New 3-Antigen HBV Vaccine With Pre-S1 and Pre-S2 for Adults Induces a High Immune Response and Long Term Persistence of Anti-HBs Antibodies in Adults

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INTRODUCTION

- Hepatitis B virus (HBV) infection is a major global health problem and is the leading cause of liver disease. HBV can be effectively prevented by immunization of adults with HBV vaccines in countries where neonatal immunization is absent[1].
- The magnitude of the immune response to HBV vaccination can be measured by serum levels of anti-HBs, persistence and durability, which is believed to be dependent upon the induced peak levels.
- Conventional single-antigen HBV vaccines (1A-HBV) are yeast derived and contain the small HBV surface antigen (HBsAg); the three-antigen HBV vaccine (3A-HBV)* is produced in mammalian cells and contains two additional HBsAgs: Pre-S1 and Pre-S2.
- Pre-S1 antigen induces key neutralizing antibodies that block virus receptor binding[2,3]. T-cell responses to Pre-S1 and Pre-S2 antigens can further boost responses to the S antigen, resulting in a greater immune response[4].
- PROTECT was a multi-center, double-blind, phase 3 randomized controlled trial comparing the immune response and safety of 3A-HBV to a widely used single-antigen vaccine (1A-HBV) in adults 18 years and older in USA, Europe, and Canada. Seroprotection rate (SPR) and geometric mean concentration (GMC) of anti-HBs were evaluated for 12 months[5].
- Following the completion of PROTECT, the lead investigator initiated a follow-up study to assess the long-term persistence of anti-HBs titers 2.5 and 3.5 years after the 3rd dose in the Finland cohort.

*Market authorization for use in adults over 18 years received in the EU, UK (PreHevbri®), and Canada (PreHevbrio™) in 2022, and in the US (PreHevbrio™) in 2021. It is the same vaccine as Sci-B-Vac®, licensed in Israel in 2000 and used in clinical trials.

STUDY DESIGN

PROTECT Phase 3 Study *[NCT03393754]*

Study Population (N)	1,607 participants
Age Range	18+ years
Randomization	1:1
Study Arm 1	10 µg 3A-HBV (PreHevbri®)
Study Arm 2 (control)	20 µg 1A-HBV (Engerix-B®, GSK)
Dosing	Intramuscular injection @ 0, 1, 6 months
Safety Follow-Up	12 months
Eligibility Criteria	• Healthy or controlled chronic conditions included • Negative serology (HBV, HCV, HIV) • No severe renal impairment

PROTECT Follow-Up Study

3A-HBV (PreHevbri®/ PreHevbrio™)	Median duration after 3rd dose: 3.5 years
1A-HBV (Engerix-B®)	Median duration after 3rd dose: 3.5 years
Eligibility Criteria	• Had been enrolled at one of the PROTECT study sites in Finland • Had received all 3 doses of their assigned vaccine (3A-HBV or 1A-HBV) • Had achieved seroprotection (anti-HBs ≥ 10 mIU/mL) by Day 196 (4 weeks after the 3rd dose)

OBJECTIVES

- To determine anti-HBs titers at 3.5 years after the completion of vaccination
- To determine the proportion of participants who retained anti-HBs ≥ 10 mIU/mL at 3.5 years following completion of the vaccination series
- To determine the proportion of participants who retained anti-HBs ≥ 100 mIU/mL for 3.5 years after the completion of vaccination

BASELINE DEMOGRAPHICS

Table 1 : Baseline data of follow-up participants at enrollment to PROTECT

Study Vaccine	3A-HBV	1A-HBV
Number of subjects	231	202
Median Age (years)	60	60.5
Age18-44 years	47 (20.3%)	41 (20.3%)
Age 45-64 years	89 (38.5%)	76 (37.6%)
Age 65+ years	95 (41.1%)	85 (42.1%)
Male	90 (39.0%)	70 (34.7%)
Female	141 (61.0%)	132 (65.3%)
Mean BMI	27.9 kg/m^2	26.6 kg/m^2
Diabetes - Yes	12 (5.2%)	6 (3.0%)
Diabetes - No	219 (94.8%)	196 (97.0%)
Smoking - Current	28 (12.1%)	26 (12.9%)
Smoking - Former	66 (28.6%)	71 (35.1%)
Non-Smoker	137 (59.3%)	105 (52.0%)

RESULTS

Figure 1 : Seroprotection rate (SPR) (%) up to 3.5 years after 3rd dose of HBV vaccines

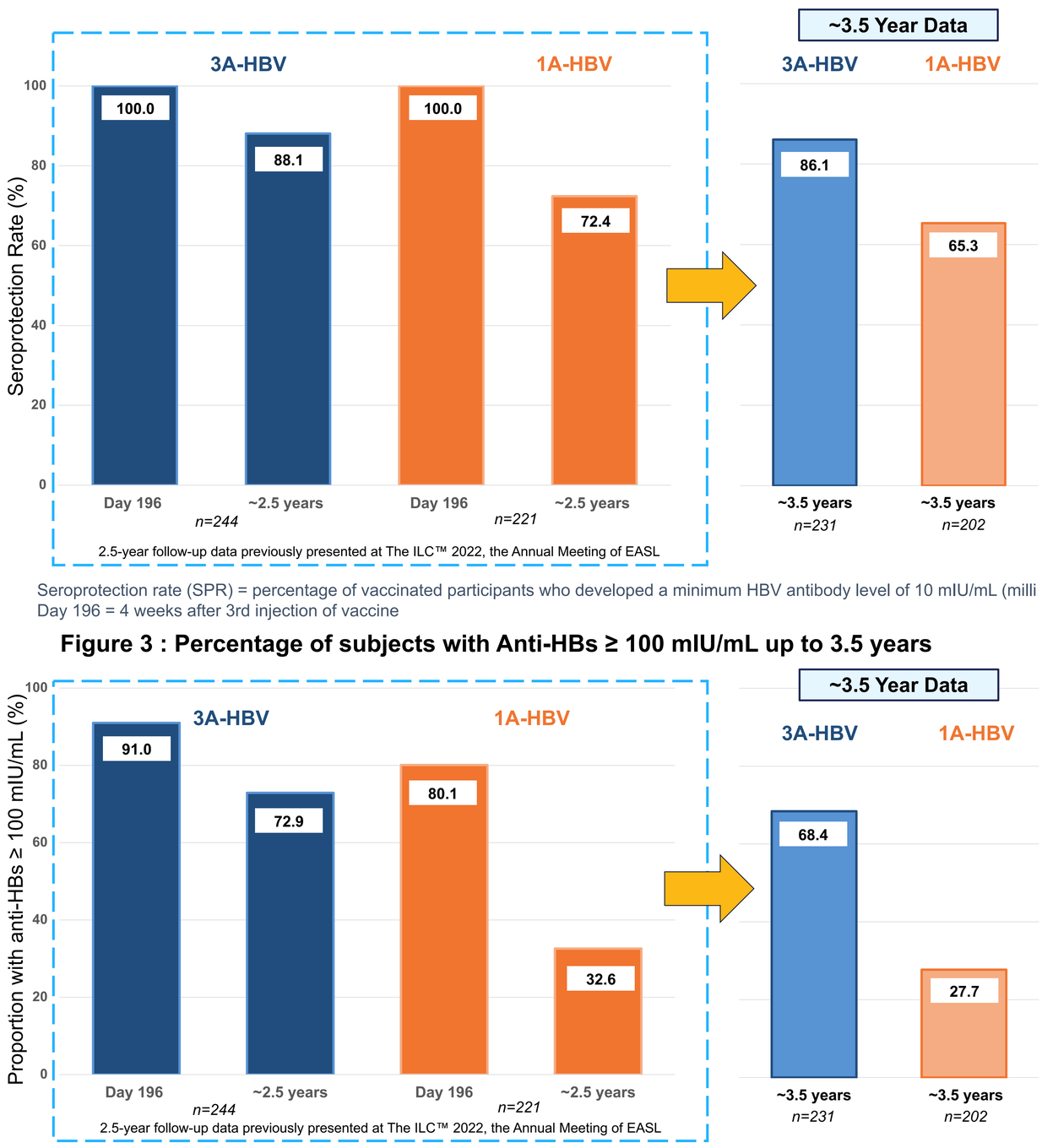
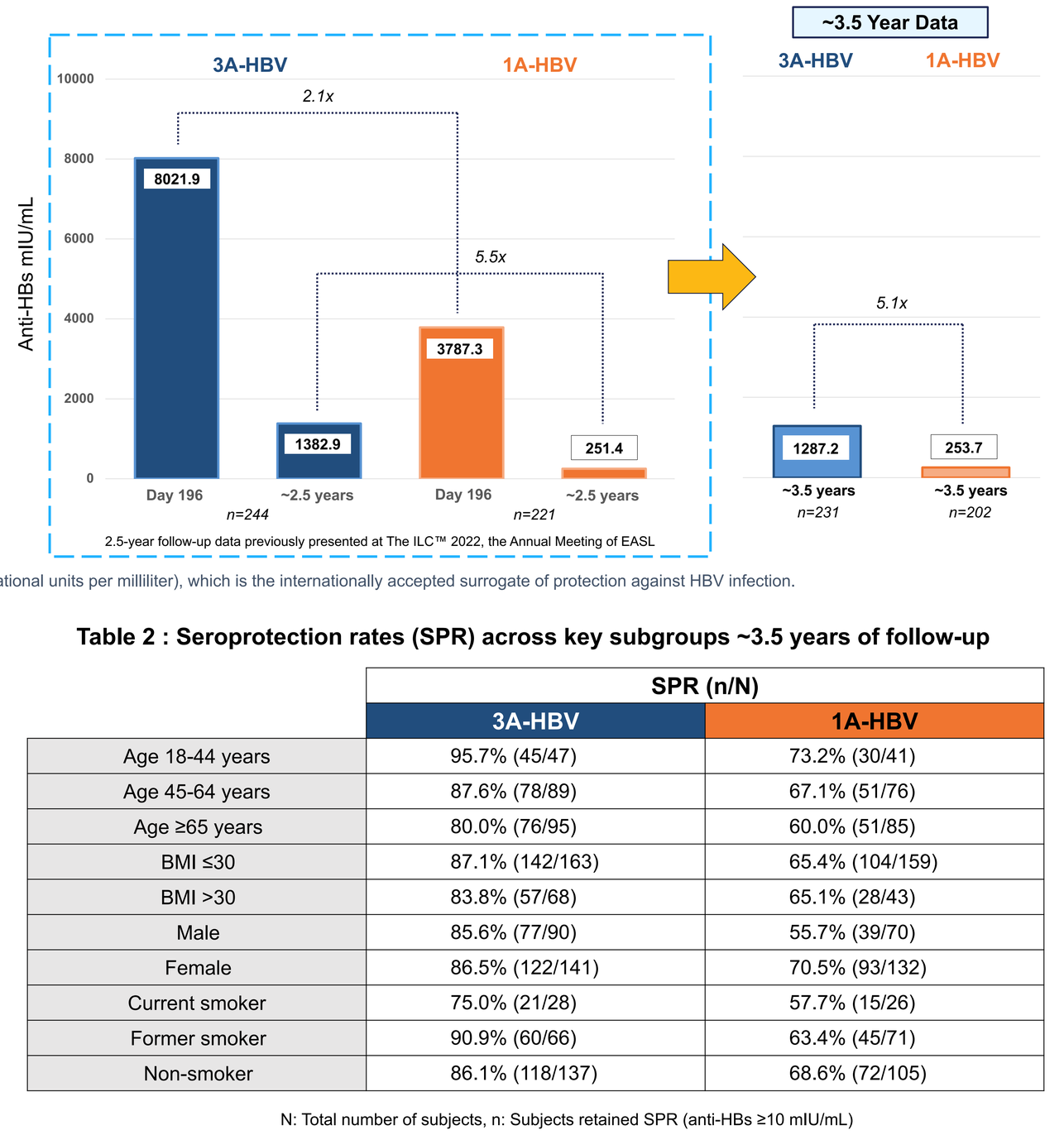


Figure 2 : Mean anti-HBs titers up to ~3.5 years after 3rd dose of HBV vaccines



Seroprotection rate (SPR) = percentage of vaccinated participants who developed a minimum HBV antibody level of 10 mIU/mL (milli international units per milliliter), which is the internationally accepted surrogate of protection against HBV infection.
Day 196 = 4 weeks after 3rd injection of vaccine

Figure 3 : Percentage of subjects with Anti-HBs ≥ 100 mIU/mL up to 3.5 years

Table 2 : Seroprotection rates (SPR) across key subgroups ~3.5 years of follow-up

	SPR (n/N)	
	3A-HBV	1A-HBV
Age 18-44 years	95.7% (45/47)	73.2% (30/41)
Age 45-64 years	87.6% (78/89)	67.1% (51/76)
Age ≥65 years	80.0% (76/95)	60.0% (51/85)
BMI ≤30	87.1% (142/163)	65.4% (104/159)
BMI >30	83.8% (57/68)	65.1% (28/43)
Male	85.6% (77/90)	55.7% (39/70)
Female	86.5% (122/141)	70.5% (93/132)
Current smoker	75.0% (21/28)	57.7% (15/26)
Former smoker	90.9% (60/66)	63.4% (45/71)
Non-smoker	86.1% (118/137)	68.6% (72/105)

N: Total number of subjects, n: Subjects retained SPR (anti-HBs ≥10 mIU/mL)

CONCLUSIONS

- In the PROTECT study, 3A-HBV demonstrated an improved immune response compared to 1A-HBV, including higher SPRs and anti-HBsAg titers after both 2 and 3 doses.
- In PROTECT Follow-up study in Finland, ~3.5 years after achieving seroprotection, the percentage of participants whose anti-HBs titers fell below seroprotective levels (<10 mIU/mL) was 2.5x greater in the 1A-HBV (34.7%) group compared to the 3A-HBV group (13.9%).
- ~3.5 years after the third dose, mean anti-HBs titers remained more than 5x higher in the 3A-HBV group (1287.2 mIU/mL) than in the 1A-HBV group (253.7 mIU/mL).
- The greater immunogenicity of 3A-HBV vs. 1A-HBV vaccine is even more pronounced upon long-term follow up

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