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Robust Immunogenicity and Rapid Onset of High Rates of Seroprotection and Anti-HBs Titers, Elicited with 3-Antigen Hepatitis B Vaccine in Adults

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Introduction

- More than 2 billion individuals worldwide have evidence of past or current hepatitis B virus (HBV) infection, with an estimated 240-350 million people currently chronically infected.
- Public health initiatives name immunization as the most effective prevention strategy, however, vaccination rates in adults remain low.
- The magnitude of the immune response to HBV vaccines can be measured by serum levels of anti-HBs, persistence and durability of which is believed to be dependent upon peak levels induced.
- 3A-HBV is a 3-antigen HBV vaccine that contains all three HBV surface antigens (HBsAg) – S, pre-S1, and pre-S2 – is adjuvanted with alum, and manufactured in mammalian CHO cells.
- The pre-S1 antigen induces key neutralizing antibodies that block virus-receptor binding. T cell response to pre-S1 and pre-S2 antigens could further boost responses to the S antigens, resulting in a more immunogenic vaccine.[1,2]
- Two Phase 3 studies – PROTECT and CONSTANT - of 3A-HBV compared to Engerix-B® (1A-HBV), a single-antigen HBV vaccine, were recently completed in Europe, the U.S., and Canada

Study Designs & Objectives

	PROTECT **2-arm safety & immunogenicity study** *[NCT03393754]*	CONSTANT **4-arm lot-to-lot consistency study** *[NCT03408730]*
N size	1,607	2,838
Age Range	18+ years	18-45 years
3A-HBV	10 µg	10 µg
Control Vaccine	20 µg 1A-HBV	20 µg 1A-HBV
Random.	1:1	1:1:1:1
Dosing	0, 4, 24 weeks	0, 4, 24 weeks
Primary Endpoint(s) *(at Day 196)*	Based on seroprotection rates (SPR): i. Non-inferiority in adults ≥ age 18 ii. Superiority in adults ≥ age 45	Consistency of immune response as measured by GMC of anti-HBs across three consecutive lots of 3A-HBV
Secondary& Exploratory Endpoint(s)	Safety and tolerability, anti-HBs titers, kinetics of immune response	Safety and tolerability, SPR, anti-HBs titers, kinetics of immune response

Study Subject Dispositions

	PROTECT		CONSTANT			
Subjects Screened	2,472		4,452			
- Screen Failure	*865 (35%)*		*1,614 (36%)*			
Subjects Randomized	1,607 at 28 study sites		2,838 at 35 study sites			
Clinical Study Arms	3A-HBV 10 µg	1A-HBV 20 µg	Lot A 3A-HBV 10 µg	Lot B 3A-HBV 10 µg	Lot C 3A-HBV 10 µg	1A-HBV 20 µg
Subjects Randomized	796	811	711	709	706	712
Mean Age	56.6	56.6	33.8	32.9	33.9	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%)	303 (43%)	313 (44%)	291 (41%)	291 (41%)
- Female	481 (60%)	508 (63%)	408 (57%)	396 (56%)	415 (59%)	421 (59%)
Mean BMI	29.4	29.1	25.9	25.8	26.0	25.7
Diabetes Status						
- Diabetics	60 (8%)	65 (8%)	*N/A*			
- Non-diabetics	736 (92%)	746 (92%)				
Smoking Status						
- Current smoker	104 (13%)	113 (14%)	139 (20%)	143 (20%)	126 (18%)	136 (19%)
- Former smoker	203 (26%)	224 (28%)	137 (19%)	131 (19%)	136 (19%)	141 (20%)
- Non-smoker	489 (61%)	474 (58%)	435 (61%)	435 (61%)	443 (63%)	435 (61%)
Country/Region						
- United States	338 (43%)	342 (42%)	191 (27%)	187 (26%)	186 (26%)	188 (26%)
- Europe	332 (42%)	336 (41%)	489 (69%)	493 (70%)	490 (70%)	493 (69%)
- Canada	126 (16%)	133 (16%)	31 (4%)	29 (4%)	30 (4%)	31 (4%)
Withdrew	40 (5.0%)	42 (5.2%)	75 (10.5%)	72 (10.2%)	81 (11.5%)	69 (9.7%)
Completed Study	756	769	636	637	625	643

Results

Figure 1 : Higher Seroprotection Rates (SPR) and Anti-HBs Titers Across Subgroups in PROTECT at Day 196

Population	# of Subjects (N)		Seroprotection Rates (SPR) at Day 196 *% with anti-HBs titers ≥ 10 mIU/mL*		Difference in SPRs : *3A-HBV – 1A-HBV*	GMC of Anti-HBs Titers at Day 196		
	3A-HBV	1A-HBV	3A-HBV	1A-HBV		3A-HBV	1A-HBV	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
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
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

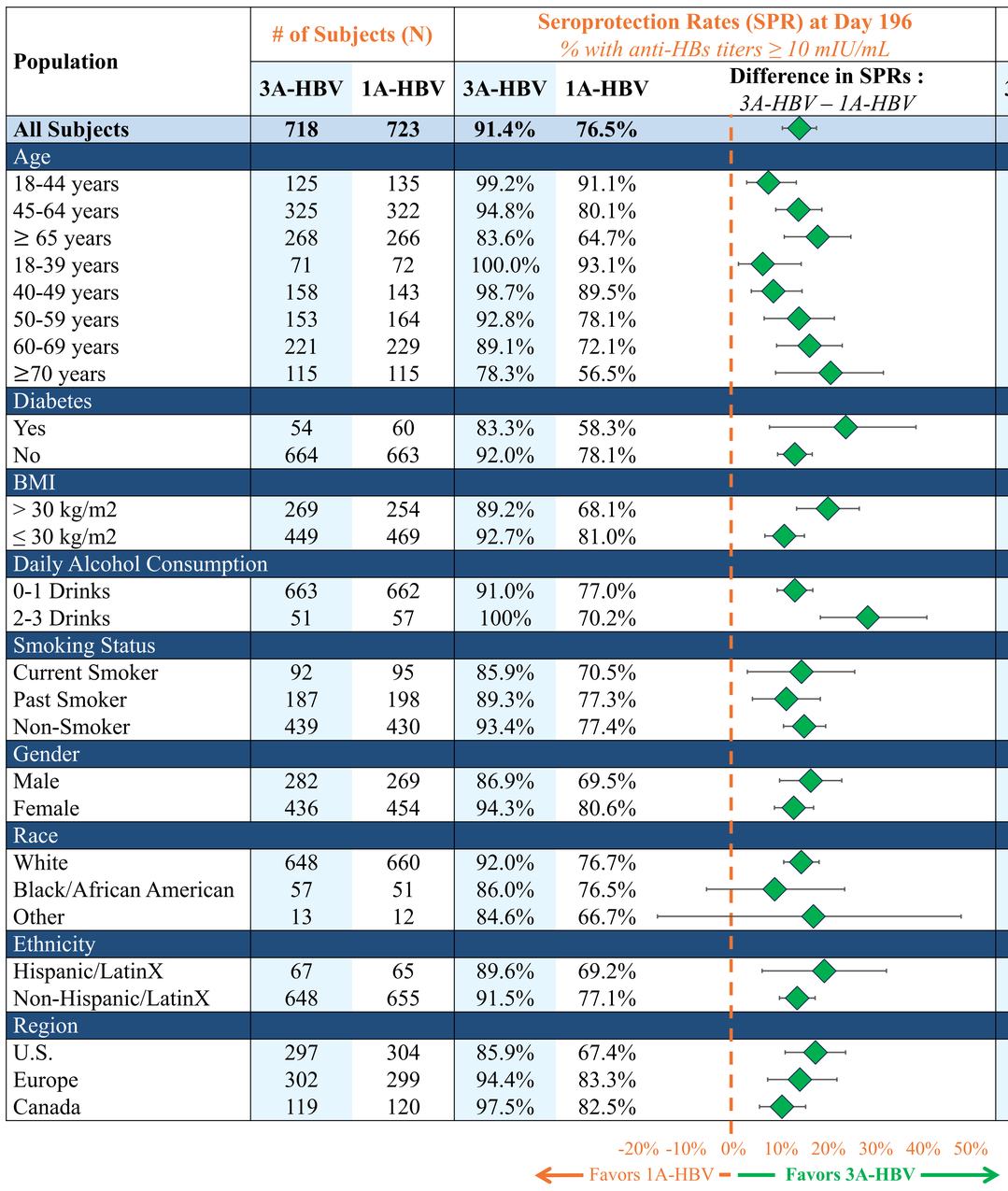
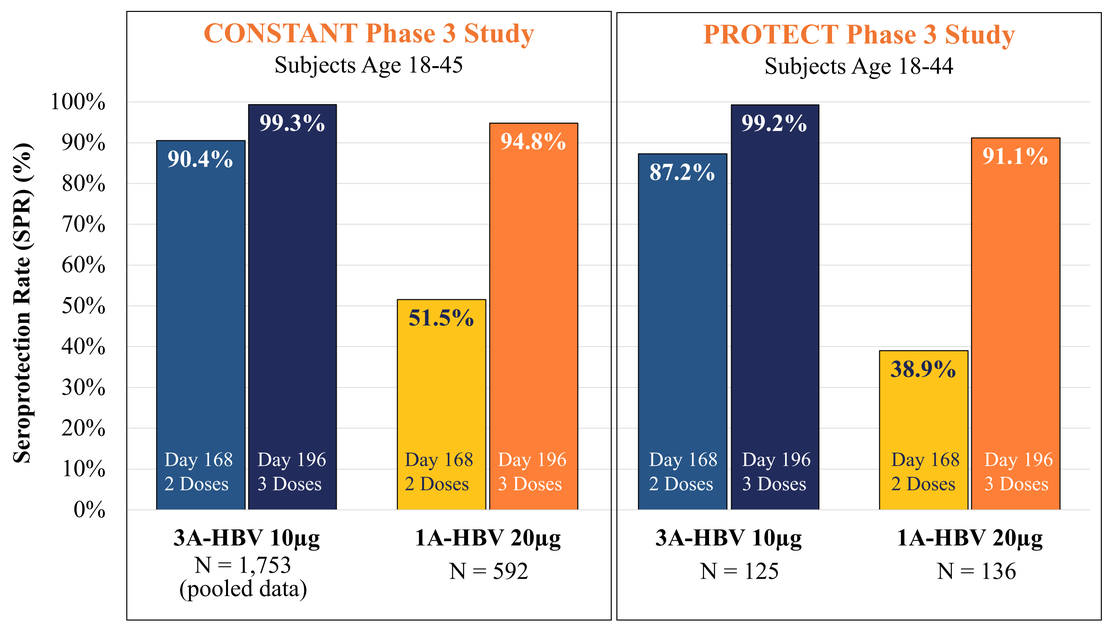
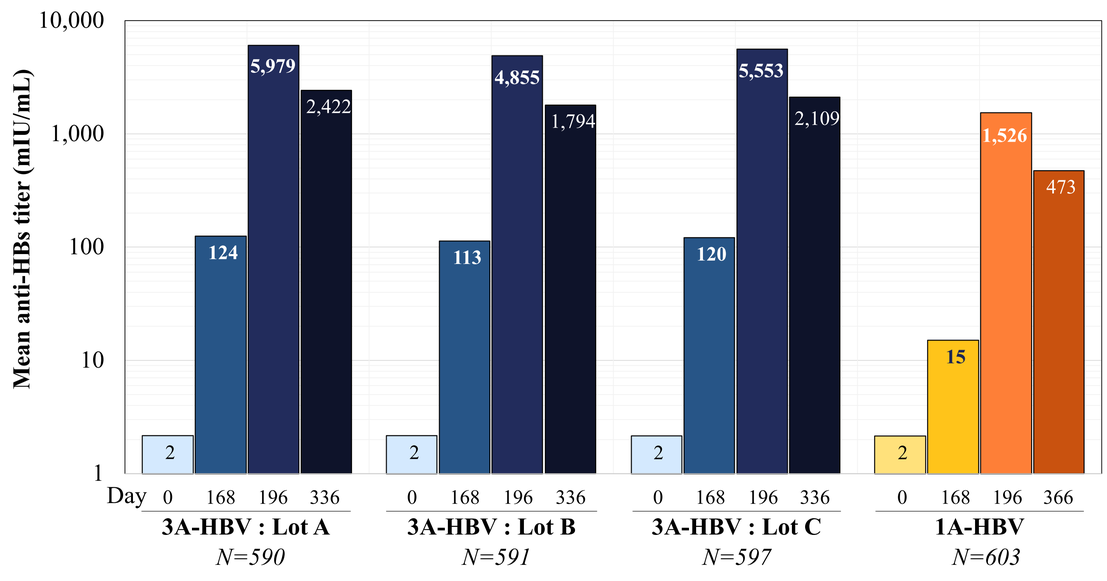


Figure 2 : Higher SPR after Both 2 (Day 168) and 3 Doses (Day 196) in Adults Age 18-45



Figures 3 : Kinetics of Mean Anti-HBs Titers in Subjects Age 18-45 Years in CONSTANT



Conclusions

- 3A-HBV successfully met all primary endpoints across both the PROTECT and CONSTANT studies
- In both Phase 3 studies, data from 3A-HBV arms suggested an ability to safely elicit rapid and robust immune responses in adults, compared to 1A-HBV
- In PROTECT, 6x higher anti-HBs GMC were achieved in subjects who received 3A-HBV compared to 1A-HBV, with higher anti-HBs titers regardless of age, gender, BMI, or diabetic status
- In CONSTANT, anti-HBs GMCs for 3A-HBV were consistent across lots (A, B, and C) and were > 7.5x higher after 2 vaccinations (Day 168) and > 3x higher after 3 vaccinations (Day 196) compared to 1A-HBV
- Across both studies, ~90% of adults age 18-45 were protected after 2 doses of 3A-HBV (at Day 168) compared to ~40-50% with 1A-HBV
- Subjects who received 3A-HBV reported higher rates of mild or moderate pain (75.6% vs. 53.9%) and tenderness (75.1% vs. 54.9%) at injection site and myalgia (44.4% vs. 32.4%) compared to 1A-HBV, which generally resolved without intervention in 2-3 days
- No major safety signals were observed – adverse events were well-balanced and consistent with the known safety profile of each vaccine

Acknowledgements

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References

1. Heermann KH *et al., J Virol*. 1984;52(2):396-402.
2. Milich DR *et al. Science*. 1985;228(4704):1195-1199.

Disclosure

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