Lower non-response rates to 3-antigen HBV vaccine among adults with diabetes, age ≥ 45, or obesity compared to a single-antigen HBV vaccine: PROTECT STUDY

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INTRODUCTION

- Hepatitis B Virus (HBV) is the most common blood-borne infection, with recent estimates of chronically-infected people ranging from 240-350 million worldwide and is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma.[1]
- Several risk factors, including older age, diabetes mellitus, and obesity (BMI >30 kg/m^2), are associated with an increased risk of severe complications if the individual is infected with HBV.
- Additionally, older age, diabetes mellitus, and obesity are associated with reduced immunogenicity to immunization with standard single-antigen HBV vaccines, highlighting a need for more immunogenic vaccination options for adults with these immunocompromising factors.[2]
- A Phase 3 study, PROTECT, was designed to assess the immunogenicity and safety of a 3-antigen HBV vaccine (3A-HBV), manufactured in mammalian cells, compared with a single antigen, yeast-derived HBV vaccine, Engerix-B® (1A-HBV).
- 3A-HBV contains all three HBV surface antigens (HBsAg) – S, pre-S1, and pre-S2 – the pre-S1 antigen induces key neutralizing antibodies that block virus-receptor binding. T cell responses to pre-S1 and pre-S2 antigens have been shown to further boost responses to the S antigens.[3,4]

STUDY DESIGN & OBJECTIVES

PROTECT Phase 3 Study *[NCT03393754]*

N Size	1,607
Age Range	18+ years
Randomization	1:1
Control Vaccine	20 µg Engerix-B® (1A-HBV)
3A-HBV	10 µg
Dosing	0, 4, 24 weeks
Safety Follow-Up	12 months
Eligibility Criteria	• Healthy of controlled chronic conditions • Negative serology (HBV, HCV, HIV) • No severe renal impairment

Study Objectives :

Co-Primary:

- Non-inferiority of seroprotection rates (SPRs) of 3A-HBV vs. 1A-HBV in all participants age ≥ 18 years, 4 weeks after 3rd vaccination (at day 196)
- Superiority of SPR of 3A-HBV vs. 1A-HBV in participants age ≥ 45 years, 4 weeks after 3rd vaccination (at day 196)

Secondary and Exploratory:

- Kinetics of SPR, GMC of anti-HBs, analysis of SPR and GMC in subgroups of interest, safety information (12-month follow-up)

SUBJECT DISPOSITION

Subjects Screened	2,472	
- Screened Failure	*865 (35%)*	
Subjects Randomized	1,607 at 28 study sites	
Clinical Study Arms	**3A-HBV**	**1A-HBV**
Subjects Randomized	796	811
Mean Age	56.6	56.6
Age Segmentation (%)		
- 18-44 years	145 (18%)	154 (19%)
- 45-64 years	355 (45%)	361 (45%)
- 65+ years	296 (37%)	296 (37%)
Gender		
- Male	315 (40%)	303 (37%)
- Female	481 (60%)	508 (63%)
Mean BMI	29.4	29.1
Diabetic Status		
- Diabetic	60 (8%)	65 (8%)
- Non-diabetic	736 (93%)	746 (92%)
Smoking Status		
- Current Smoker	104 (13%)	113 (14%)
- Former Smoker	203 (26%)	224 (28%)
- Non-smoker	489 (61%)	474 (58%)
Country/Region		
- Europe	332 (42%)	336 (41%)
- United States	338 (43%)	342 (42%)
- Canada	126 (16%)	133 (16%)
Withdrew	40 (5.0%)	42 (5.2%)
Completed Study	756	769

SAFETY & TOLERABILITY

	3A-HBV n=796	1A-HBV n=811
Vaccine withdrawal due to AE	0.8%	0.6%
Study discontin. due to TEAE	0.1%	0.4%
Local Reactogenicity (most common)		
Injection site pain	63.2%	36.3%
Injections site tenderness	60.8%	34.8%
Systemic Reactogenicity (most common)		
Myalgia	34.7%	24.3%
Headache	31.3%	29.3%
Fatigue	30.4%	30.7%
Treatment-emergent AEs	52.5%	54.4%
Medically-attended AEs	25.4%	28.5%
New Onset of Chronic Illness	3.3%	3.7%
SAEs	4.0%	2.6%
Death	0	0%

RESULTS

Figure 1: Overall lower non-response rates in 3A-HBV arm (8.6%) compared with 1A-HBV arm (23.5%)

% of participants who did not achieve anti-HBs titers ≥ 10 mIU/mL (non-responders)

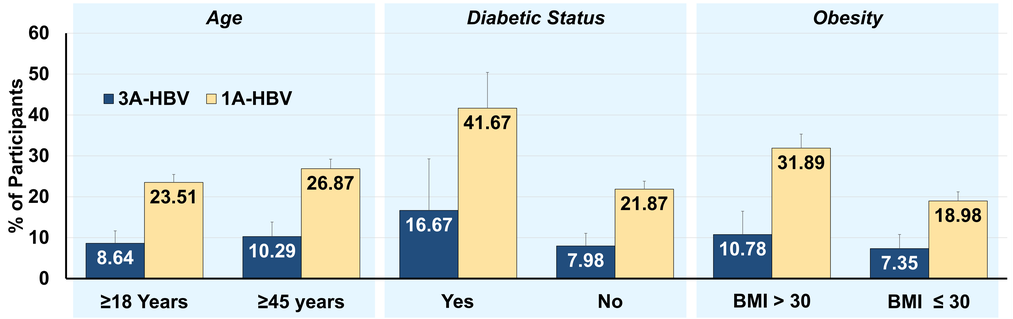

Figure 2 : 3A-HBV achieved consistently higher anti-HBs titers across all key subpopulations compared to 1A-HBV at Day 196

Population	3A-HBV N	1A-HBV N	Anti-HBs Geometric Mean Concentration (GMC) 3A-HBV	1A-HBV	Fold Increase in Anti-HBs GMC : 3A-HBV/1A-HBV
All Participants	**718**	**723**	**1424.52**	**235.43**	6.0x
Age					
18-44 years	125	135	4550.4	727.7	6.3x
45-64 years	325	322	1558.3	274.8	5.7x
≥ 65 years	268	266	414.2	64.3	6.4x
18-39 years	71	72	5092.7	911.5	5.7x
40-49 years	158	143	2857.5	642.8	4.4x
50-59 years	153	164	1224.9	210.0	6.9x
60-69 years	221	229	787.6	124.0	5.7x
≥70 years	115	115	244.0	35.1	6.9x
Gender					
Men	282	269	1029.1	150.1	5.1x
Women	436	454	1753.9	306.8	6.9x
Diabetic Status					
Yes	54	60	448.9	73.7	6.1x
No	664	663	1546.7	258.7	5.9x
BMI					
> 30 kg/m^2	269	254	1005.2	131.4	7.6x
≤ 30 kg/m^2	449	469	1788.1	328.2	5.4x
Daily Alcohol Consump.					
2-3 Drinks	51	57	3623.1	146.0	24.8x
0-1 Drinks	663	662	1348.0	246.2	5.4x
Smoking Status					
Current Smoker	92	95	469.5	154.4	3.0x
Past Smoker	187	198	1707.1	190.5	9.0x
Non-smoker	439	430	1641.0	281.4	5.8x

CONCLUSIONS

- The PROTECT study met both co-primary endpoints – at day 196, SPR in adults age ≥ 18 was 91.4% for 3A-HBV vs 76.5% for 1A-HBV, and in adults age ≥ 45, 89.4% vs. 73.1%.
- 3A-HBV induced a more robust immune response as measured by both SPR and GMC of anti-HBs in all study participants, compared to 1A-HBV, reducing the percentage of non-responders in older adults (≥45 years), those with diabetes mellitus, and obesity (BMI > 30 kg/m^2).
- Both vaccines were well tolerated with > 95% completion rates for the full course of vaccination.
- 3A-HBV had higher rates of mild or moderate myalgia and injection site pain and tenderness compared to 1A-HBV – symptoms generally resolved within 1-2 days.
- No new or unexpected safety signals were observed, and safety and tolerability were consistent with the known profile of 3A-HBV.

REFERENCES

1. MacLachlan JH, Cowie BC. *Cold Spring Harb Perspect Med*. 2015;5(5):a021410.
2. Yang S, Tian G, Cui Y, *et al. Sci Rep*. 2016;6:27251
3. Heermann KH *et al., J Virol*. 1984;52(2):396-402
4. Milich DR *et al. Science*. 1985;228(4704):1195-1199.

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