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Higher seroprotection rates (SPR) and higher anti-HBs concentrations in adults age 18-45 immunized with 3-antigen hepatitis B vaccine (3A-HBV) compared to 1-antigen hepatitis B vaccine (1A-HBV):

Results from the pivotal, double-blind, randomized Phase 3 study (CONSTANT)

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INTRODUCTION

- Hepatitis B Virus (HBV) remains a significant public health risk, with an estimated 240-350 million people chronically infected worldwide
- In Canada, an estimated 250,000-460,000 individuals have chronic hepatitis B, with highest rates found in urban centres[1]
- Though infection rates in Canada have declined, reported acute infection rates are likely an underestimate because of the asymptomatic nature of the disease, and therefore patients do not get tested and remain unidentified[2]
- Rates of new HBV infections are highest among individuals age 30-39 years, underscoring the importance of continued adult vaccination against HBV, as well as the need for a highly effective and safe HBV vaccine with a rapid onset of protection
- 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[3,4]

STUDY OBJECTIVES & DESIGN

[NCT03408730]

- The CONSTANT study was one of two studies in the pivotal Phase 3 program of 3A-HBV that was conducted from 2017-2020
- CONSTANT was a four-arm lot-to-lot consistency study
- **Primary Objective :** To demonstrate the manufacturing equivalence, in terms of immunogenicity, of 3 independent consecutive lots of 3A-HBV at Day 196, four weeks post-3rd vaccination
- **Secondary and Exploratory Objectives :**
  - *Safety, tolerability, and reactogenicity :* Standardized methods for local and systemic vaccine reactions, repeated vital signs and physical examinations, 48 weeks follow-up for serious adverse events (SAEs), medically-significant events (MAAEs) or new onset of chronic illness (NOCI), and changes in concomitant medication
  - *Immunogenicity :* Seroprotection rates (SPR), GMC of anti-HBs titers, and kinetics of immunogenicity

N size	2,838
Age Range	18-45 years
3A-HBV	10 µg
Control Vaccine	20 µg 1A-HBV
Random.	1:1:1:1
Dosing	0, 4, 24 weeks

STUDY SUBJECT DISPOSITION

Individuals Screened	4,452			
- Screened Failure	1,614 (36%)			
Participants Randomized	2,838 at 35 study sites			
Clinical Study Arms	**Lot A 3A-HBV**	**Lot B 3A-HBV**	**Lot C 3A-HBV**	**1A-HBV**
Participants Randomized	711	709	706	712
Mean Age	33.8	32.9	33.9	33.4
Gender				
- Male	303 (43%)	313 (44%)	291 (41%)	291 (41%)
- Female	408 (57%)	396 (56%)	415 (59%)	421 (59%)
Mean BMI	25.9	25.8	26.0	25.7
Race				
- White	650 (91%)	642 (91%)	651 (92%)	654 (92%)
- Asian	9 (1%)	15 (2%)	13 (2%)	9 (1%)
- Black or African American	46 (7%)	43 (6%)	34 (5%)	38 (5%)
- Other	6 (1%)	9 (1%)	8 (1%)	11 (2%)
Ethnicity				
- Hispanic or LatinX	64 (9%)	70 (10%)	61 (9%)	74 (10%)
- Non-Hispanic or LatinX	643 (90%)	639 (90%)	644 (91%)	636 (89%)
- Not collected	4 (1%)	0 (0%)	1 (0.1%)	2 (0.3%)
Country/Region				
- United States	191 (27%)	187 (26%)	186 (26%)	188 (26%)
- Europe	489 (69%)	493 (70%)	490 (70%)	493 (69%)
- Canada	31 (4%)	29 (4%)	30 (4%)	31 (4%)
Withdrew	75 (10.5%)	72 (10.2%)	81 (11.5%)	69 (9.7%)
Completed Study	636 (89.5%)	637 (89.8%)	625 (88.5%)	643 (90.3%)

SAFETY & TOLERABILITY RESULTS

	Pooled 3A-HBV *n=2,124* (% of subjects)	**1A-HBV** *n=712* (% of subjects)
Vaccine withdrawal due to AE/SAE	0.5	0.3
Study discontinuation due to AE/SAE	0.4	0.1
Local Reactogenicity (most common)		
Injection site pain	75.6	53.9
Injections site tenderness	75.1	54.9
Systemic Reactogenicity (most common)		
Myalgia	44.4	32.4
Fatigue	40.1	39.9
Headache	38.2	37.6
Treatment-emergent AEs (TEAEs)	53.1	52.1
Medically-attended AEs (MAAEs)	21.7	17.6
New Onset of Chronic Illness (NOCI)	1.6	1.1
SAEs	2.0	0.4
Death	1	0

IMMUNOGENICITY RESULTS

Figure 1 : Anti-HBs GMCs for 3A-HBV were consistent across lots (A, B, C) and were >7.5x higher after 2 vaccinations (Day 168) and >3x higher after 3 vaccinations (Day 196) compared to 1A-HBV

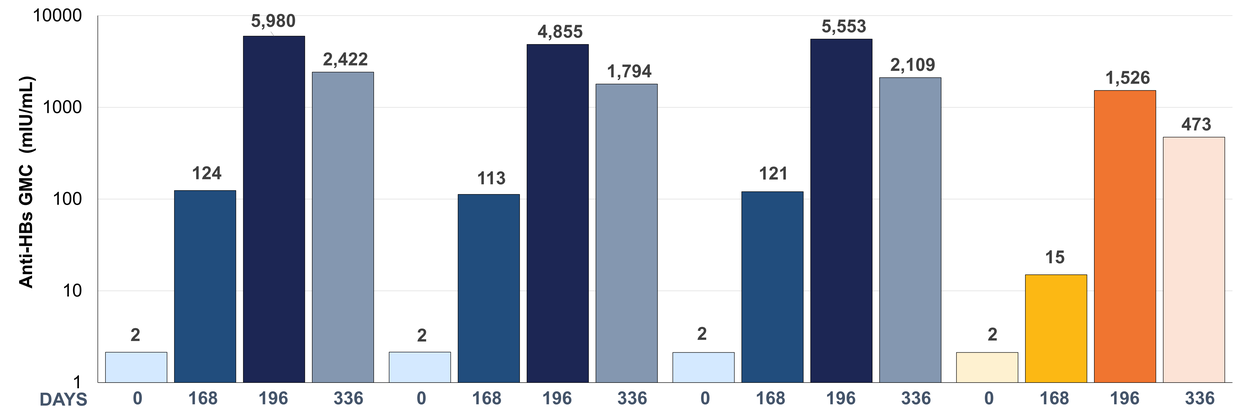
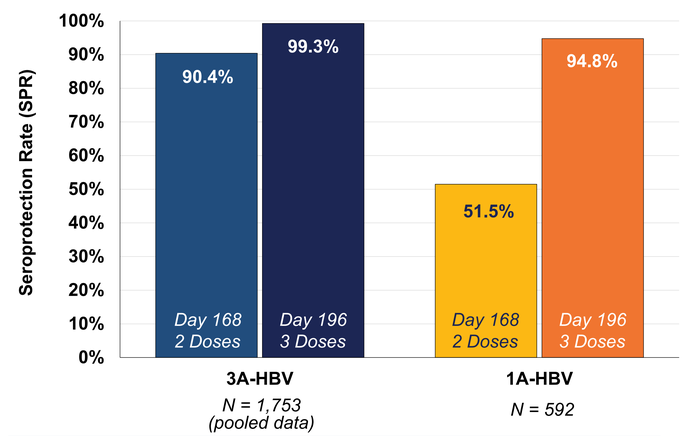


Figure 2 : SPR achieved with 3A-HBV was higher after both the 2nd and 3rd vaccination and was statistically non-inferior at Day 196 compared to the SPR achieved with 1A-HBV



DISCLOSURE

Dr. Francisco Diaz-Mitoma is the Chief Medical Officer of VBI Vaccines Inc.

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CONCLUSIONS

- Lot-to-lot manufacturing consistency of 3A-HBV was demonstrated at Day 196
- SPR of 99.3% after the 3rd vaccination with 3A-HBV was non-inferior to that achieved with 1A-HBV (94.8%)
- SPR of 90.4% after the 2nd vaccination with 3A-HBV was higher than that achieved with 1A-HBV (51.6%)
- 3A-HBV induced robust immune response; anti-HBs GMCs > 7.5x higher after the 2nd dose and > 3x higher after the 3rd dose vs.1A-HBV
- No new or unexpected safety signals – safety profile remains consistent with known profile of 3A-HBV
- Most common AEs mild or moderate local reactogenicity symptoms, which resolved without intervention within 1-2 days and with no increase of reactogenicity with subsequent dosing
- SAEs uncommon with either vaccines

We thank all clinicians, nurses, and volunteers who contributed to this study. The contribution of scientists and technologists at VBI Vaccines Inc. is greatly appreciated.

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