T-cell responses to Pre-S1 and Pre-S2 are correlated to anti-HBs antibody titers, which are higher and persist longer in volunteers vaccinated with 3-antigen vs. 1-antigen hepatitis B vaccine

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Introduction

- PreHevbri®* is a 3-antigen HBV vaccine that contains three distinct HBV surface antigens (S, Pre-S1, and Pre-S2), is adjuvanted with alum, and is produced in mammalian CHO cells – the conventional HBV vaccine is single-antigen (S only) and is yeast-derived.
- Pre-S1 and Pre-S2 proteins serve important roles in the viral invasion of hepatocytes, and in viral infection, viral assembly, viral replication, and stimulation of immune responses in the body.[1] Additionally, Pre-S antigens have CD4+ T-cell epitopes that may mediate improved antibody responses against HBsAg, activating both cellular and humoral immune responses.
- PROTECT was a multi-center, double-blind, Phase 3 randomized controlled trial comparing immune responses and safety of PreHevbri to a widely used single-antigen vaccine (Engerix-B®) in adults 18+ in Europe, the U.S., and Canada. Seroprotection rate (SPR) and geometric mean concentration (GMC) of anti-HBs were assessed for 12 months.[2]
- After the completion of PROTECT, the lead investigator-initiated follow-up studies to assess long-term persistence of anti-HBs titers 2.5 and 3.5 years after the 3rd dose in participants enrolled in Finland.
- Data presented in this poster are the result of a further analysis comparing T-cell and antibody responses to Pre-S1, Pre-S2, and S antigens in participants vaccinated with PreHevbri and Engerix-B at timepoints during both the PROTECT and follow-up studies.

**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.*

Method & Objectives

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

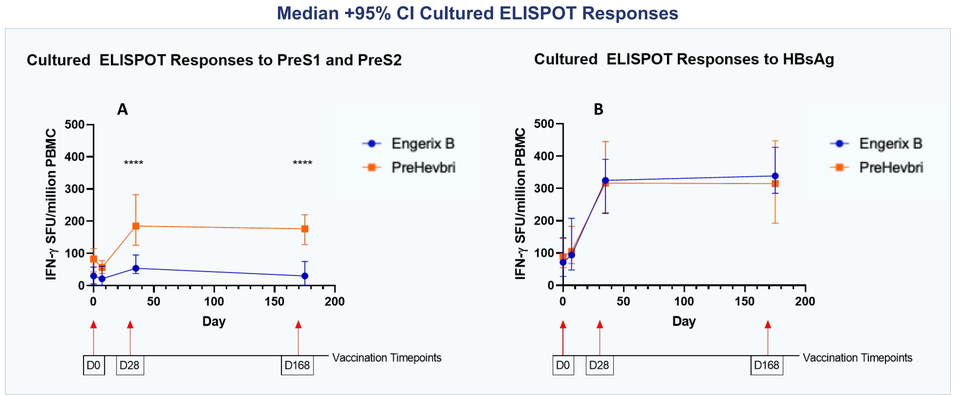
- A subset of participants (n=80) from in the PROTECT study were vaccinated with 3 doses of either PreHevbri or Engerix-B; T-cell responses were measured at pre- and post-vaccination timepoints
- In separate investigator-initiated follow-up study, anti-HBs titers were tested in an additional subset of volunteers 3.5 years post-vaccination.
- T-cell responses were measured with a 14 day cultured IFN-γ ELISPOT in the presence of PreS1, PreS2 or HBsAg pepmixes (JPT peptides) and rhIL-2.
- **Objective :** To assess the potential relationship between T-cell responses induced with 3-antigen (PreHevbri) and 1-antigen (Engerix-B) HBV vaccines and the magnitude and persistence of antibody responses up to 3.5 years after the completion of vaccination

Conclusions

- The 3-antigen HBV vaccine, PreHevbri, induces significant T-cell responses to the Pre-S domains after 2 vaccinations.
- PreHevbri and Engerix-B elicit equivalent T cell responses against HBsAg after 2 or 3 vaccinations.
- After 2 vaccinations of PreHevbrio, T-cell responses elicited against both Pre-S1/2 and HBsAg correlate more strongly with anti-HBs antibody titers vs. HBsAg-specific T-cell responses induced by Engerix-B.
- At all measured timepoints, anti-HBsAg antibody titers were significantly higher (P<0.0001) in subjects vaccinated with PreHevbri vs. those vaccinated with Engerix-B.
- T-cell responses against the Pre-S1 and Pre-S2 proteins in the 3-antigen HBV vaccine PreHevbri correlate with higher anti-HBsAg antibody titers and may contribute to their greater durability compared to those induced with a 1-antigen HBV vaccine.

Results

Figure 1 :
Median +95%CI cultured IFN-γ ELISPOT responses to a PreS1+PreS2 pepmix (**A**) or HBsAg pepmix (**B**) in subjects vaccinated with 1-antigen (Engerix-B) or 3-antigen (PreHevbri) HBV vaccines. Significant (Mann-Whitney U test) T-cell responses to the Pre-S antigen peptide pools are induced following the second (Day 35) and third (Day 175) vaccinations with PreHevbri. Statistically equivalent T-cell responses against the HBsAg pepmix are induced after the second and third doses with PreHevbri and Engerix-B.



Cultured ELISpot Response (D35) & Anti-HBs Titers (D56) – Post 2nd Dose

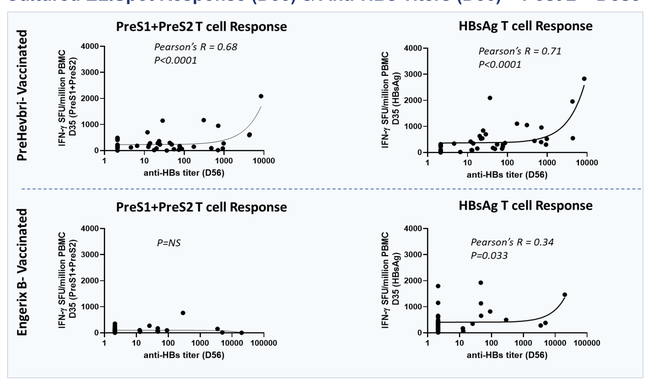


Figure 2 : Correlations between PreS1/2 and HBsAg T-cell responses at Day 35 and anti-HBs antibody titers at Day 56 following 2 vaccinations with PreHevbri or Engerix-B.

Cultured ELISpot Response (D175) & Anti-HBs Titers (D196) – Post 3rd Dose

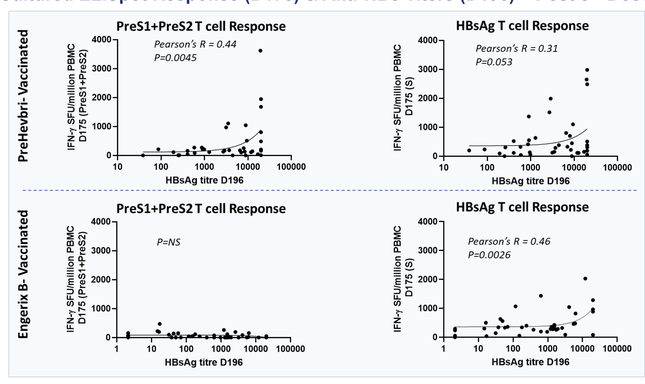
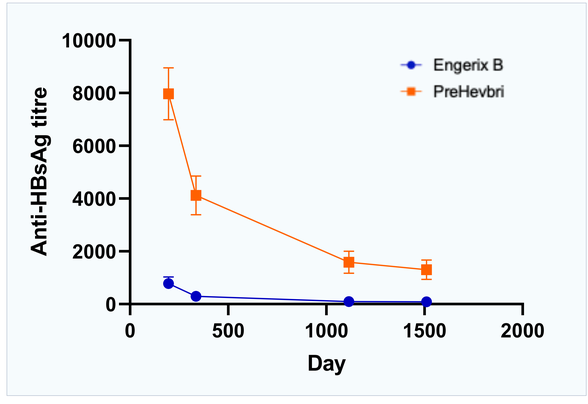


Figure 3 : Correlations between PreS1/2 and HBsAg T-cell responses at Day 175 and anti-HBs antibody titers at Day 196 following 3 vaccinations with PreHevbri or Engerix-B.

Figure 4 :
Anti-HBs antibody titers among seropositive PreHevbri- and Engerix-B-vaccinated donors over time, beginning at Day 196 (4 weeks after 3rd injection of vaccine) through 3.5-years of follow-up time; mean +95%CI.

There is a significant difference between titers induced by PreHevbri vs. Engerix-B at all timepoints (P<0.0001)

Mean +95% CI Anti-HBsAg Titers up to 3.5-Year Follow Up



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2. Vesikari T, Langley J, et al. Immunogenicity and safety of a tri-antigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomised, double-blind, phase 3 trial. *The Lancet Infectious Diseases, 2021,9;* 1271-1281).

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