 1985; 228 (4704)1195-1199;
[3]Madalinski K, et al. Antibody responses to preS components after immunization of children with low doses of BioHepB. *Vaccine.* 2001, Vol 20, Iss 1-2; 92-97;
[4]Hellstrom U, et al. PreS1 epitope recognition in newborns after vaccination with the third-generation Sci-B-Vac vaccine and their relation to the antibody response to hepatitis B surface antigen. *Virology Journal.* 2009, 6:7;
[5]Shouval D, et al. Improved immunogenicity in mice of a mammalian cell-derived recombinant hepatitis B vaccine containing pre-S1 and pre-S2 antigens as compared with conventional yeast-derived vaccines. *Vaccine.* 1994 Vol 12, Num 15; 1453-1459;
[6]Inoue T, Tanaka Y. Cross-protection of Hepatitis B vaccination among different genotypes. *Vaccines.* 2020, 8, 456;
[7]Zeinab Nabil Ahmed S, Kouka Saadeldin A. Induced Immunity Against Hepatitis B Virus. *World J Hepatology.* Jun 28, 2015; 7(12):1660-1670;
[8]Collola N, et al. Clinical significance of hepatitis B surface antigen mutants. *World J Hepatol.* Nov 28, 2015; 7(27):2729-2739

Extensive History of 3-Antigen HBV Vaccine

- U.S. Activity :
  - Phase 3 program (PROTECT & CONSTANT), designed to achieve licensure in adults in U.S., Europe, and Canada, initiated at end of 2017 and completed in 2020
  - November 30, 2021 : U.S. FDA approved PreHevbrio™ for the prevention of infection caused by all known subtypes of hepatitis B virus (HBV) in adults age 18 and older
  - American Medical Association (AMA) Current Procedural Terminology (CPT®) Panel established a unique CPT code for a 3-antigen (S, Pre-S1, Pre-S2) Hepatitis B (HBV) vaccine (90759)
- Ex-U.S. History :
  - Originally developed at Weizmann Institute in Israel
  - Supported by data from 20+ clinical studies in neonates, children and adults ("legacy studies"), initial marketing authorization received in Israel in 2000
  - Licensed in Israel in three dose levels:
    - 2.5 µg & 5 µg HBsAg/0.5 mL (neonates, infants, and children)
    - 10 µg HBsAg/1 mL (adolescents and adults)
    - *Note : High-dose 20 µg HBsAg/1 mL formulation has also been evaluated in several clinical studies*
- Distribution Data : 750,000+ individuals estimated to have received vaccine in Israel

PROTECT & CONSTANT Studies

Design & Enrollment

Pivotal Phase 3 Program Designed to Achieve Licensure in the U.S., Europe, and Canada

Pivotal Phase 3 program was comprised of two studies – PROTECT & CONSTANT

Phase 3 Study	PROTECT *2-arm safety and immunogenicity study*	CONSTANT *4-arm lot-to-lot consistency study*
N size	1,607	2,838
Study Population	18-90 years (including those with well-controlled chronic conditions)	18-45 years
Control Vaccine	Engerix-B (GSK)	Engerix-B (GSK)
Primary Endpoint(s)	Based on seroprotection rates (SPR) at Day 196: i. Non-inferiority[1] in adults ≥ age 18 ii. Superiority[2] in adults ≥ age 45	Consistency of Geometric Mean Concentration (GMC) of antibodies at Day 196 across three consecutively manufactured lots of VBI's vaccine
Secondary and Exploratory Endpoint(s)	• Safety and tolerability • Serum concentrations of anti-HBs titers, kinetics of SPR, and immunogenicity in subgroups	• Safety, tolerability, and reactogenicity • SPR, serum concentrations of anti-HBs titers, kinetics of immunogenicity, and subgroup analyses

[1]*Non-inferiority:* The lower bound of the 95% CI of the difference between the SPR in the VBI arm minus the SPR in the Engerix-B arm is > -5%
[2]*Statistical superiority: T*he lower bound of the same 95% CI is >0% - *Clinical superiority: T*he lower bound of the same 95% CI is >5%

Enrolled Subjects in Phase 3 Program : PROTECT : ~80% Age 45+ | CONSTANT : 100% Age 18-45

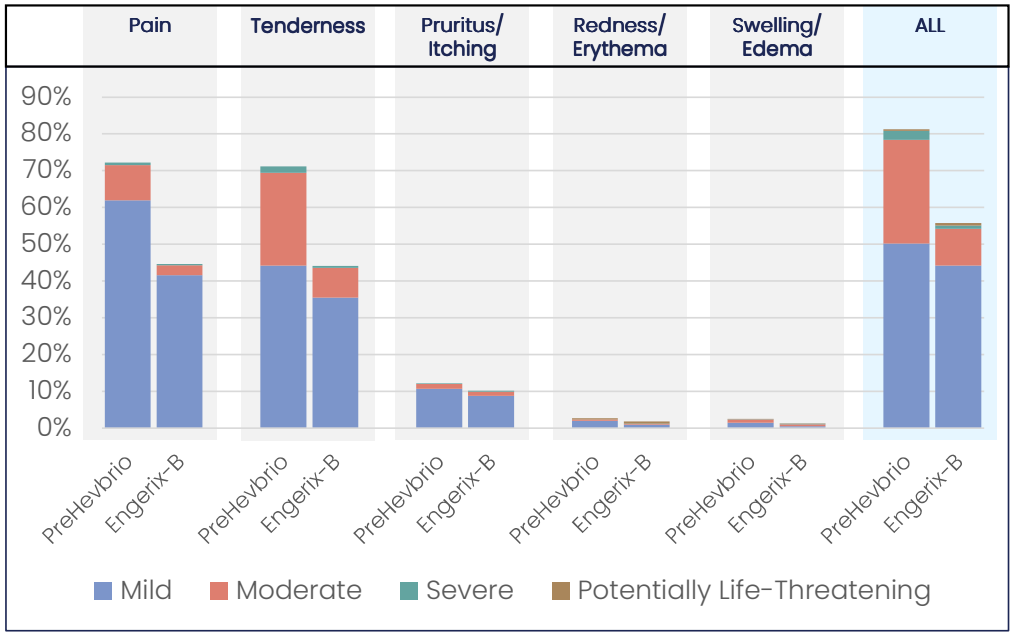
	PROTECT		CONSTANT	
Individuals Screened	2,472		4,452	
- Screened Failure	865 (35%)		1,614 (36%)	
Participants Randomized	1,607 at 28 study sites		2,838 at 35 study sites	
Clinical Study Interventions	PreHevbrio™ 10 µg	Engerix-B® 20 µg	PreHevbrio™ 10 µg	Engerix-B® 20 µg
Participants Randomized	796	811	2126	712
Mean Age	56.6	56.6	33.5	33.4
Age Segmentation				
- 18-44 years	145 (18%)	154 (19%)	100% age 18-45 years	
- 45-64 years	355 (45%)	361 (45%)		
- 65+ years	296 (37%)	296 (37%)		
Gender				
- Male	315 (40%)	303 (37%)	907 (43%)	291 (41%)
- Female	481 (60%)	508 (63%)	1219 (57%)	421 (59%)
Mean BMI	29.4	29.1	25.9	25.7
Diabetic Subjects	54 (7%)	60 (7%)	-	-
Race				
- White	715 (90%)	730 (90%)	1943 (91%)	654 (92%)
- Asian	8 (1%)	4 (0.5%)	37 (2%)	9 (1%)
- Black or African American	66 (8%)	65 (8%)	123 (6%)	38 (5%)
- Other	7 (1%)	12 (1.5%)	23 (1%)	11 (2%)
Ethnicity				
- Hispanic or LatinX	79 (10%)	75 (9%)	195 (9.2%)	74 (10%)
- Non-Hispanic/LatinX	714 (90%)	732 (90%)	1926 (90.6%)	636 (89%)
- Not collected	3 (0.4%)	4 (0.5%)	5 (0.2%)	2 (0.3%)
Country/Region				
- United States	338 (43%)	342 (42%)	564 (27%)	188 (26%)
- Europe	332 (42%)	336 (41%)	1472 (69%)	493 (69%)
- Canada	126 (16%)	133 (16%)	90 (4%)	31 (4%)
Withdrew	40 (5.0%)	42 (5.2%)	228(10.7%)	69 (9.7%)
Completed Study	756 (95%)	769 (94.8%)	1898 (89.3%)	643 (90.3%)

PROTECT & CONSTANT Studies

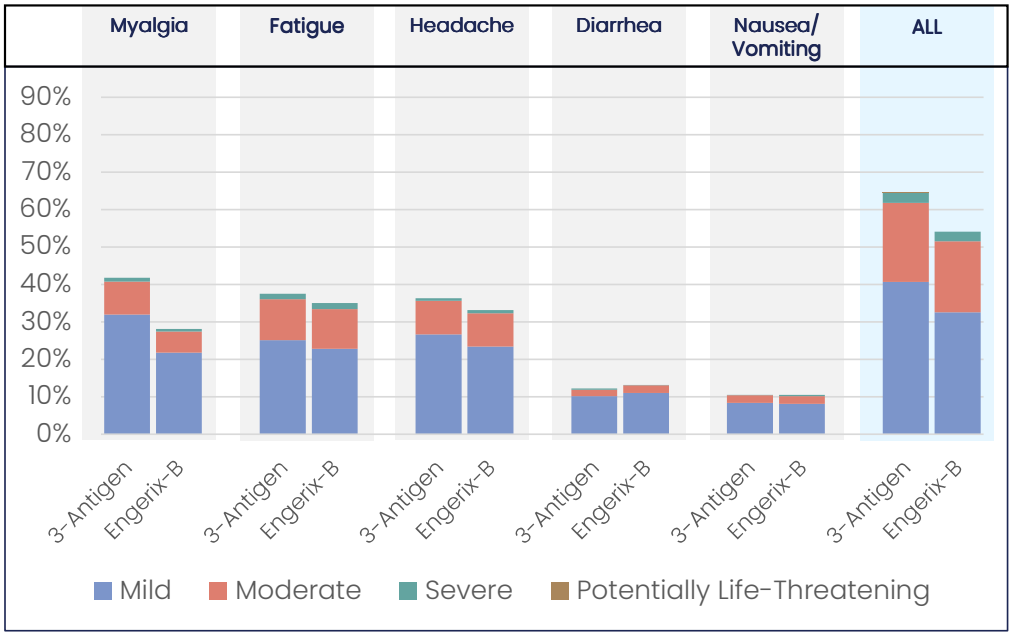
Integrated Safety Analysis

Reactogenicity: Solicited Local and Systemic Adverse Events

Local (Injection Site) Solicited AEs Within 7 Days After Vaccination



Systemic Solicited AEs Within 7 Days After Vaccination



- Higher rates of mild-to-moderate pain and tenderness at injection site and myalgia for PreHevbrio – generally resolved without intervention in 1-2 days
- No increase in reactogenicity symptoms over the 3-dose vaccination schedule
- Very low rates of vaccine discontinuation due to AEs (0.4% for PreHevbrio; 0.3% for Engerix-B)

Unsolicited Adverse Events

No unexpected safety signals associated with either vaccine and no unusual patterns or concerning clusters of SAEs, medically-attended AEs, or NOCIs

Overview of Unsolicited Adverse Events Through End of Study (Day 336) *Subjects With at Least 1:*	PreHevbrio™ N=2,920 N (%)	Engerix-B® N=1,523 N (%)
Adverse Event (AE)	1546 (52.9)	812 (53.3)
AE within 28 days of vaccination	1411 (48.3)	737 (48.4)
Vaccine-related AE	445 (15.2)	198 (13.0)
Medically-attended AE (MAAE)	663 (22.7)	356 (23.4)
New Onset of Chronic Illness (NOCI)	59 (2.0)	38 (2.5)
AE leading to treatment withdrawal	15 (0.5)	6 (0.4)
Vaccine-related AE leading to treatment withdrawal	5 (0.2)	1 (0.1)
AE leading to study withdrawal	8 (0.3)	3 (0.2)
Vaccine-related AE leading to study withdrawal	3 (0.1)	1 (0.1)
Serious Adverse Event (SAE)	74 (2.5)	24 (1.6)
AE leading to death	1 (0.0)	0

Overview of SAEs Reported Through End of Study (Day 336)	PreHevbrio™ N=2,920 N (%)	Engerix-B® N=1,523 N (%)
Subjects with ≥ 1 SAE	74 (2.5)	24 (1.6)
SAEs reported by ≥ 2 subjects		
Appendicitis	4 (0.1)	0
Intervertebral disc protrusion	3 (0.1)	0
Ankle fracture	2 (0.1)	1 (0.1)
Back pain	2 (0.1)	0
Cardiac failure congestive	2 (0.1)	0
Vertigo	2 (0.1)	0
Erysipelas	2 (0.1)	0
Pneumonia	2 (0.1)	0
Joint dislocation	2 (0.1)	0
Tendon rupture	2 (0.1)	0
Syncope	2 (0.1)	0
Atrial fibrillation	1 (0.0)	2 (0.1)
Colon cancer	0	2 (0.1)

Consistent Safety Profile Across Both Phase 3 Studies & Comparable to Engerix-B

- High 3-dose completion rates for both vaccines

- AEs :
  - Most common were local reactogenicity symptoms, mostly of mild-to-moderate severity
  - Resolved without intervention within 1-2 days – no increase with subsequent dosing
  - Most frequently reported reactogenicity symptoms : injection site pain & tenderness

- MAAEs :
  - Similar incidence in both studies across both study arms
  - PROTECT 25.4% and 28.5%; CONSTANT 21.7% and 17.6% for PreHevbrio and Engerix-B, respectively

- SAEs :
  - Uncommon for both vaccines
  - No clustering or unusual pattern of SAEs
  - Two SAEs assessed as possibly related by site investigators - PROTECT gastroenteritis viral; CONSTANT ankyloglossia congenital (an infant born to a female study participant)

- Deaths :
  - No deaths reported in PROTECT
  - In CONSTANT, one sudden cardiac death secondary to preexisting hypertrophic heart disease in a participant randomized to PreHevbrio

PROTECT & CONSTANT Studies

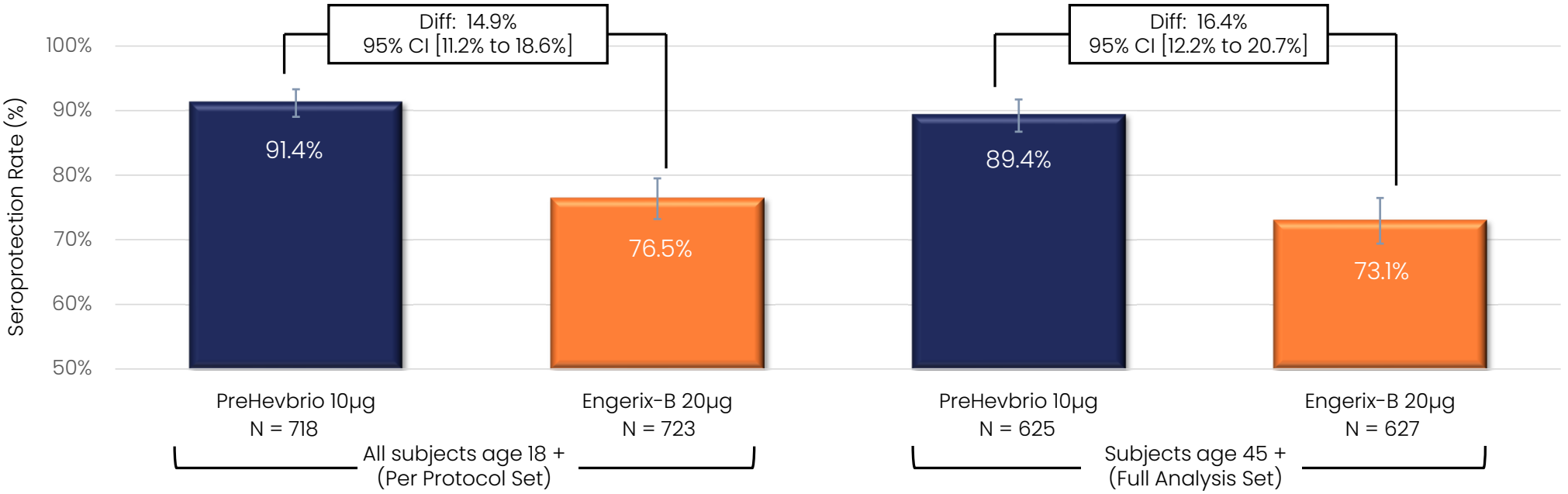
Immunogenicity Results

PROTECT Phase 3 Results: Both Primary Endpoints Successfully Met

Seroprotection rate (SPR) at Day 196, 4 weeks post third vaccination

1. Non-Inferiority of SPR achieved in all subjects age 18+

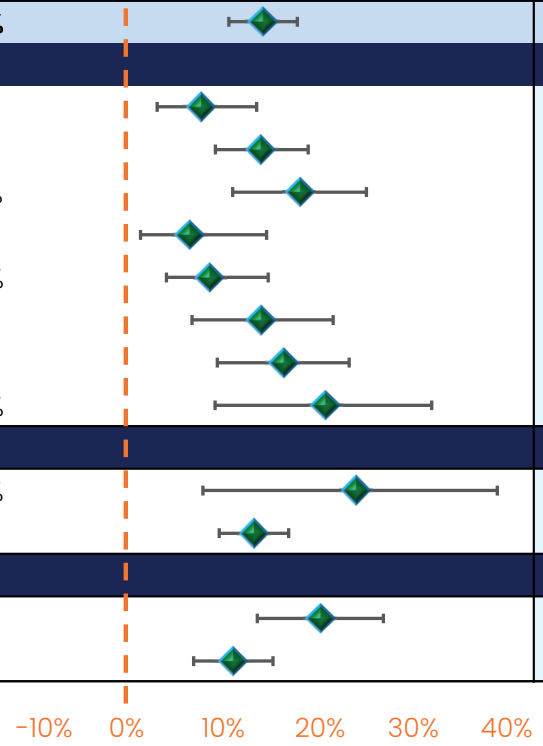
2. Statistical and clinical superiority, as defined in the protocol, achieved in subjects age 45+



- *Non-inferiority*: The lower bound of the 95% CI of the difference between the SPR in the PreHevbrio arm minus the SPR in the Engerix-B arm is > -5%
- *Statistical superiority*: The lower bound of the same 95% CI is >0%
- *Clinical superiority*: The lower bound of the same 95% CI is >5%

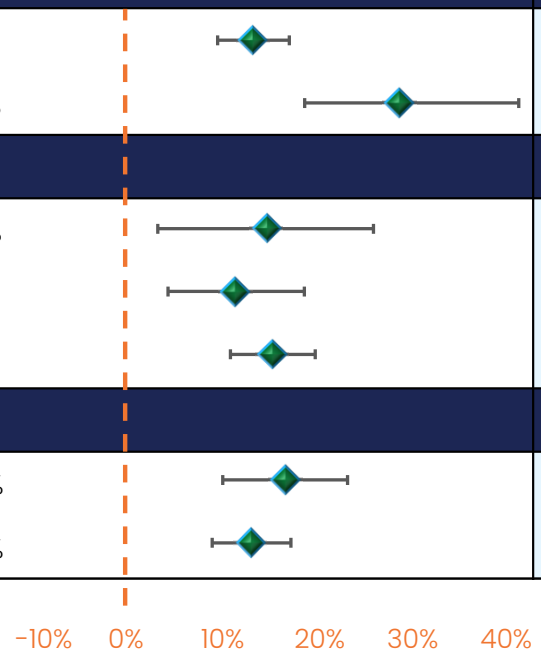
PROTECT Phase 3 Results: Higher SPRs and Anti-HBs Titers Across Subgroups

Population	# of Subjects (N)		Seroprotection Rates (SPR) at Day 196			GMC of Anti-HBs Titers at Day 196		
	PreHevbrio (VBI)	Engerix-B (EB)	VBI	EB	Difference in SPRs : VBI – EB	VBI	EB	X-Fold Increase
All Subjects	**718**	**723**	**91.4%**	**76.5%**		**1148.2**	**192.6**	**6.0x**
Age								
18-44 years	125	135	99.2%	91.1%		4570.4	720.6	6.3x
45-64 years	325	322	94.8%	80.1%		1577.3	276.5	5.7x
>= 65 years	268	266	83.6%	64.7%		410.2	63.7	6.4x
18-39 years	71	72	100.0%	93.1%		5164.2	903.3	5.7x
40-49 years	158	143	98.7%	89.5%		2869.6	645.7	4.4x
50-59 years	153	164	92.8%	78.1%		1250.0	211.6	5.9x
60-69 years	221	229	89.1%	72.1%		780.5	122.9	6.4x
>=70 years	115	115	78.3%	56.5%		241.8	34.8	6.9x
Diabetes								
Yes	54	60	83.3%	58.3%		222.3	41.3	5.4x
No	664	663	92.0%	78.1%		1312.2	221.4	5.9x
BMI								
> 30 kg/m2	269	254	89.2%	68.1%		884.0	110.0	8.0x
≤ 30 kg/m2	449	469	92.7%	81.0%		1343.0	260.9	5.1x



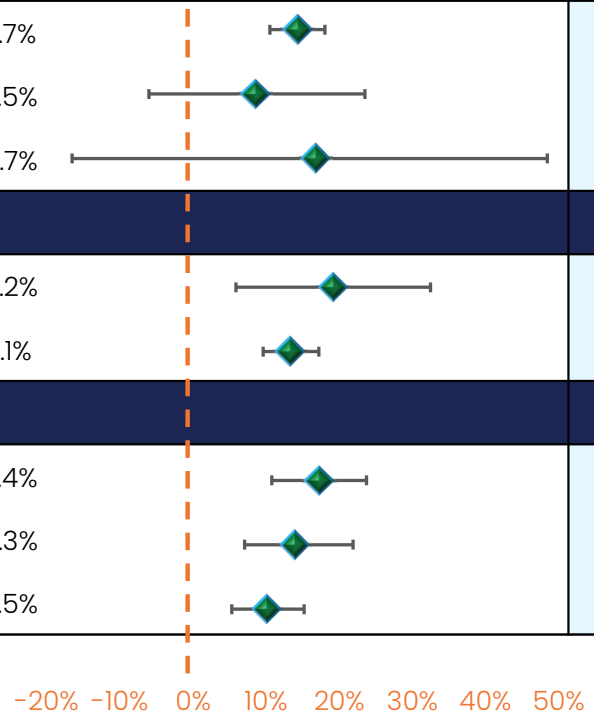
PROTECT Phase 3 Results: Higher SPRs and Anti-HBs Titers Across Subgroups (2)

Population	# of Subjects (N)		Seroprotection Rates (SPR) at Day 196			GMC of Anti-HBs Titers at Day 196		
	PreHevbrio (VBI)	Engerix-B (EB)	VBI	EB	Difference in SPRs : VBI – EB	VBI	EB	X-Fold Increase
Daily Alcohol Consumption								
0-1 Drinks	663	662	91.0%	77.0%		1093.4	202.0	5.4x
2-3 Drinks	51	57	100%	70.2%		2643.8	110.6	23.9x
Smoking Status								
Current Smoker	92	95	85.9%	70.5%		449.4	161.9	2.8x
Past Smoker	187	198	89.3%	77.3%		1162.9	141.1	8.2x
Non-Smoker	439	430	93.4%	77.4%		1390.1	231.0	6.0x
Gender								
Male	282	269	86.9%	69.5%		761.0	106.6	7.1x
Female	436	454	94.3%	80.6%		1498.2	273.5	5.5x



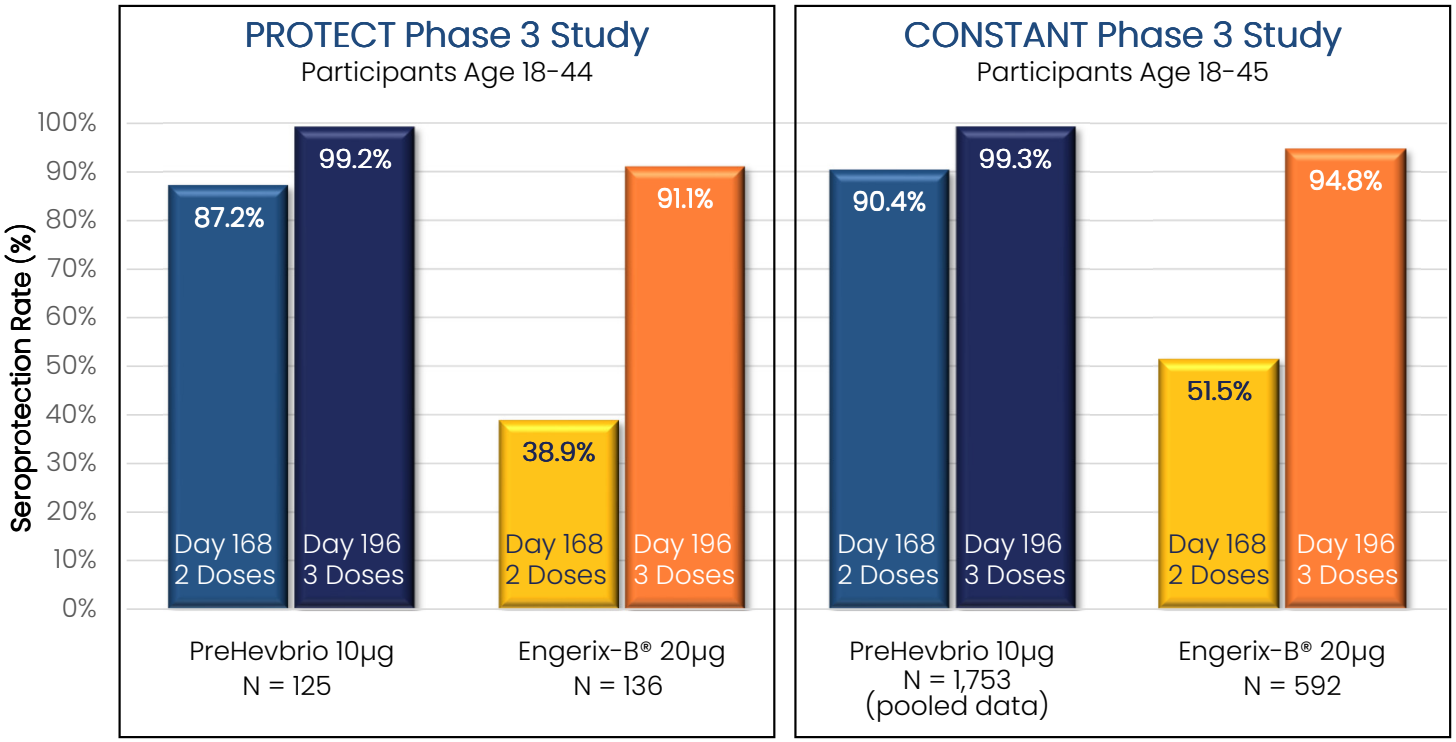
PROTECT Phase 3 Results: Higher SPRs and Anti-HBs Titers Across Subgroups (3)

Population	# of Subjects (N)		Seroprotection Rates (SPR) at Day 196			GMC of Anti-HBs Titers at Day 196		
	PreHevbrio (VBI)	Engerix-B (EB)	VBI	EB	Difference in SPRs : VBI – EB	VBI	EB	X-Fold Increase
Race								
White	648	660	92.0%	76.7%		1229.6	187.8	6.5x
Black/African American	57	51	86.0%	76.5%		535.9	291.4	1.8x
Other	13	12	84.6%	66.7%		1066.4	131.8	8.1x
Ethnicity								
Hispanic/LatinX	67	65	89.6%	69.2%		820.9	81.1	10.1x
Non-Hispanic/LatinX	648	655	91.5%	77.1%		1189.2	206.4	5.8x
Region								
U.S.	297	304	85.9%	67.4%		544.0	95.7	5.7x
Europe	302	299	94.4%	83.3%		1851.2	274.5	4.7x
Canada	119	120	97.5%	82.5%		2204.5	468.1	6.7x

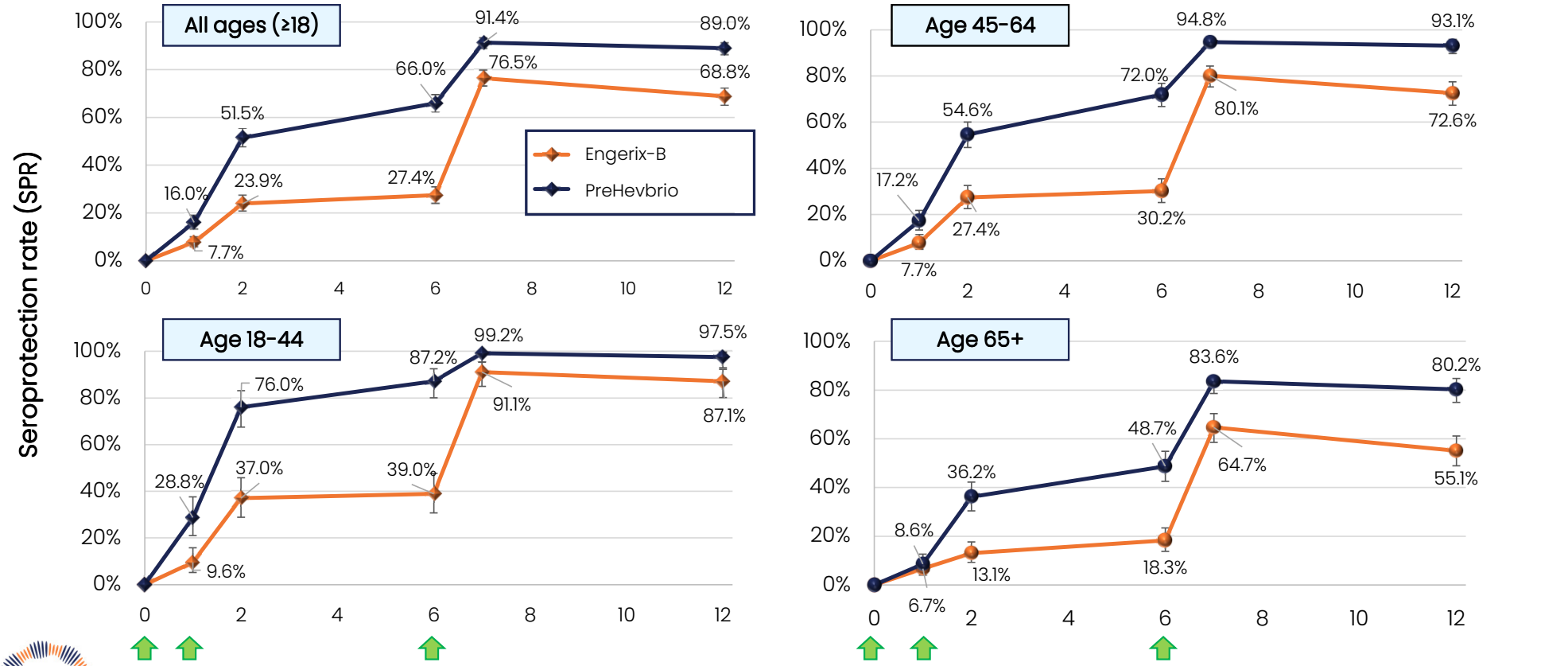


PROTECT & CONSTANT Phase 3 Results: Higher SPR after Both 2 and 3 Doses in Adults Age 18-45

On average, ~90% of adults age 18-45 vaccinated with PreHevbrio were protected after 2 doses (Day 168) vs. ~40-50% of those who received Engerix-B

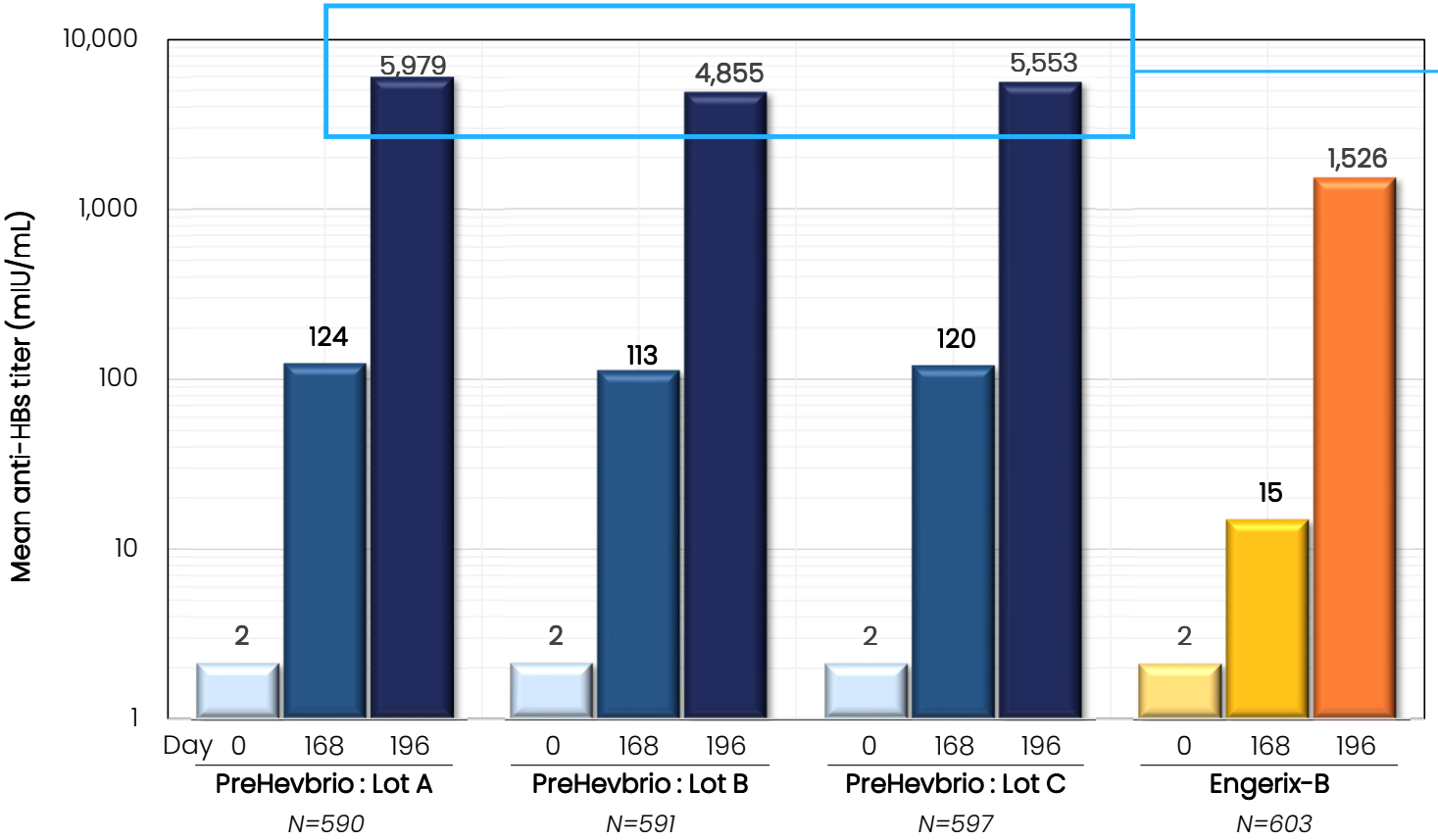


PROTECT Phase 3 Results: Higher SPR at All Timepoints in All Age Groups



CONSTANT Phase 3 Results: Rapid Induction of High Anti-HBs Titers

Kinetics of Mean Anti-HBs Titers in Participants Age 18-45 Years



CONSTANT Primary Endpoint:
Consistency of immune response achieved

Legacy Studies

Highlighted Immunogenicity Results

Note : These earlier studies are referenced in the BLA & have been previously published

Improved Immunogenicity in Key High-Risk Groups in Investigator-Initiated Studies

ESRD

ESRD patients who had not developed protective anti-HBs titers after 4 x 40µg of Engerix-B[1]

N=29

Proactive Clinical Study

- 3 x 10µg of 3-antigen HBV vaccine
- SPR was 86% (25/29)
- Mean anti-HBs titer : 267 ± 59.5 mIU/mL

Retroactive Analysis (Control)

- Retrospective analyses of Engerix-B vaccination for 1999-2001
- SPR 56% (19/34)
- Mean anti-HBs titer : 109.7 ± 35.6 mIU/mL

HIV

HIV+ patients, age 18+, with negative HBV serology[2]

N=31

Proactive Clinical Study

- 3 x 10µg of 3-antigen HBV vaccine
- **After 2nd Dose:**
  - SPR : 65%
  - Mean anti-HBs titer : 30 (6-126) mIU/mL
- **After 3rd Dose:**
  - SPR : 84%
  - Mean anti-HBs titer : 253 (81-408) mIU/mL

Historic Patient Controls

- SPR in response to standard single-antigen HBV vaccines among HIV-infected individuals has been 17.5% - 53%

Non-/Low-Responders

Non-/Low-responders after ≥ 3 doses of conventional yeast-derived HBV vaccines – Age 18+[3]

*N=15 non-responders, 6 low-responders**

- 3 x 10µg of 3-antigen HBV vaccine
- **After 1st Dose:**
  - Non-Responders:
    - % anti-HBs ≥ 10 mIU/mL : 87% (13/15)
    - % anti-HBs ≥ 100 mIU/mL : 67% (10/15)
  - Low-Responders:
    - 67% (4/6) w/ titers 881-3978 mIU/mL
- **After 3rd Dose:**
  - Non-Responders:
    - % anti-HBs ≥ 10 mIU/mL : 93% (14/15)
    - % anti-HBs ≥ 100 mIU/mL : 80% (12/15)
  - Low-Responders:
    - 100% w/ titers 603-6569 mIU/mL

**Defined as anti-HBs titers ≥ 10 mIU/mL but < 100 mIU/mL*

References:
[1]Weinstein et al., "Improved Immunogenicity of a Novel Third-Generation Recombinant Hepatitis B Vaccine in Patients with End-Stage Renal Disease," Nephron Clin Pract 2004; 97: c67-c72;
[2]Alon et al. Immunogenicity of Sci-B-Vac (a Third-Generation Hepatitis B Vaccine) in HIV-Positive Adults. *IMAJ*. March 2017, Vol. 19.;
[3]Krawczyk A, et al. Induction of a robust T- and B-cell immune response in non- and low-responders to conventional vaccination against hepatitis B by using a third generation PreS/S vaccine. *Vaccine*. 2014; 32:5077-5082

Summary

Supported by an Extensive Dataset, PreHevbrio Has Demonstrated Benefit for Adults

In adults vaccinated with PreHevbrio, data demonstrated:

- ✓ A well-established safety profile
- ✓ Higher rates of seroprotection in adults
- ✓ Robust immunogenicity regardless of age
- ✓ Rapid onset of protection
- ✓ Higher immunogenicity in key high-risk populations

Thank you!


VBI

Existing Publications Relating to VBI's 3-Antigen HBV Vaccine (1)

- Alon D, Stein GY, Rn VH-G, Tau L, Brosh T, Turner D. "Immunogenicity of Sci-B-Vac (a Third-Generation Hepatitis B Vaccine) in HIV-Positive Adults." *Isr Med Assoc J.* 2017;19:4.
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Existing Publications Relating to VBI's 3-Antigen HBV Vaccine (2)

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- Rendi-Wagner P, Shouval D, Genton B, Lurie Y, Rümke H, Boland G, et al. "Comparative immunogenicity of a PreS/S hepatitis B vaccine in non- and low responders to conventional vaccine". *Vaccine*. 2006 Apr 5;24(15):2781–9.
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Existing Publications Relating to VBI's 3-Antigen HBV Vaccine (3)

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Existing Publications Relating to VBI's 3-Antigen HBV Vaccine (4)

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