Higher seroprotection rates (SPR) and anti-HBs titers achieved in adults with a 3-antigen hepatitis B vaccine (3A-HBV) compared to a 1-antigen hepatitis B vaccine (1A-HBV): Results of the PROTECT study

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Hepatitis B Disease Burden

Hepatitis B Virus (HBV) is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma worldwide

- Chronic HBV infections worldwide range from **240 million to 350 million**, with an estimated 2.2 million in the US alone, and more than 2 billion people globally ever infected with HBV (acutely or chronically)[1,2]
- Acute HBV infection rates in the US **increased by 11%** from 2014-2018, increases most notable in states impacted most by the ongoing opioid epidemic[3]
- New HBV infections in the US are the **highest among adults ages 30-49**
- Of all chronic HBV infections, 33.2% are among 25-39, 32.0% are among 45-54, and 27.6% are among adults > 55 years[4]
- Healthcare workers, the military, and travelers to endemic regions are most in need of a HBV vaccine that ensures rapid seroprotection
- With no currently-available functional cure for HBV, **vaccination is a critical pillar of the public health** response to HBV
- **Improved HBV vaccines are needed** to ensure safe and effective seroprotection against HBV for those who are older, obese, or those with impaired immune function, including diabetics

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Sources : [1]World Health Organization. Hepatitis B Fact Sheet. https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b#. Accessed June 2020; [2]HHS. Viral Hepatitis in the United States: Data and Trends. https://www.hhs.gov/hepatitis/learn-about-viral-hepatitis/data-and-trends/index.html; Accessed February 2021; [3]HHS Viral Hepatitis National Strategic Plan for the United States: A Roadmap to Elimination (2021-2025). https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf; [4] https://www.cdc.gov/hepatitis/statistics/2016surveillance/pdfs/2016HepSurveillanceRpt.pdf

Phase 3 Clinical Program of a 3-Antigen HepB Vaccine

Objective : Assess the immunogenicity, safety, and manufacturing consistency of 10µg of a 3-antigen HepB vaccine (3A-HBV), and compare it to 20 µg of Engerix-B® (1A-HBV), a single antigen HepB vaccine considered to be standard-of-care:

- **PROTECT** : A head-to-head safety and immunogenicity study [NCT03393754]
  - Co-primary objectives of : (1) non-inferiority of seroprotection rates (SPR) in adults ≥ age 18 years, and (2) superiority of SPR in adults ≥ age 45 years

Focus of today's presentation

- **CONSTANT** : A four-arm lot-to-lot consistency study [NCT03408730]
  - Primary objective : consistency of immune response as measured by geometric mean concentration (GMC) of anti-HBs titers across three consecutively manufactured lots of 3A-HBV

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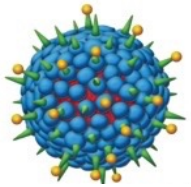
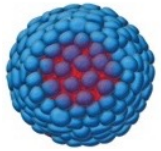
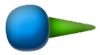
3A-HBV vs. 1A-HBV : Vaccine Design & Function

	3A-HBV	1A-HBV
		
Viral antigens mimicked:		
S Antigen 	✓	✓
Pre-S2 	✓	
Pre-S1 	✓	
Dose of S Antigen:	10µg	20µg
Adjuvant:	Alum	Alum
Derivation:	Mammalian Cell	rDNA yeast

- **Pre-S1 antigen induces key neutralizing antibodies that block virus receptor binding** *[Neurath AR et al., 1989]*
- **T cell response to pre-S1 and pre-S2 antigens can further boost responses to the S antigens, resulting in a more immunogenic response** *[*Hellström UB et al., 2009*]*

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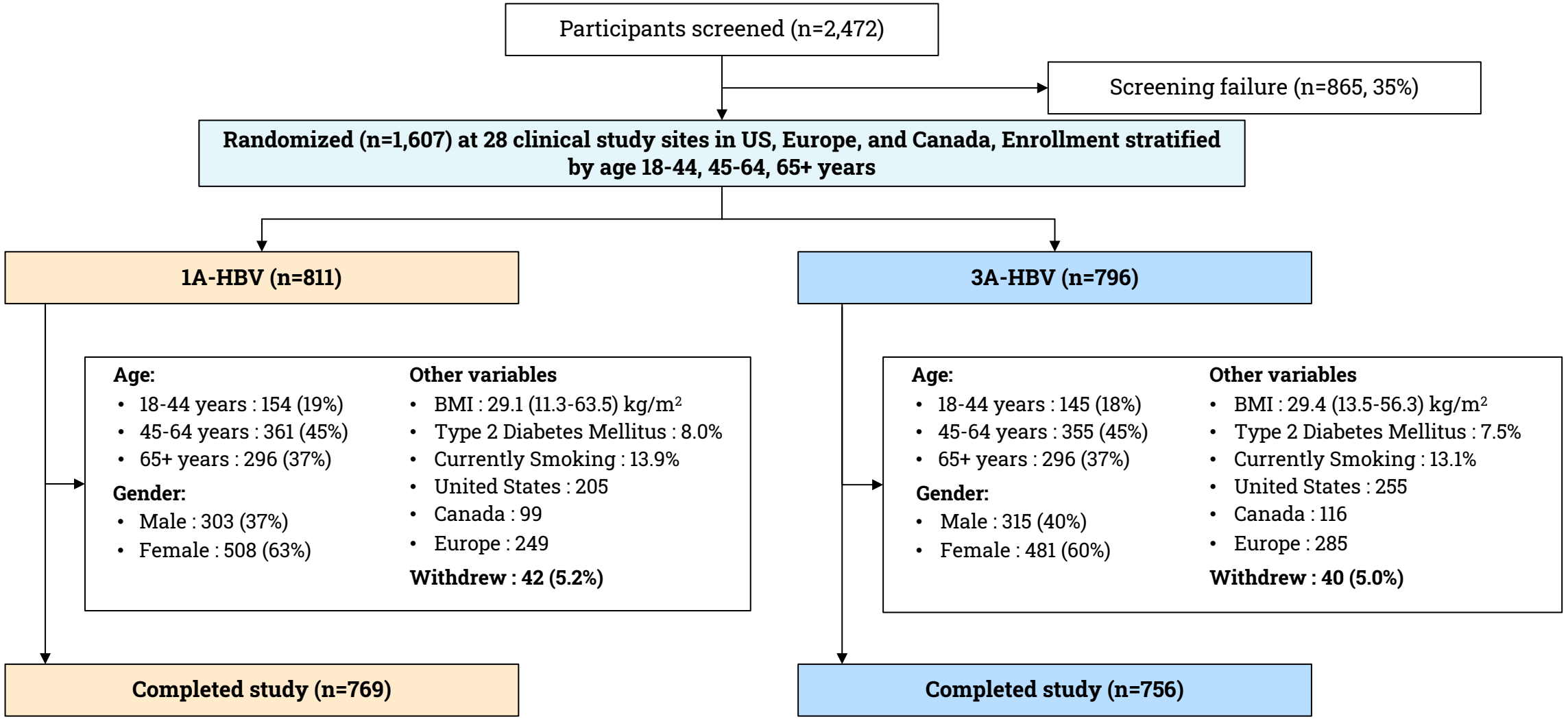
PROTECT Study Participant Disposition



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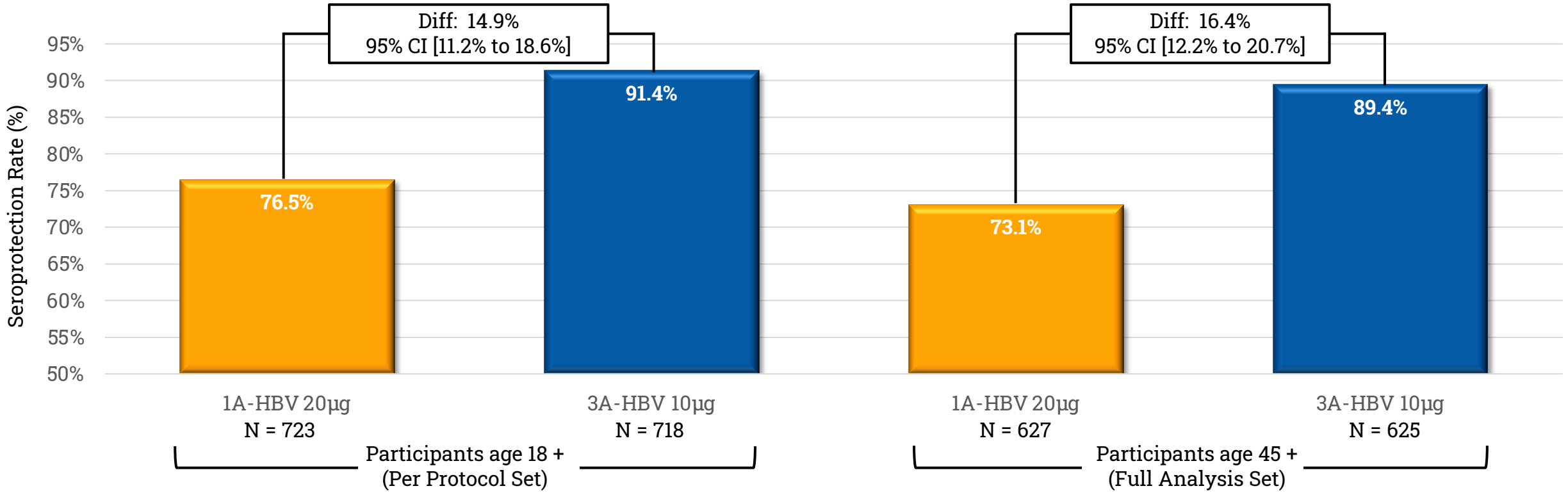
PROTECT : Both Co-Primary Endpoints Met

Co-Primary Endpoints at Day 196, 4 weeks post-3rd vaccination

1. Non-Inferiority of seroprotection rate (SPR) achieved in all subjects age 18+

2. Statistical and clinical superiority, as defined in the protocol, achieved in subjects age 45+



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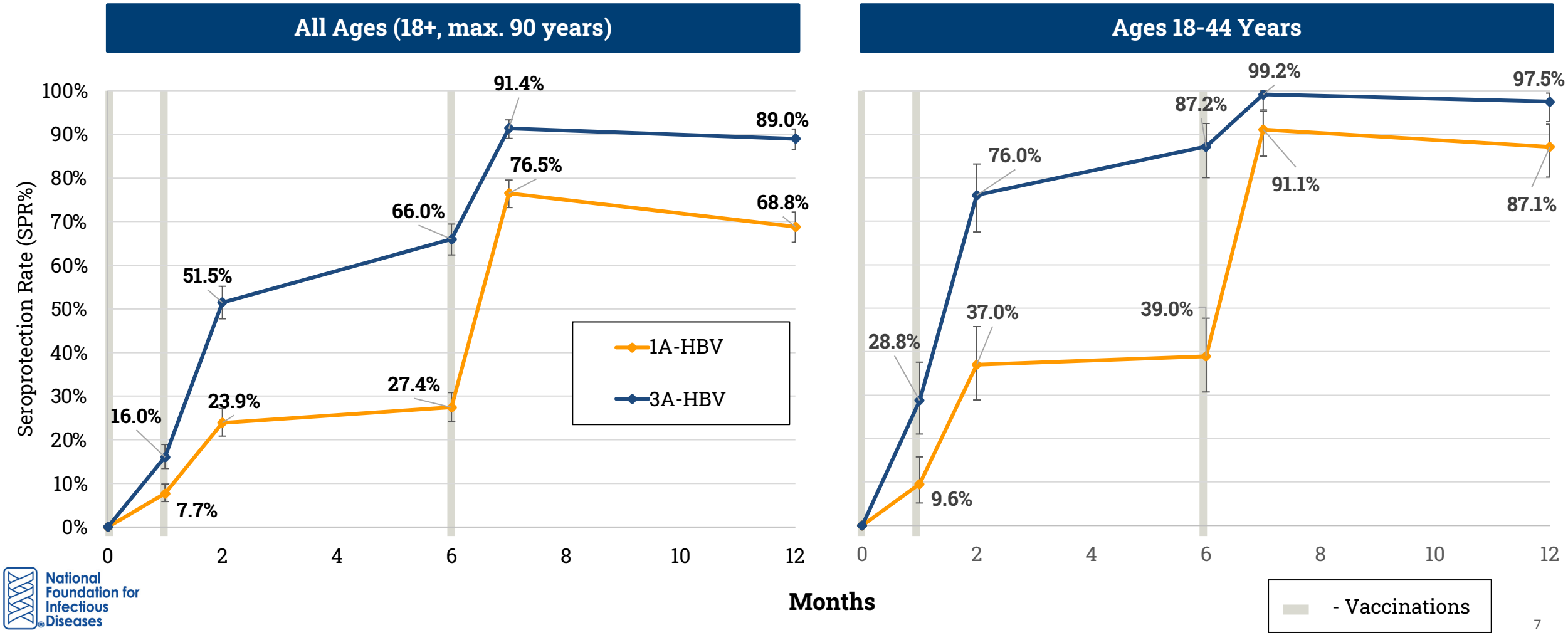
- *Non-inferiority:* The lower bound of the 95% CI of the difference between the SPR in the 3A-HBV arm minus the SPR in the 1A-HBV arm is > -5%
- *Statistical superiority:* The lower bound of the same 95% CI is >0%
- *Clinical superiority:* The lower bound of the same 95% CI is >5%

PROTECT : Kinetics of SPR by Age

3A-HBV achieved higher SPR vs. 1A-HBV at all time points – in participants age 18-44, 87.2% were protected after 2 doses of 3A-HBV vs. 39.0% for 1A-HBV



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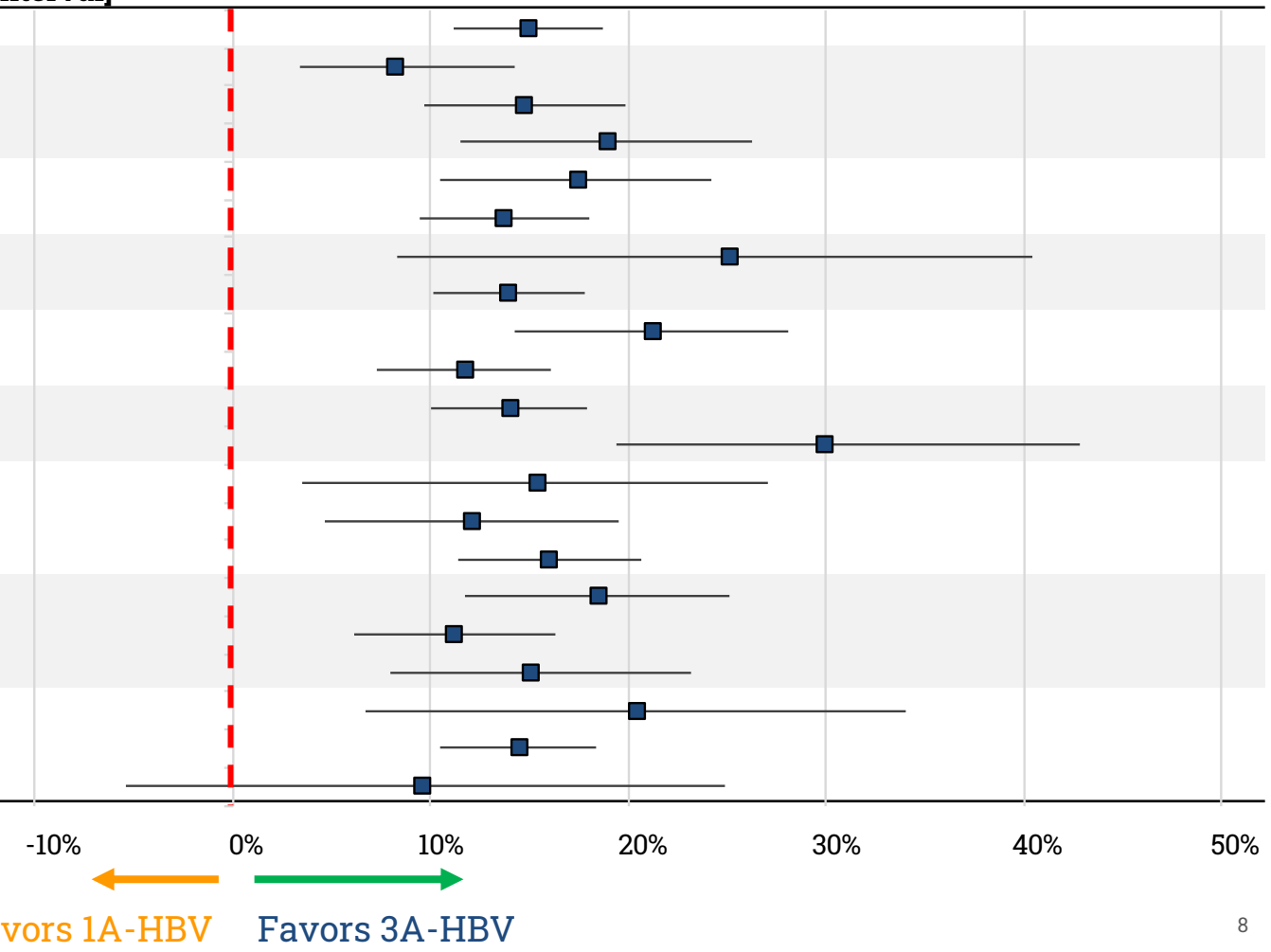
PROTECT : SPR in Subgroup Populations

3A-HBV achieved higher SPR vs. 1A-HBV in key subgroup analyses at Day 196

Participant Populations*		N	Difference in SPR (%) [95% Confidence Interval]
All Participants		1,441	**14.9%** [11.2%, 18.6%]
Age	18-44 Years	260	**8.1%** [3.4%, 14.2%]
	45-64 Years	647	**14.7%** [9.8%, 19.8%]
	65+ Years	534	**18.9%** [11.6%, 26.1%]
Gender	Men	551	**17.4%** [10.6%, 24.2%]
	Women	890	**13.7%** [9.5%, 18.0%]
Diabetic Status	Diabetics	114	**25.0%** [8.4%, 40.4%]
	Non-Diabetics	1,327	**13.9%** [10.2%, 17.7%]
Body Mass Index (BMI)	BMI > 30 (Obese)	523	**21.1%** [14.3%, 28.0%]
	BMI ≤ 30	918	**11.6%** [7.4%, 16.0%]
Alcohol Consumption	0-1 Drinks/Day	1,325	**13.9%** [10.1%, 17.8%]
	2-3 Drinks/Day	108	**29.8%** [19.5%, 42.7%]
Smoking Status	Smoker	187	**15.3%** [3.5%, 27.0%]
	Past Smoker	385	**12.0%** [4.7%, 19.5%]
	Non-Smoker	869	**16.0%** [11.4%, 20.6%]
Geography	US	601	**18.4%** [11.8%, 25.0%]
	Europe	601	**11.1%** [6.2%, 16.3%]
	Canada	239	**15.0%** [8.0%, 23.1%]
Ethnicity/ Race	Hispanic or Latino	132	**20.3%** [6.8%, 33.9%]
	Non-Hispanic or Latino	1,303	**14.4%** [10.6%, 18.3%]
	Black or African-American	108	**9.5%** [-5.4%, 24.8%]



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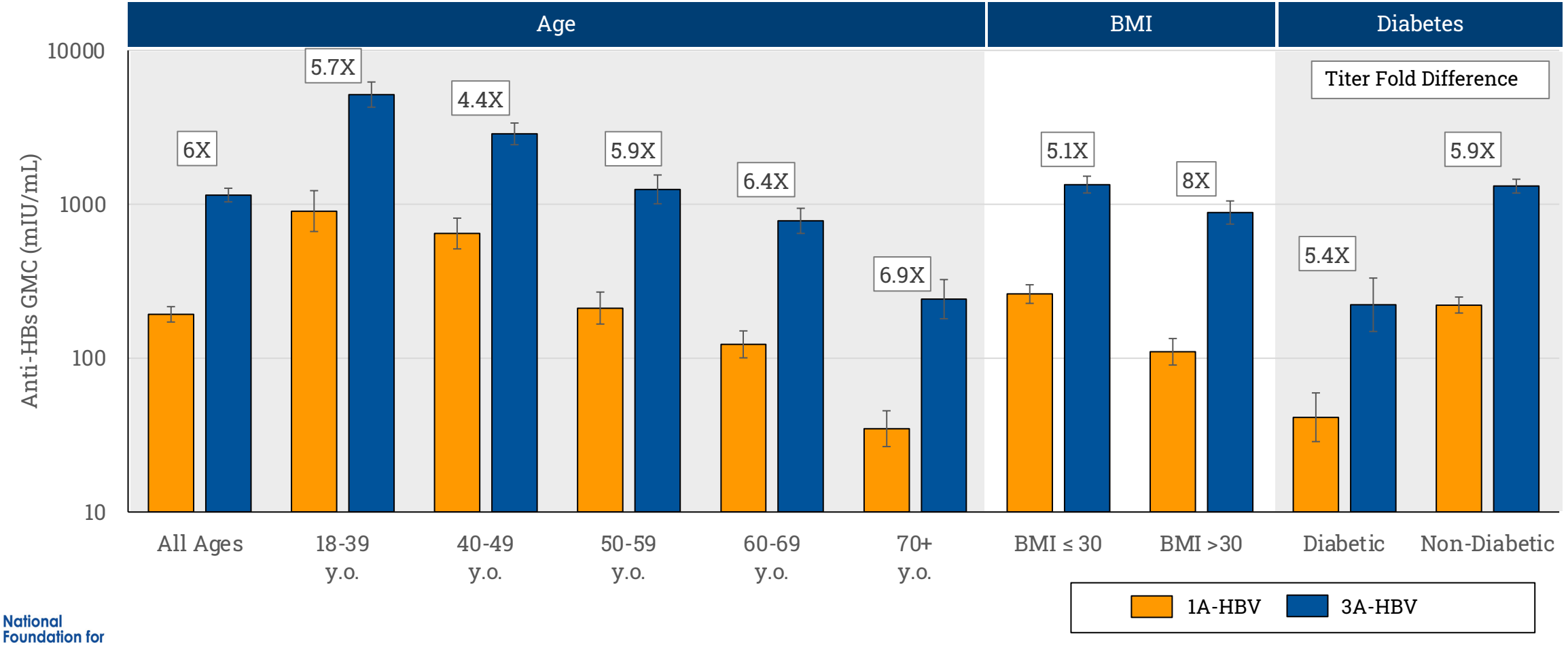
* Per Protocol Set

PROTECT : Anti-HBs Titers in Subgroups

5-8x higher antibody GMC is maintained for participants who received 3A-HBV vs. 1A-HBV, regardless of age, BMI, or diabetic status



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Error bars = SE; Geometric Mean Concentration (GMC) and SE are calculated based on log10-transformed data, then transformed back to anti-HBs titer

PROTECT : Safety Evaluation

Serious Adverse Events (SAEs)

	3A-HBV	1A-HBV
SAEs occurring in ≥ 2 participants:		
Atrial Fibrillation	1 (0.1%)	2 (0.2%)
Cardiac failure congestive	2 (0.3%)	-
Colon cancer	-	2 (0.2%)
Cholelithiasis	1 (0.1%)	1 (0.1%)
Ankle fracture	1 (0.1%)	1 (0.1%)
Osteoarthritis	1 (0.1%)	1 (0.1%)
Cerebrovascular accident	1 (0.1%)	1 (0.1%)

- 95.2% in 3A-HBV and 96.8% participants in 1A-HBV completed full course of vaccination
- Low rate of vaccine discontinuation due to non-serious AEs of 0.4% vs. 0.4% and 0.3% vs. 0.2% due to SAEs for 3A-HBV and 1A-HBV, respectively
- Low rates of SAEs reported (1A-HBV: 2.6% and 3A-HBV: 4.0%)
- Only one SAE, viral gastroenteritis, probably related to 3A-HBV
- Higher rates of mild or moderate injection site pain, tenderness, and myalgia reported by subjects receiving 3A-HBV compared to 1A-HBV

Unsolicited AEs

	3A-HBV	1A-HBV
1+ AEs reported throughout study (% of participants)	**52.5%**	**54.5%**
AEs reported by ≥ 1% of participants:		
Headache	8.5%	8.3%
URI	6.3%	6.7%
Fatigue	4.1%	4.9%
Nasopharyngitis	3.9%	3.5%
Injection site pain	2.9%	1.6%
Back pain	4.4%	2.8%
Arthralgia	2.1%	2.5%
Diarrhea	1.3%	2.6%
UTI	2.1%	2.1%
Oropharyngeal pain	1.9%	2.2%
Dizziness	1.5%	1.2%
Sinusitis	1.4%	2.1%
Hypertension	1.3%	1.6%
Respiratory rate increase	1.3%	0.9%
Gastroenteritis	1.3%	0.5%
Nausea	0.4%	1.2%
Cough	1.1%	1.0%
Neck pain	0.8%	1.1%
Bronchitis	1.0%	0.7%
Muscle strain	1.0%	0.7%

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Summary of PROTECT Data

In PROTECT, when compared to 20 µg of 1A-HBV, 10 µg of 3A-HBV demonstrated:

- Non-inferiority to 1A-HBV in all adults age 18+ (91.4% vs. 76.5%) *[difference 14.9%; 95% CI: 11.2, 18.6%]* and superiority, as defined in the clinical protocol, in adults ≥ age 45 years (89.4% vs. 73.1%) *[*difference 16.4%; 95% CI: 12.2, 20.7%*]*
- Higher SPR in key high-risk and immunocompromised populations including obese individuals (89.2% vs. 68.1%), diabetics (83.3% vs. 58.3%), and subjects age 65+ (83.6% vs. 64.7%)
- A more rapid immune response, resulting in higher SPR at each time point compared
- A safety profile consistent with previous studies - no safety signals observed

Next Steps:

- U.S. FDA accepted filing of BLA for 3A-HBV for the prevention of infection caused by all known subtypes of HBV in adults
- The FDA has set a Prescription Drug User Fee Act (PDUFA) target action date of November 30, 2021

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