Cell-mediated and humoral immune responses after vaccination with a 3-antigen HBV vaccine containing pre-S1, pre-S2, and S antigens, compared to a single-antigen HBV vaccine: Results from a pivotal phase III, randomized clinical trial (PROTECT)

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Introduction

- The hepatitis B virus (HBV) genome encodes for 3 distinct surface antigens – pre-S1, pre-S2, and S – on the surface of wildtype HBV.
- Vaccination with pre-S1 induces key neutralizing antibodies and, together with pre-S2, renders S more immunogenic and may augment anti-HBs titers [1,2].
- Additionally, T cells recognizing pre-S1 and pre-S2 epitopes can provide help to B cells responding to S antigen [1,2].
- The inclusion of the pre-S1 and pre-S2 antigens may help induce an enhanced immune response to HBV vaccination, including robust cellular and humoral responses against HBV [1,2].
- A phase 3 clinical study (PROTECT) assessed a 3-antigen HBV vaccine (3A-HBV) that contains all three HBV surface antigens (HBsAg) – S, pre-S1, and pre-S2 – is adjuvanted with alum, and manufactured in mammalian CHO cells [3].

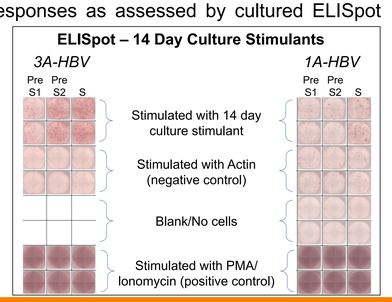
PROTECT Study Design & Results

- A Phase 3 study designed to assess the immunogenicity and safety of 3A-HBV compared with a single-antigen HBV vaccine, Engerix-B® (1A-HBV).
- The study enrolled 1607 adults, age ≥ 18 years, stratified by age (18-44, 45-64, and 65+), with 80% ≥ 45 years, at sites in the U.S., Europe, and Canada.
- Additional eligibility criteria included: (i) healthy or controlled chronic conditions (e.g. Type 2 Diabetes), (ii) negative serology (HBV, HCV, HIV), and (iii) no severe renal impairment
- Study arms:
  - 3A-HBV: 10µg, 1mL injection at 0, 4, and 24 weeks
  - 1A-HBV: 20µg, 1mL injection at 0, 4, and 24 weeks
- Safety follow-up for 12 months
- *Overall Study Results* : Primary Endpoints Achieved
  - Noninferiority of Seroprotection rates (SPRs) in adults age ≥ 18 achieved with 3A-HBV (91.4%) vs. 1A-HBV (76.5%), at day 196
  - Superiority (as defined in the protocol) of SPRs in adults age ≥ 45 achieved with 3A-HBV (89.4%) vs. 1A-HBV (73.1%), at day 196

Clinical Trials Identifier: NCT03393754

PROTECT Sub-Study Design & Methods

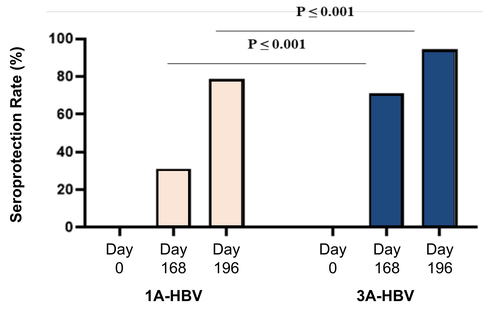
- An exploratory analysis on a sub-group in PROTECT designed to determine if T cell responses to pre-S1 and pre-S2 were elicited after vaccination with 3A-HBV, and whether there was a correlation between T cell responses and the magnitude of anti-HBs titers.
- A proprietary ELISA used to quantitate high avidity antibodies against pre-S1 and pre-S2 in a subset of 224 study participants (115 3A-HBV; 109 1A-HBV)
- A further subset of 80 participants (40 3A-HBV; 40 1A-HBV) analysed to determine the magnitude of cell-mediated immune (CMI) responses as assessed by cultured ELISpot against pre-S1, pre-S2, and S.
- Subjects matched on baseline characteristics of age, gender, and body-mass index (BMI).
- CMI response expressed as spot forming units (SFU)/million peripheral blood mononuclear cells (PBMCs)
- PBMCs collected pre-vaccination (Day 0), 7 days post-1st (Day 7), post-2nd (Day 35), and post-3rd (Day 175) vaccination
- Pearson's correlation (r) determined between cultured ELISpot and anti-HBs titers.



Sub-Study Cellular and Humoral Results

Figure 1: Seroprotection Rates After 2 and 3 Doses 3A-HBV vs. 1A-HBV

Seroprotection rates (SPRs) were determined in 224 participants.
SPRs were significantly increased at all timepoints in 3A-HBV arm vs. 1A-HBV arm (p ≤ 0.001).



Seroprotection rate (SPR) defined as % of subjects with anti-HBs titers ≥ 10 mIU/mL

Figure 2: Pre-S1 and Pre-S2 Antibody Titers After 2 and 3 Doses of 3A-HBV vs. 1A-HBV

Pre-S1 (A) and pre-S2 (B) antibody concentrations were determined in 224 participants.
Pre-S1 antibody response was not significantly increased at all timepoints in both vaccine arms.
Pre-S2 antibody response showed a significant increase in titers in 3A-HBV arm vs. 1A-HBV arm at Study Day 196 (p ≤ 0.001).

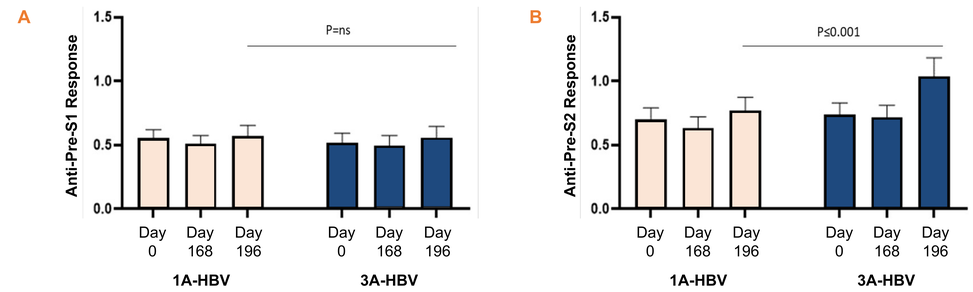


Figure 3: Correlations of Mean Interferon- γ-secreting PBMC to S (HBsAg), Pre-S1, and Pre-S2 on Day 35, with Anti-HBs GMTs on Day 56, after 2 Doses of 3A-HBV vs. 1A-HBV

In 3A-HBV participants (n = 40), sig. association between anti-HBs titers and ELISpot responses to pre-S2 (Pearson's Coefficient = 0.69, p<0.0001), and S pepmix (Pearson's Coefficient = 0.71, p < 0.0001).
In 1A-HBV participants (n = 40), sig. association between ELISpot responses to S pepmix and anti-HBs titers (Pearson's Coefficient = 0.34, p<0.03).

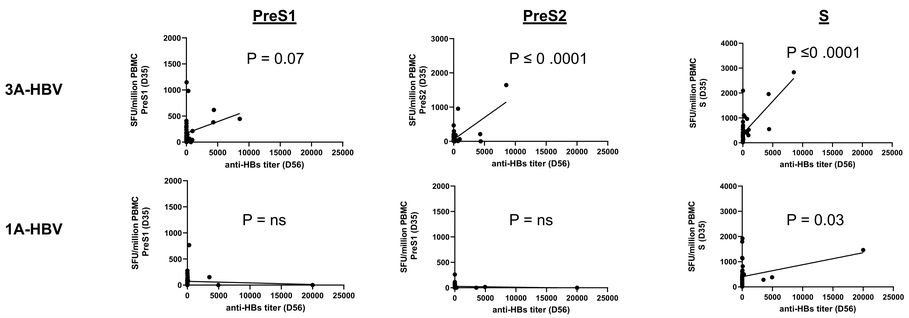
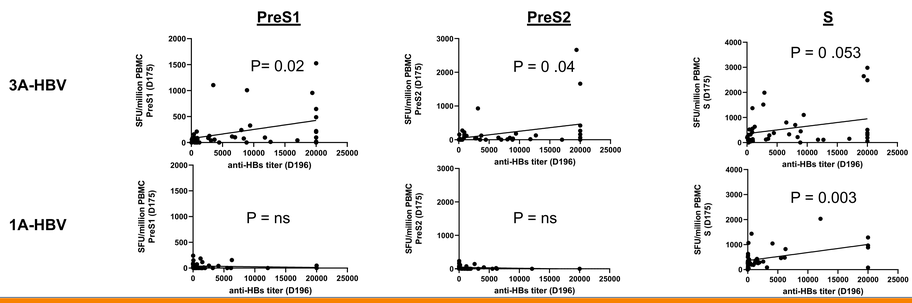


Figure 4: Correlations of Mean Interferon- γ-secreting PBMC to S (HBsAg), Pre-S1, and Pre-S2 on Day 175, with Anti-HBs GMTs on Day 196, after 3 Doses of 3A-HBV vs. 1A-HBV

In 3A-HBV participants (n = 40), sig. association between anti-HBs titers and ELISpot responses to pre-S1 (Pearson's Coefficient = 0.39, p = 0.02), and pre-S2 (Pearson's Coefficient = 0.33, p = 0.04) pepmixes, and a trend toward significance detected between ELISpot response to S pepmix and anti-HBs titers (Pearson's Coefficient = 0.31, p = 0.053).
In 1A-HBV participants (n = 40), sig. association between ELISpot responses to S pepmix and anti-HBs titers (Pearson's Coefficient = 0.46, p = 0.003).



Conclusions

- SPR and anti-HBs titers were consistently higher for 3A-HBV compared to 1A-HBV
- After two doses of 3A-HBV, there was a significant correlation between anti-HBs titer measured at Study Day 56 and cultured ELISpot response to pre-S2
- After three doses of 3A-HBV, there was a significant correlation between anti-HBs titer measured at Study Day 196 and cultured ELISpot response to pre-S1
- This data demonstrate that induction of T cell responses against pre-S1/S2 may contribute to the higher and faster anti-HBs titers elicited with 3A-HBV, despite expressing half the antigen content of 1A-HBV

References

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2. Milich DR *et al.,* Enhanced immunogenicity of the pre-S region of hepatitis B surface antigen. *Science*. 1985;228(4704):1195-1199.
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