

# HEPLISAV-B

**Robert Janssen, MD**  
**Dynavax Technologies Corporation**

---

Advisory Committee on Immunization Practices

October 25, 2017

# HEPLISAV-B Antigen Similar to Current HBV Vaccines

---

- Contains yeast-derived recombinant hepatitis B surface antigen
- Adjuvant
  - HEPLISAV-B uses Toll-like receptor 9 (TLR9) agonist, 1018
  - Currently licensed vaccines use alum
- Sterile, liquid dosage form in 0.5 mL dose vials
  - 20 µg HBsAg
  - 3 mg 1018
- Administered: 2 doses over 1 month
  - Compared to 3 doses over 6 months

# 1018 Adjuvant

---

- Small synthetic oligonucleotide with immunostimulatory CpG motifs
- Mimics natural innate immune response to bacterial and viral DNA
- Enhances B and T cell responses to co-administered vaccine antigens
- 1018 targets well-characterized cellular receptor
  - TLR9

# Proposed Indication for HEPLISAV-B

---

- Active immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.
- PDUFA action date - November 9

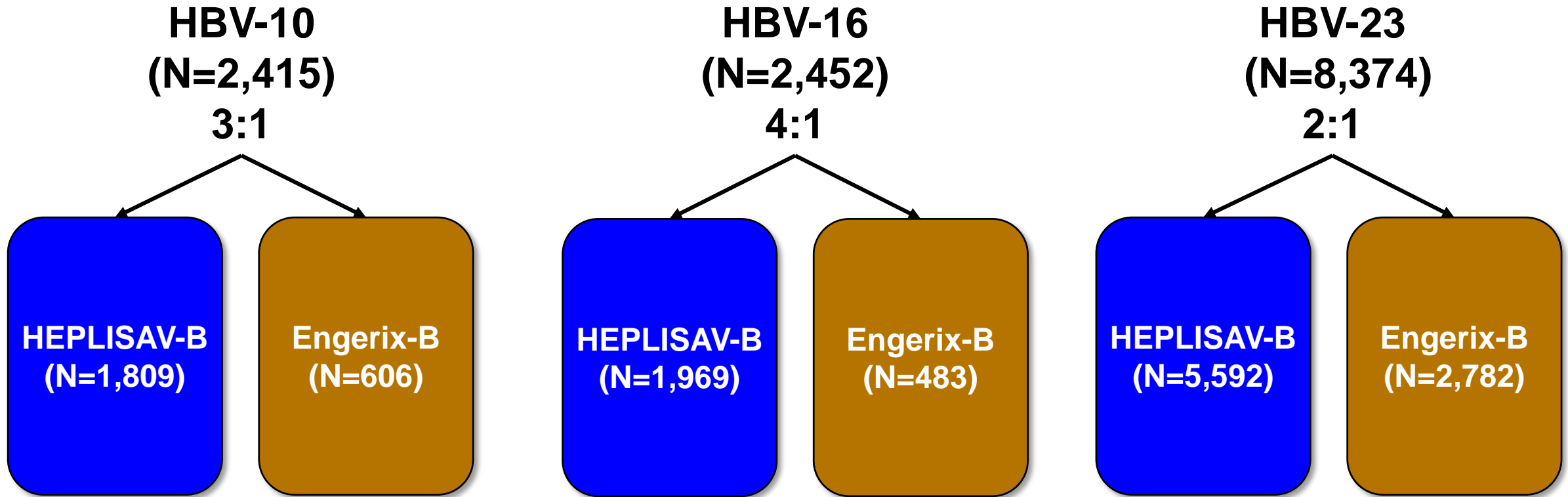
# Immunogenicity

---

# Pivotal Studies

## HBV-10, HBV-16 and HBV-23

---



# Common Study Design Features

---

- Observer-blinded, randomized, active-controlled, multi-center
- Exclusions
  - Current or previous hepatitis B infection or hepatitis B vaccine
  - HIV infection, immunosuppression, or history of autoimmune disease
- Seroprotection rate (% with anti-HBs  $\geq$  10 mIU/mL) compared with Engerix-B
- Anti-HBs levels measured by approved standardized assay (Ortho Vitros ECI)

# Study Statistics

---

## Primary

Demonstrate non-inferiority of HEPLISAV-B SPR to Engerix-B at primary endpoint (in subjects with diabetes mellitus in HBV-23)

## Non-inferiority Criterion

HEPLISAV-B non-inferior to Engerix-B if lower limit of 95% confidence interval of the difference in SPRs was greater than -10%.

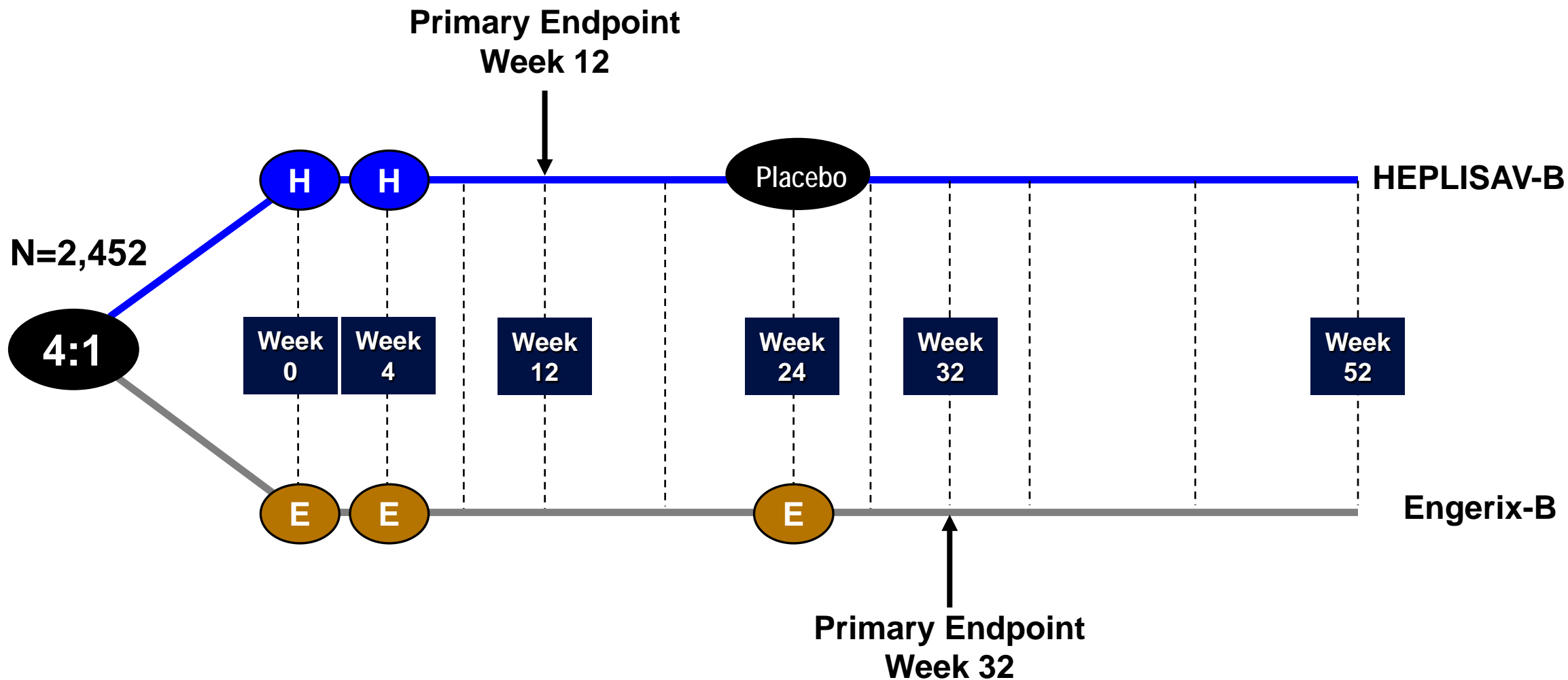
## Statistical Significance Criterion

If HEPLISAV-B seroprotection was non-inferior, then HEPLISAV-B seroprotection was considered statistically significantly higher if lower limit of 95% confidence interval was greater than 0.

Per-protocol population used in analyses.



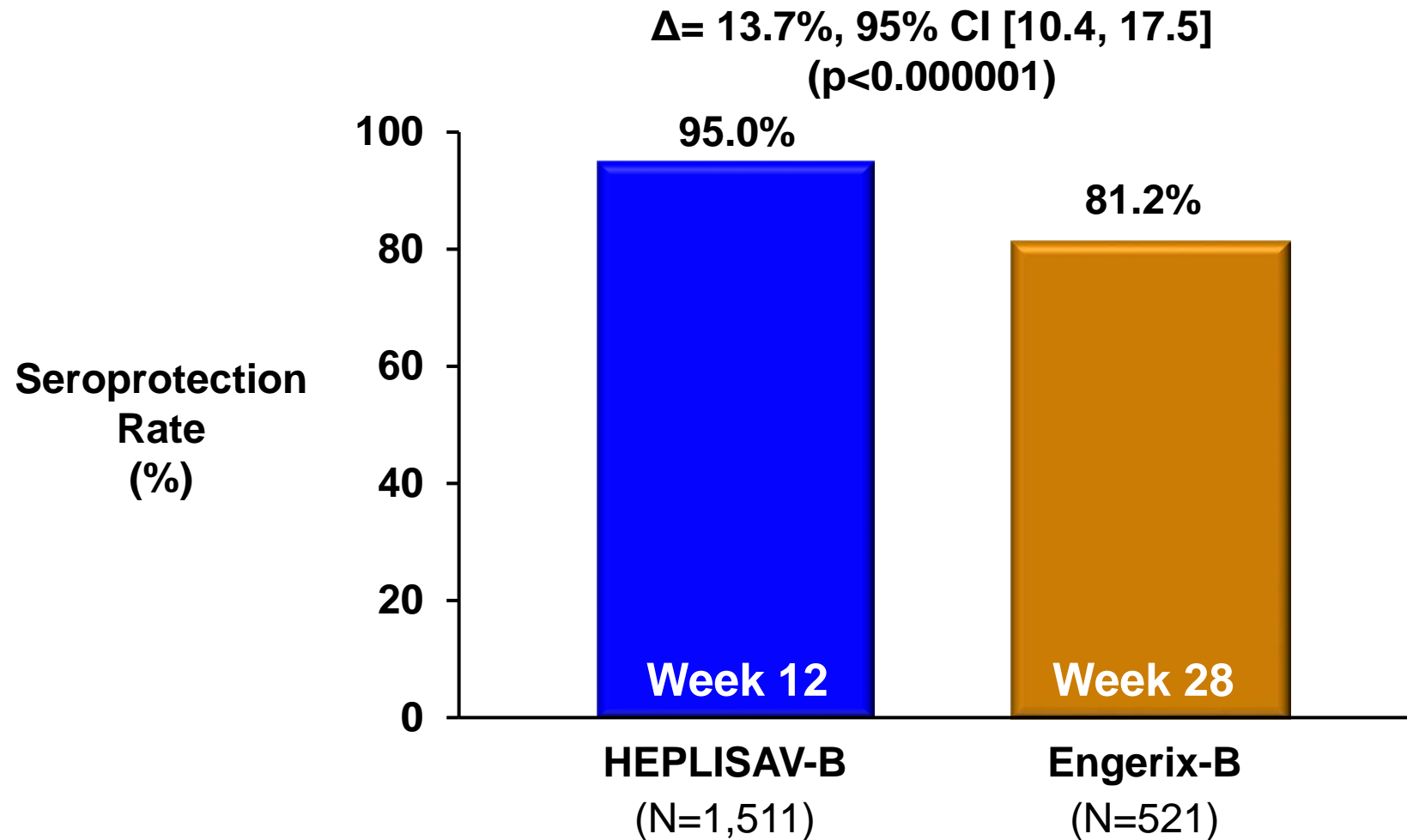
# Illustrative Study Design (HBV-16) (40 – 70 Years, United States and Canada)



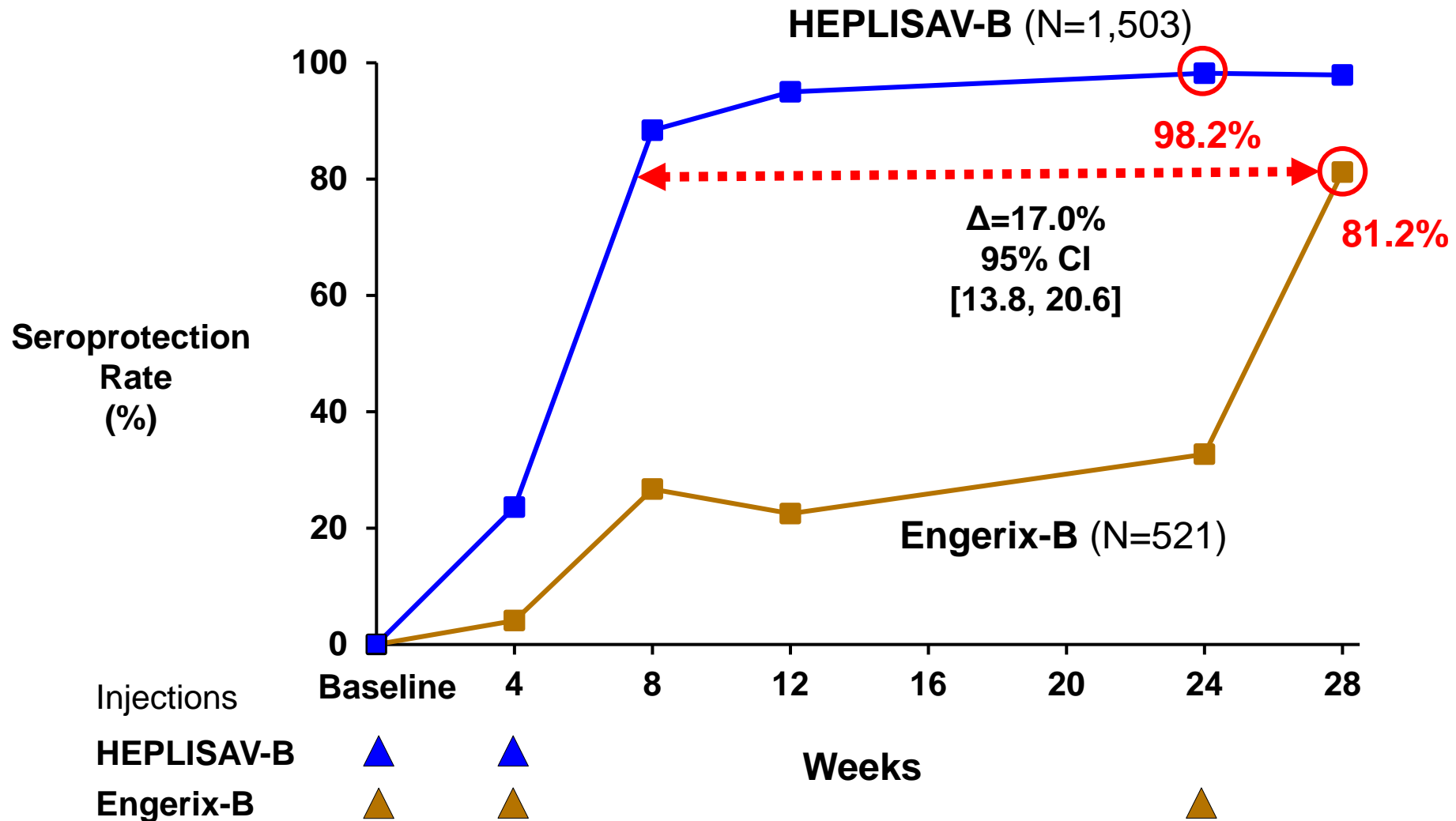
# Demographic and Baseline Characteristics

Trial	HBV-10		HBV-16		HBV-23	
Subgroup	18 to 55 Years		40 to 70 Years		18 to 70 Years	
Per-Protocol Population	HEPLISAV-B (N = 1557)	Engerix-B (N = 533)	HEPLISAV-B (N = 1123)	Engerix-B (N = 359)	HEPLISAV-B (N = 4537)	Engerix-B (N = 2289)
Mean Age (SD)	40.2 (9.25)	40.4 (8.87)	53.9 (7.80)	54.3 (7.85)	51.0 (11.53)	50.9 (11.40)
Sex						
Men	46.2%	42.0%	47.7%	49.6%	50.3%	50.2%
Race						
White	94.1%	92.3%	83.2%	84.4%	70.9%	73.2%
Black	1.8%	3.3%	14.5%	13.3%	26.3%	24.2%
Asian	2.3%	3.1%	1.1%	0.6%	1.0%	1.3%
Other	1.9%	1.3%	1.2%	1.7%	1.8%	1.4%
BMI > 30 kg/m <sup>2</sup>	24.4%	27.6%	44.0%	42.8%	49.5%	47.0%
Smoker	35.6%	36.3%	20.3%	20.7%	31.1%	31.1%

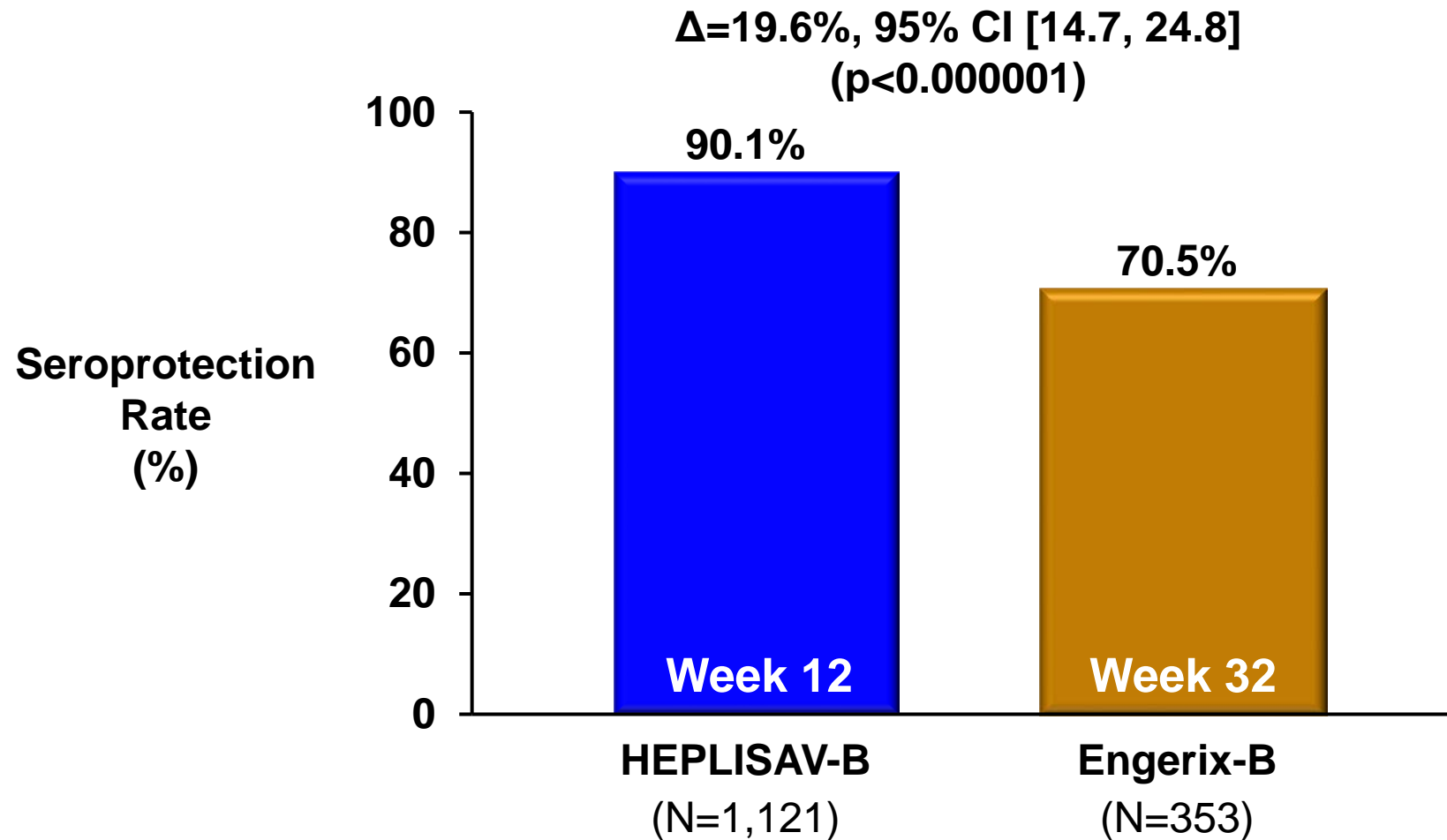
# HBV-10: HEPLISAV-B Met Primary Endpoint



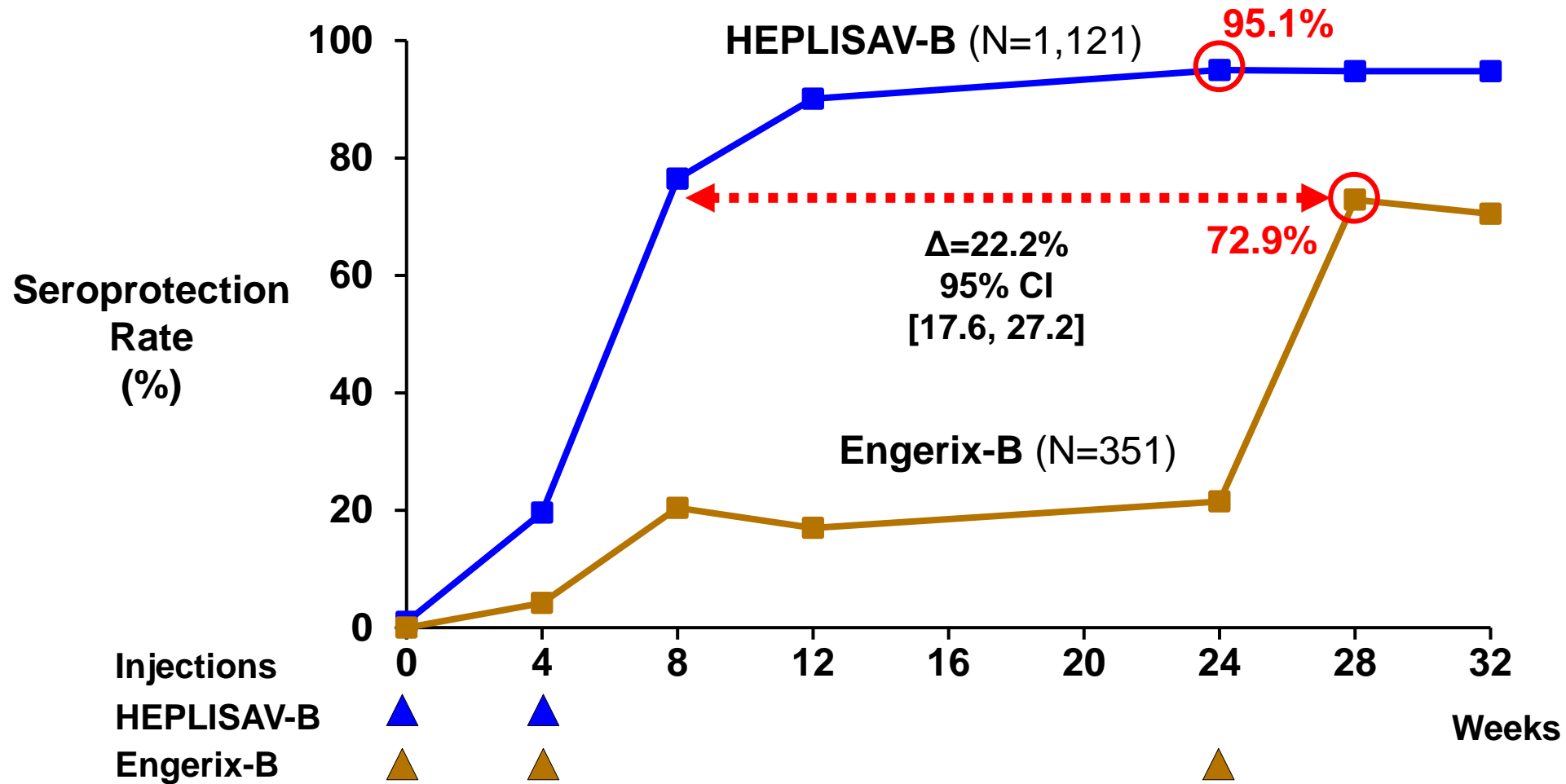
# HBV-10: HEPLISAV-B Induced Significantly Higher Peak SPR



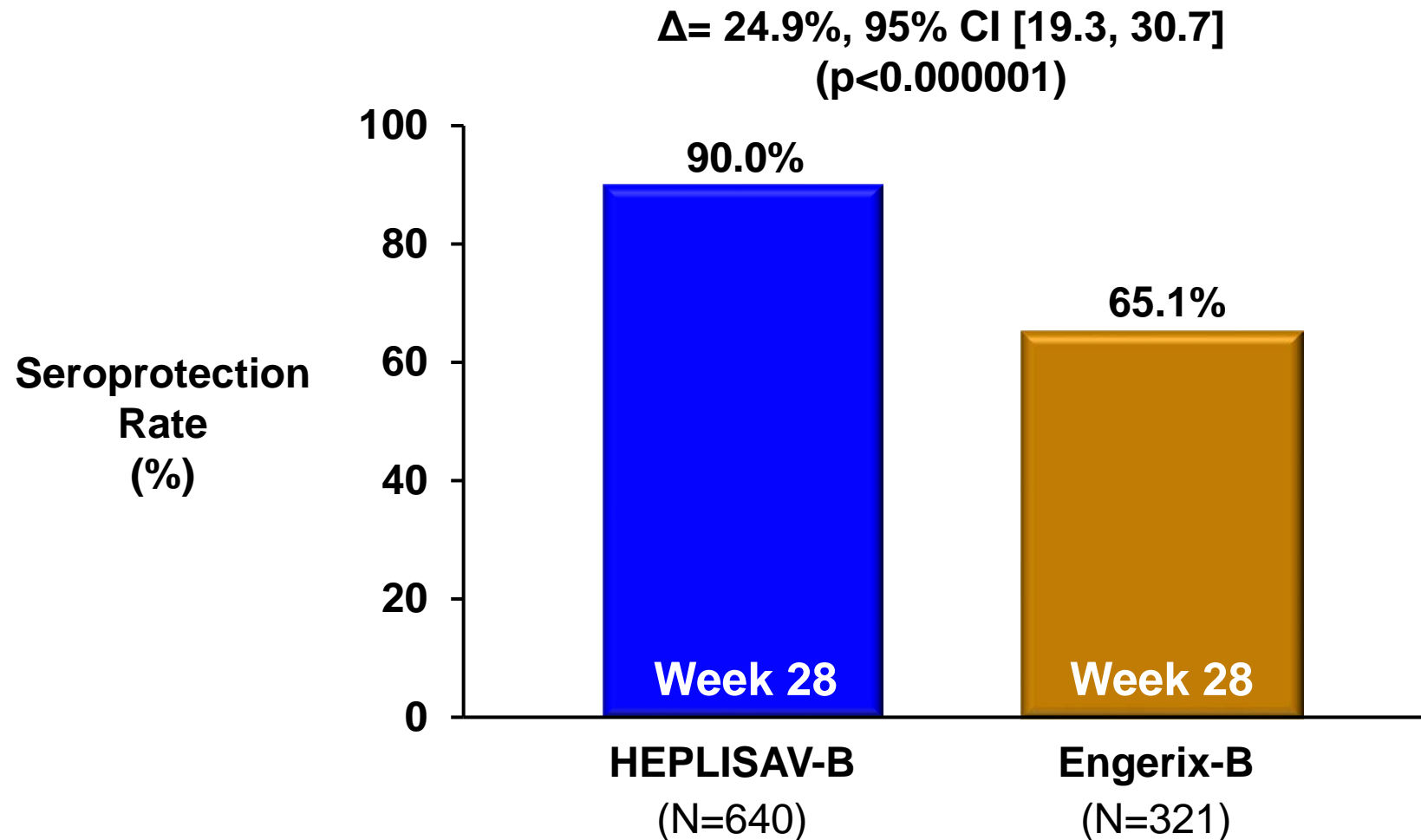
# HBV-16: HEPLISAV-B Met Primary and Secondary Endpoints



# HBV-16: HEPLISAV-B Induced Significantly Higher Peak SPR



# HBV-23: HEPLISAV-B Met Primary Endpoint in Type 2 Diabetes Mellitus

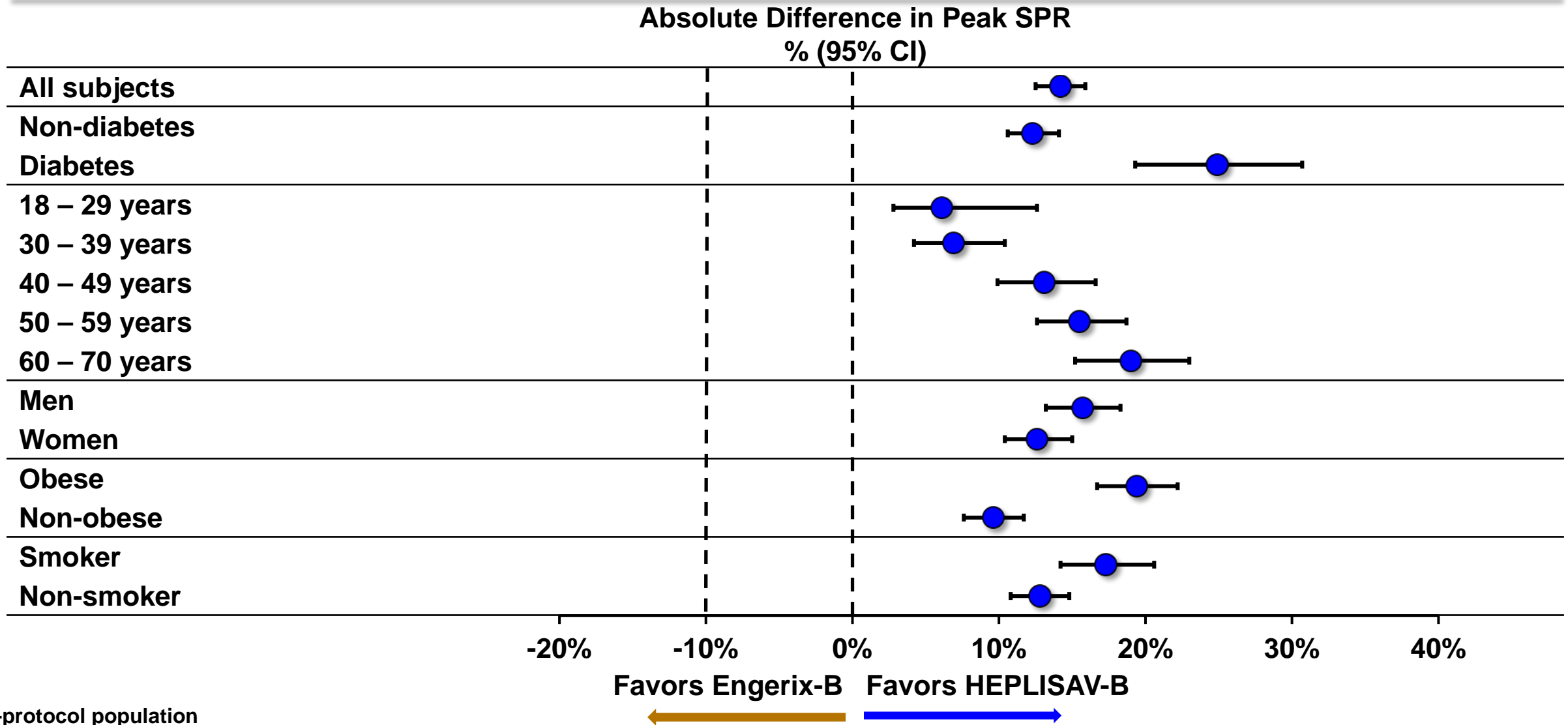


# HBV-23: Higher Seroprotection Rates for HEPLISAV-B in Prespecified Populations

	HEPLISAV-B N	Engerix-B N	Peak SPR (%)	
			HEPLISAV-B	Engerix-B
<b>Total population</b>	<b>4,376</b>	<b>2,289</b>	<b>95.4%</b>	<b>81.3%</b>
<b>Non-diabetes</b>	<b>3,762</b>	<b>1,968</b>	<b>96.2%</b>	<b>83.9%</b>
<b>Diabetes</b>	<b>640</b>	<b>321</b>	<b>90.0%</b>	<b>65.1%</b>
<b>18 – 29 years</b>	<b>174</b>	<b>99</b>	<b>100.0%</b>	<b>93.9%</b>
<b>30 – 39 years</b>	<b>632</b>	<b>326</b>	<b>98.9%</b>	<b>92.0%</b>
<b>40 – 49 years</b>	<b>974</b>	<b>518</b>	<b>97.2%</b>	<b>84.2%</b>
<b>50 – 59 years</b>	<b>1,439</b>	<b>758</b>	<b>95.2%</b>	<b>79.7%</b>
<b>60 – 70 years</b>	<b>1,157</b>	<b>588</b>	<b>91.6%</b>	<b>72.6%</b>
<b>Men</b>	<b>2,203</b>	<b>1,150</b>	<b>94.5%</b>	<b>78.8%</b>
<b>Women</b>	<b>2,173</b>	<b>1,139</b>	<b>96.4%</b>	<b>83.8%</b>
<b>Obese</b>	<b>2,165</b>	<b>1,076</b>	<b>94.7%</b>	<b>75.4%</b>
<b>Non-obese</b>	<b>2,208</b>	<b>1,212</b>	<b>96.1%</b>	<b>86.6%</b>
<b>Smoker</b>	<b>1,371</b>	<b>711</b>	<b>95.9%</b>	<b>78.6%</b>
<b>Non-smoker</b>	<b>3,005</b>	<b>1,578</b>	<b>95.2%</b>	<b>82.4%</b>



# HBV-23: Differences in SPR Statistically Significant in Prespecified Subgroups



# Summary of HEPLISAV-B Immunogenicity

---

- Met primary objective of non-inferiority as well as secondary endpoint of statistical significance in healthy subjects and in subjects with diabetes
- Significantly higher SPRs at early time points
- Significantly higher SPRs at peak
- Significantly higher SPRs in all adult groups

# Safety

---

# Safety Populations in HEPLISAV-B Pivotal Studies

<b>Population</b>	<b>HEPLISAV-B</b>	<b>Engerix-B</b>	<b>Assessments</b>
<b>HBV-10 and HBV-16</b>	<b>3,778</b>	<b>1,086</b>	<b>Reactogenicity, AEs</b>
<b>HBV-23</b>	<b>5,587</b>	<b>2,781</b>	<b>Medically-attended AEs (MAEs)</b>
<b>Primary safety population (PSP) (HBV-10, HBV-16, HBV-23)</b>	<b>9,365</b>	<b>3,867</b>	<b>Deaths, SAEs Immune-mediated AEs</b>

# HEPLISAV-B Safety Profile Similar to Engerix-B

	HEPLISAV-B %	Engerix-B %
<b>HBV-10 and HBV-16</b>	<b>N=3,778</b>	<b>N=1,086</b>
<b>Any post injection reaction (PIR)<sup>a</sup></b>	<b>55.1</b>	<b>57.1</b>
<b>Any AE</b>	<b>55.3</b>	<b>58.1</b>
<b>HBV-23</b>	<b>N=5,587</b>	<b>N=2,781</b>
<b>Any MAE</b>	<b>46.0</b>	<b>46.2</b>

For PIRs HEPLISAV-B N= 3,777 and Engerix-B N= 1,086.

One subject in HBV-10 erroneously included in Engerix-B was correctly included in HEPLISAV-B group in the PSP.

# Post-Injection Reactions (PIR) Balanced Between HEPLISAV-B and Engerix-B

HBV-10 and HBV-16	HEPLISAV-B N=3,777 %	Engerix-B N=1,087 <sup>a</sup> %
Any solicited PIR	55.1	57.1
Local PIR	42.8	41.1
Pain	41.7	40.5
Redness	3.7	1.1
Swelling	2.4	1.3
Systemic PIR	32.3	37.4
Fatigue	21.4	25.1
Headache	20.1	25.3
Malaise	13.8	16.0
Fever $\geq 38^{\circ}\text{C}$	1.7	3.4

a. One subject in HBV-10 erroneously included in Engerix-B was correctly included in HEPLISAV-B group in the PSP.

# HEPLISAV-B Safety Profile Generally Similar to Engerix-B in Primary Safety Population

PSP (HBV-10, HBV-16 and HBV-23)	HEPLISAV-B N=9,365 %	Engerix-B N=3,867 %
Deaths	0.28	0.21
SAEs	4.8	4.8
Any new-onset immune-mediated AE	0.20	0.13

# Type and Frequency of SAEs Generally Similar Between HEPLISAV-B and Engerix-B

PSP (HBV-10, HBV-16 and HBV-23) Preferred Term	HEPLISAV-B	Engerix-B
	N=9,365 %	N=3,867 %
At least 1 SAE	4.8	4.8
Pneumonia	0.17	0.21
Osteoarthritis	0.17	0.13
Acute myocardial infarction	0.17	0.05
Non-cardiac chest pain	0.13	0.21
Chronic obstructive pulmonary disease	0.11	0.10
Cellulitis	0.07	0.10
Prostate cancer	0.04	0.18



# Acute Myocardial Infarction (HBV-10, HBV-16, and HBV-23)

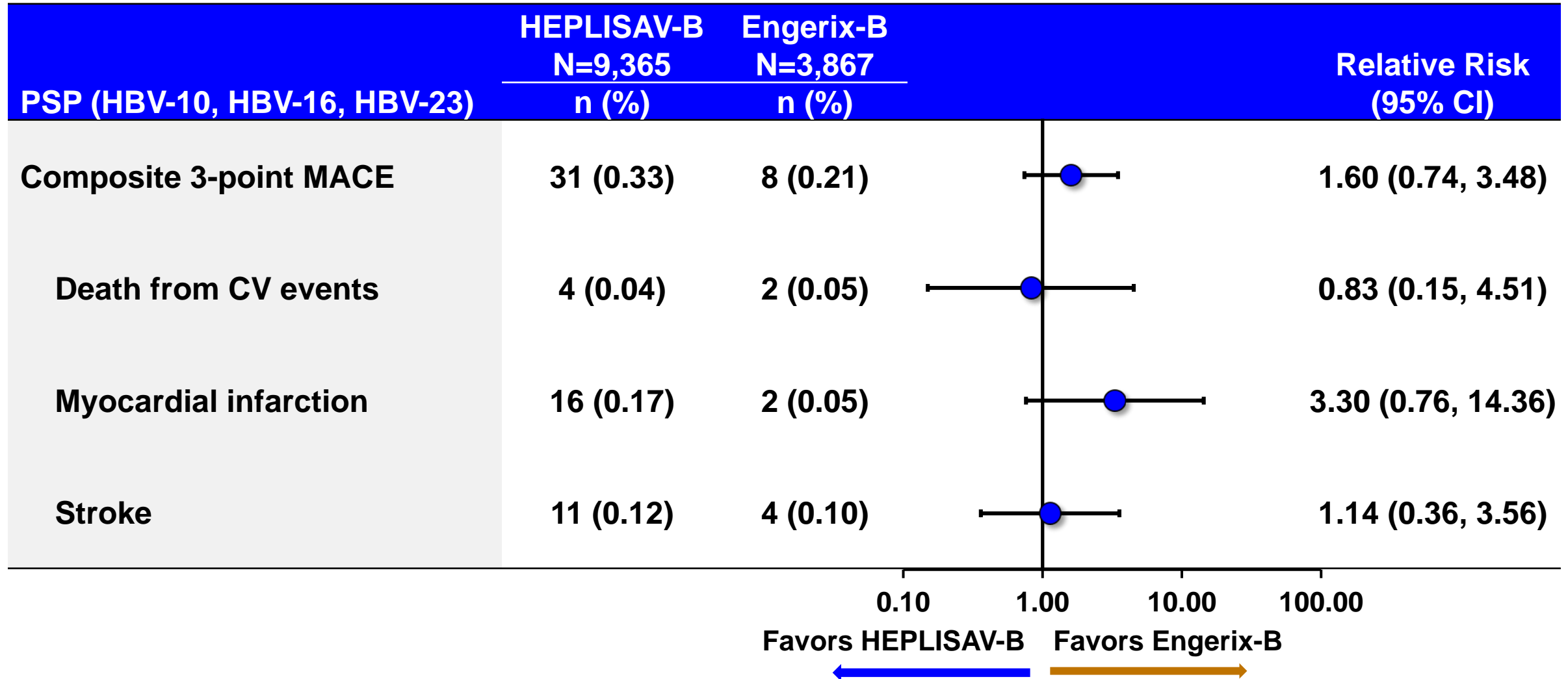
Study	HEPLISAV-B		Engerix-B		Relative Risk	95% CI
	n/N	%	n/N	%		
HBV-23	14/5587	0.25%	1/2781	0.04%	6.97	(0.92, 52.97)
HBV-16	2/1968	0.10%	1/481	0.21%	0.49	(0.04, 5.38)
HBV-10	0/1810	0	0/605	0	N/A	N/A

# Strategy to Explore Myocardial Infarction Imbalance

---

- Identification and post-hoc, blinded adjudication of potential atherosclerotic outcomes
- 3-point Major Adverse Cardiovascular Events (MACE)
  - Cardiovascular death
  - Myocardial infarction
  - Stroke
- Evaluation of events:
  - Risk factors among those with MACE outcomes
  - Comparison of observed rates with expected
  - Temporal relationship of events to vaccine administration

# Adjudication-Confirmed 3-Point MACE Outcomes



# Prevalent Risk Factors Among Subjects with MACE

PSP (HBV-10, HBV-16 and HBV-23)	MACE		Primary Safety Population	
	N=39		HEPLISAV-B N=9,365	Engerix-B N=3,867
Age - median in years (range)	60 (39-70)		50 (18-70)	50 (18-70)
Medical condition	n	%	%	%
Hypertension	29	74.4	29.8	30.5
Diabetes mellitus	8	20.5	10.3	11.0
Hyperlipidemia	10	25.6	10.9	11.8
Obesity	18	46.2	43.2	42.8
Smoking	11	28.2	31.3	32.4

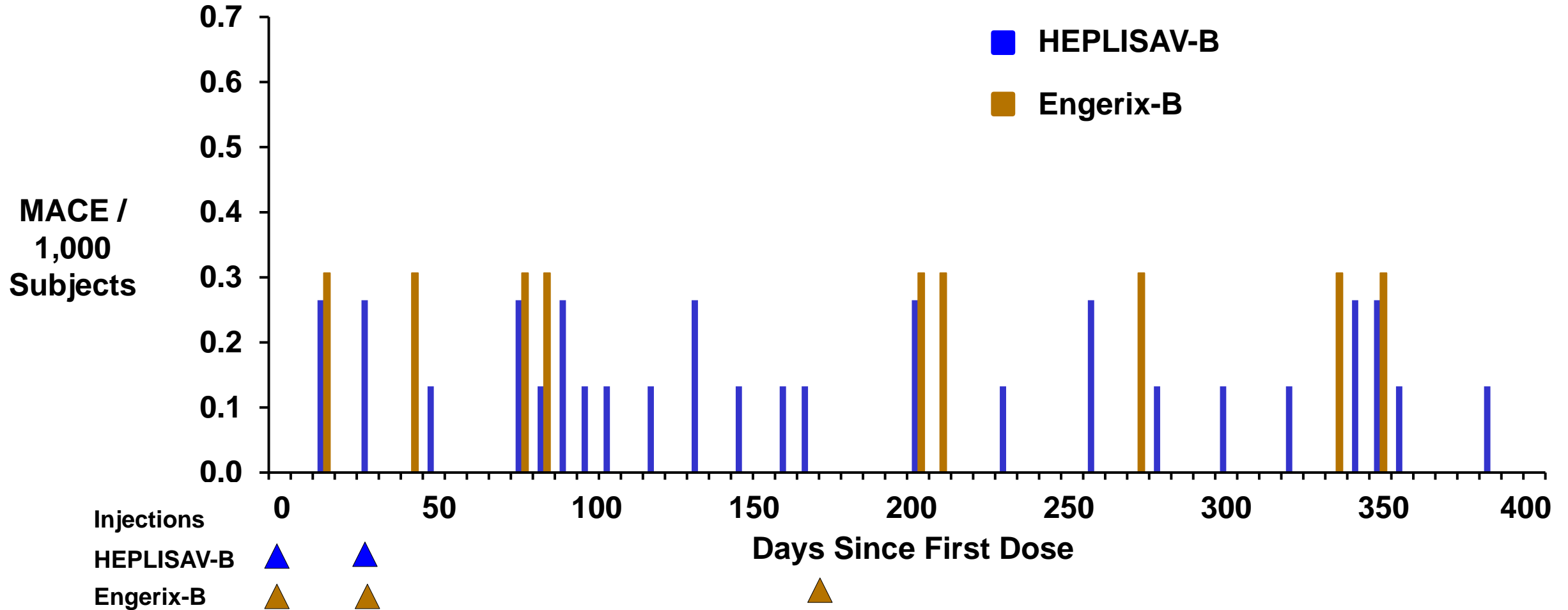
# Age-, Sex-, and Race-Adjusted Incidence of Confirmed 3-Point MACE Lower than Expected

	HEPLISAV-B N=6,724 p-y	Engerix-B N=2,903 p-y	Expected Rate
	1,000 p-y	1,000 p-y	1,000 p-y
Observed 3-point MACE	4.6	2.8	6.5
Observed cardiovascular deaths	0.6	0.7	1.6 <sup>1</sup>
Observed myocardial infarction	2.4	0.7	2.6 <sup>2</sup>
Observed stroke	1.6	1.4	2.3 <sup>3</sup>

Black and white subjects in HBV-16 and HBV-23.

1. Vital statistics 2. Atherosclerosis Risk in Communities Surveillance 3. Greater Cincinnati/Northern Kentucky Stroke Study

# MACE Occurred Throughout Trials



# Cardiovascular Conclusion

---

- No biologically plausible explanation for imbalance
- Lack of consistency across trials
- CV events occurred at expected rates in patients with CV risk
- No temporal association

# New-Onset Immune-Mediated Events

PSP (HBV-10, HBV-16 and HBV-23)	HEPLISAV-B N=9,365		Engerix-B N=3,867	
	n	%	n	%
<b>New-onset immune-mediated</b>	<b>19</b>	<b>0.20</b>	<b>5</b>	<b>0.13</b>
<b>Bell's palsy</b>	<b>6</b>	<b>0.06</b>	<b>2</b>	<b>0.05</b>
<b>Hypothyroidism</b>	<b>3</b>	<b>0.03</b>	<b>0</b>	<b>0</b>
<b>Other</b>	<b>10</b>	<b>0.11</b>	<b>3</b>	<b>0.08</b>



# Rare Serious Immune-Mediated Events Balanced Between Groups

Study	AESI	Time Since Last Dose (months)
<b>HEPLISAV-B</b>		
HBV-10	c-ANCA vasculitis (Granulomatosis with polyangiitis)	2.4
HBV-10	Guillain-Barré syndrome ▪ 5 days after influenza vaccine	3.7
HBV-16	Cavernous sinus syndrome ▪ Tolosa-Hunt syndrome not confirmed by radiology	8.5
<b>Engerix-B</b>		
HBV-10	p-ANCA vasculitis (Microscopic polyangiitis)	4.2

# Similar Autoantibody Development in HEPLISAV-B and Engerix-B Groups

---

## ANCA

- HEPLISAV-B: N = 1972; Engerix-B: N = 596
- No confirmed positive result

## ANA

- HEPLISAV-B: N = 4164; Engerix-B: N = 1209
- 5.5% of HEPLISAV-B and 5.1% of Engerix-B recipients developed antibodies

## Anti-dsDNA

- HEPLISAV-B: N = 4117; Engerix-B: N = 1177
- 1.2% of HEPLISAV-B and 1.0% of Engerix-B recipients developed antibodies

## Antiphospholipid antibodies (HBV-23 Laboratory Substudy, N=309)

- No difference in anti-cardiolipin IgM or IgG, lupus anticoagulant, anti-beta2 glycoprotein 1 IgG
- Transient increase in anti-beta2 glycoprotein 1 IgM at Week 8 in 7.7% of HEPLISAV-B and 1.0% of Engerix-B recipients

# Safety Summary – Similar to Engerix-B

---

- Similar rates of post-injection reactions, AEs / MAEs
- SAEs similar with imbalances in individual terms
  - Acute MI for HEPLISAV-B
  - Prostate cancer for Engerix-B
- No evidence for an increase in the rate of any single immune-mediated event
- Autoantibody conversions balanced

# Post-Marketing Surveillance Studies at Kaiser Permanente Southern and Northern California

---

- Electronic Medical Record analysis
  - Acute myocardial infarction (Southern region)
    - 25,000 HEPLISAV-B: 25,000 other hepatitis B vaccine
    - Non randomized cluster design
  - Immune-mediated events (Southern and Northern regions)
    - 30,000 HEPLISAV-B: 30,000 other hepatitis B vaccine

# HEPLISAV-B Conclusions

---

- Induces high rates of seroprotection in all adults
  - Including populations with reduced response to current vaccines
- Provides earlier seroprotection
- Similar safety profile
- Should increase adherence with 2-dose schedule over 1 month

# Cost-effectiveness

Vaccine 31 (2013) 4024–4032



Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)



## Cost-effectiveness of hepatitis B vaccination using HEPLISAV™ in selected adult populations compared to Engerix-B® vaccine

Renee Kim Kuan<sup>a,\*</sup>, Robert Janssen<sup>b</sup>, William Heyward<sup>b</sup>, Sean Bennett<sup>b</sup>, Robert Nordyke<sup>a</sup>

<sup>a</sup> Health Economics and Outcomes Research, PriceSpective, 2101 Rosecrans Ave, Suite 5280, El Segundo, CA 90245, United States

<sup>b</sup> Dynavax Technologies Corporation, 2929 Seventh Street, Suite 100, Berkeley, CA 94710, United States

		Patients with Diabetes	Healthcare Workers	Travelers
HEPLISAV-B (\$100)	Discounted Cost	\$25,373,976	\$120,183,203	\$26,225,377
	Discounted QALY	1,442,023	2,799,372	2,799,206
Engerix-B (\$52.50)	Discounted Cost	\$23,584,710	\$119,466,431	\$24,934,339
	Discounted QALY	1,441,881	2,799,307	2,798,974
	Incremental Cost	\$1,789,266	\$716,772	1,291,038
	Incremental QALY	142	65	232
	<b>ICER</b>	<b>\$12,613</b>	<b>\$11,062</b>	<b>\$5,564</b>

*Table was adapted from published article*

## Potential Public Health Benefit of 2 Dose HEPLISAV-B

---

- HEPLISAV-B may reduce impact of low adherence in high-risk adults
- For example:
  - Estimates of effective (“real world”) SPR calculated by adjusting SPRs after each dose in HEPLISAV-B trials using adherence data in 18-39 year old MSM from Gunn study in STD clinic
  - Estimated effective SPR in 18-39 year old MSM:
    - HEPLISAV-B: 76%
    - Engerix-B: 47%.
    - Difference in “real world” SPRs = 29%
    - Difference in clinical trial SPRs = 10%

# Additional Benefit of HEPLISAV-B in Averting Hepatitis-B Related Health Outcomes in Patients with Diabetes

Condition Prevented	CDC Estimate for Engerix-B <sup>1</sup>	Estimate Using HEPLISAV-B*	Added Benefit from HEPLISAV-B	Benefit applied to ~50% of unvaccinated patients (~5,000,000)
Infection	4,271	7,359	3,088	29,000
Hospitalization	467	805	338	3,200
Chronic hepatitis B	256	441	185	1,800
HCC	33	57	24	220
Liver transplant	13	22	9	80
Death	130	224	94	900

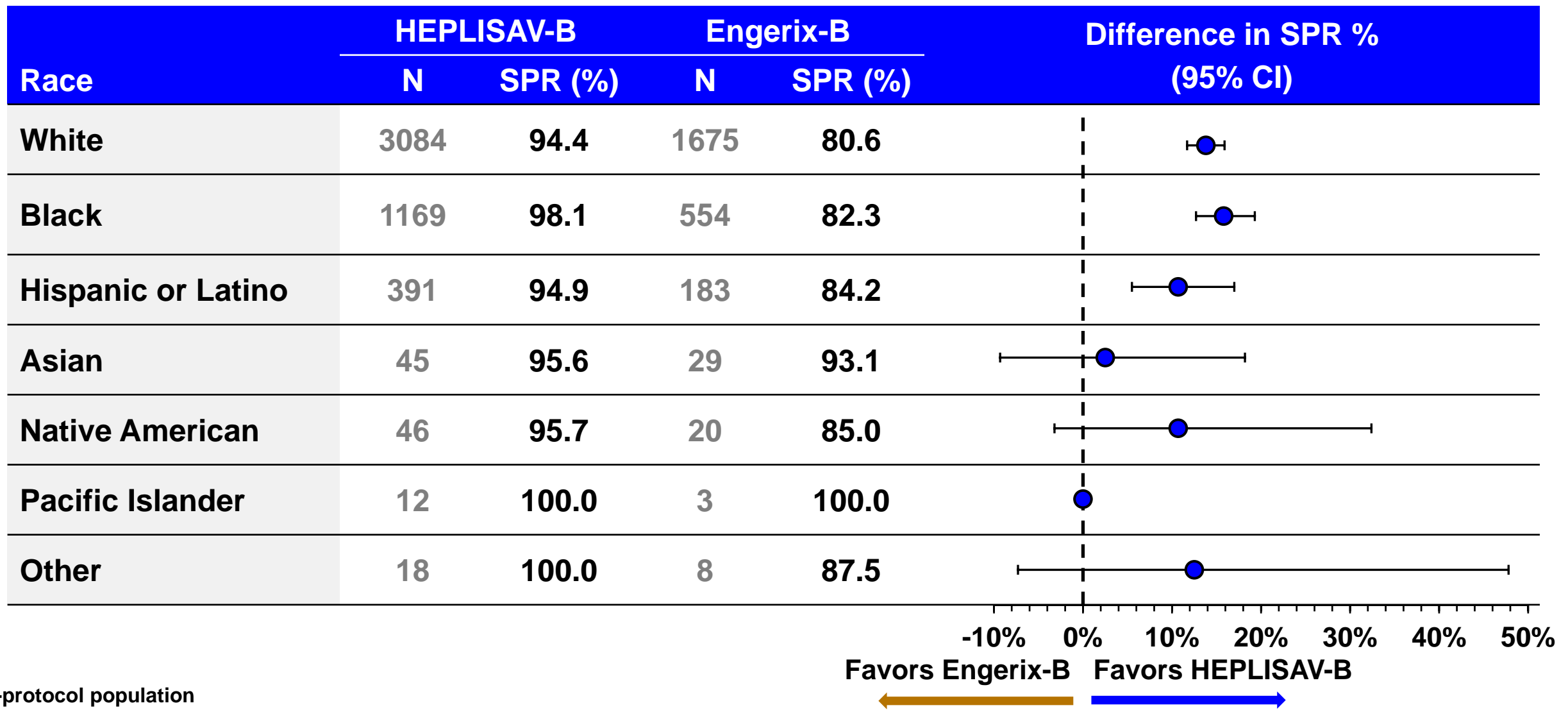
- HEPLISAV-B provides ~72% decrease in hepatitis B related outcomes

\*Assumptions: Vaccine Safety Datalink adherence rates<sup>2</sup>; SPRs in HEPLISAV-B clinical trials; HCC= hepatocellular carcinoma

1. Hoerger, 2013. 2. Nelson, 2013



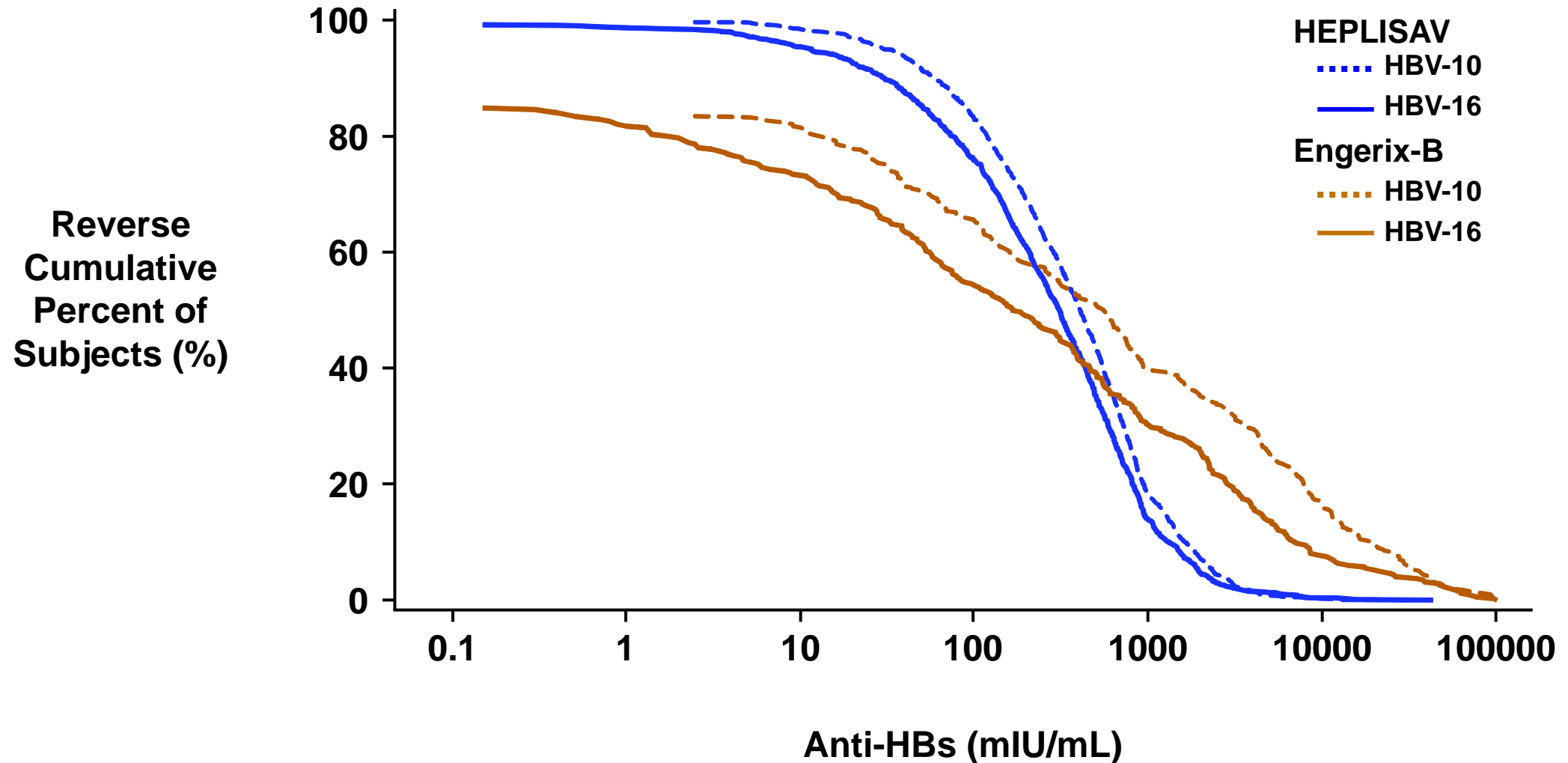
# HBV-23: Seroprotection Rates by Race and Ethnicity Consistent Across Groups



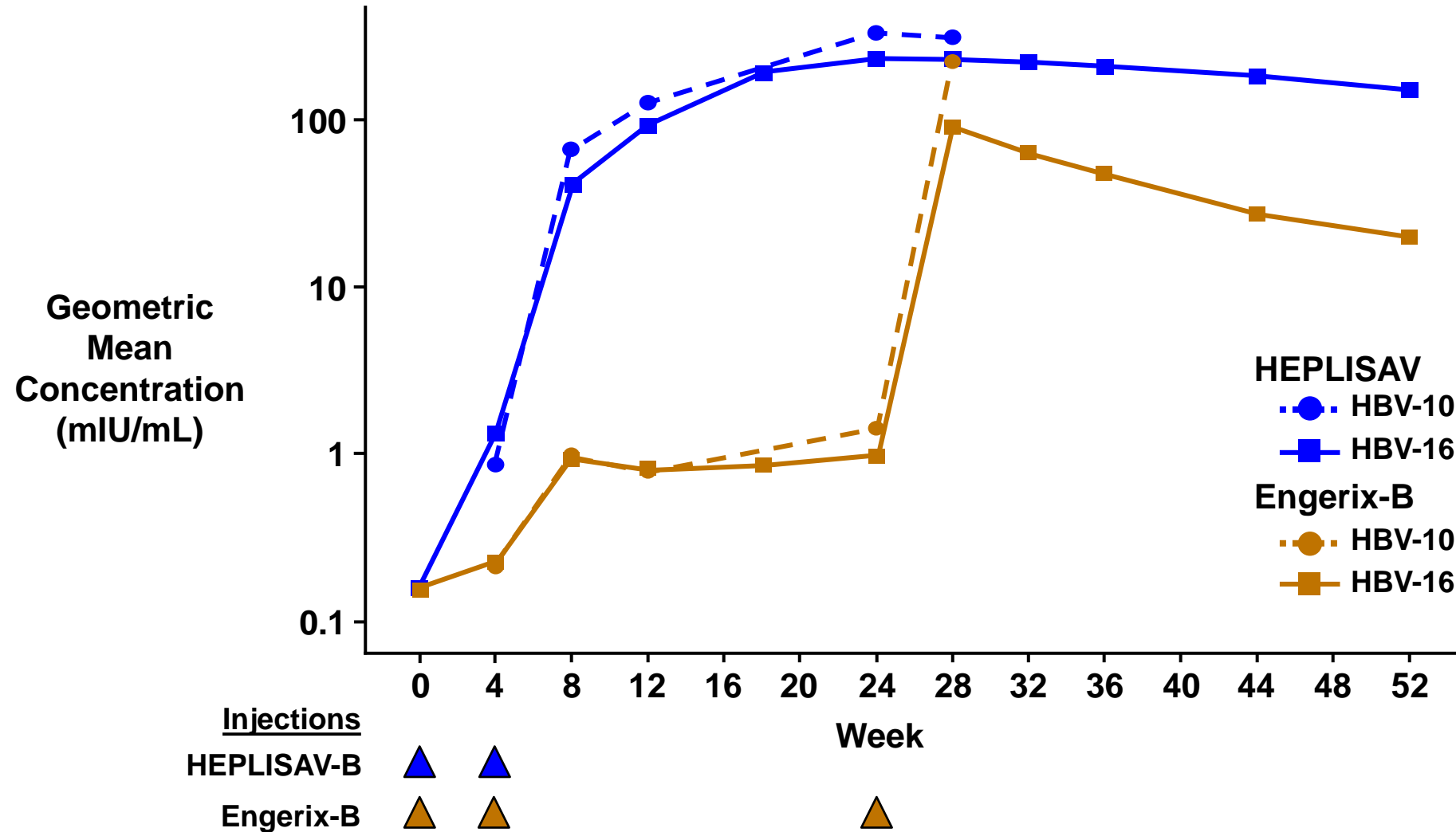
# HEPLISAV-B SPRs Post-Single Dose

<b>TRIAL</b>	<b>N</b>	<b>Mean Age (years)</b>	<b>Week 4 or 8 SPR (%)</b>
HBV-03	47	23	78.9
HBV-08 (0/8 Group)	23	27	69.9
HBV-04	205	50	29.7
HBV-05	42	51	34.8

# Reverse Cumulative Frequency Plot of Anti-HBs Concentration for HEPLISAV Week 24 and Engerix-B Week 28 in HBV-16 and HBV-10 (PP Population)



# 2 Pivotal Trials: GMCs Higher or Similar for HEPLISAV-B vs Engerix-B



# New-Onset AESIs Excluding Bell's Palsy

<b>PSP (HBV-10, HBV-16 and HBV-23)</b>	<b>Age/ Sex</b>	<b>Last Active Dose</b>	<b>Days Since Last Active Dose</b>	<b>Immune Classification<sup>a</sup></b>
<b>HEPLISAV-B<sup>b</sup> (N=9,365)</b>				
Grave's (Basedow's) disease	41/F	2	44	Classical autoimmune / T cell
Vitiligo	69/M	2	2	Classical autoimmune / T cell
Granulomatosis with polyangiitis	54/F	2	73	Classical autoimmune / Ab
Erythema nodosum	62/M	2	20	Innate immune-mediated
Lichen planus	48/F	2	26	Innate immune-mediated
Alopecia areata	52/F	2	229	Innate immune-mediated
Polymyalgia rheumatic	68/M	2	292	Innate immune-mediated
Guillain-Barré syndrome	35/F	2	111	Molecular mimicry / Ab
Ulcerative colitis	46/F	2	221	Intermediate MHC-class I
Cavernous sinus syndrome / THS	68/M	2	292	Unknown
<b>Engerix-B (N=3,867)</b>				
Grave's (Basedow's) disease	30/F	2	78	Classical autoimmune / T cell
ANCA+ vasculitis	44/F	2	127	Classical autoimmune / Ab
Scleroderma				Innate immune-mediated
Raynaud's phenomenon	46/M	3	33	Vasospasm

<sup>a</sup> Koenig 2011. <sup>b</sup> HEPLISAV-B 2.4:1 randomization; THS = Tolosa-Hunt Syndrome

# HBV-23: MAE Imbalances with 95% CIs that Exclude 1

	HEPLISAV-B N=5,587		Engerix-B N=2,781		Relative Risk	95% CI
	n	%	n	%		
					<b>HEP-B/Eng-B</b>	
Herpes zoster	38	0.68	9	0.32	2.10	(1.02 - 4.34)
					<b>Eng-B/HEP-B</b>	
Thyroid neoplasm	0	0	5	0.18	22.1	(1.22 – 399)
Pleurisy	2	0.04	7	0.25	7.03	(1.46 – 33.8)
Hypomagnesemia	2	0.04	6	0.22	6.03	(1.22 – 29.8)
Arthropod sting	3	0.05	8	0.29	5.36	(1.42 - 20.2)
Exostosis	6	0.11	14	0.50	4.69	(1.80 – 12.2)
Positional vertigo	3	0.05	6	0.22	4.02	(1.01 – 16.1)
Impaired glucose tolerance	4	0.07	7	0.25	3.52	(1.03 – 12.0)
Inguinal hernia	5	0.09	8	0.29	3.21	(1.05 – 9.82)
Tooth infection	17	0.30	17	0.61	2.01	(1.03 – 3.93)

# HBV-23: MAE Imbalances with Relative Risk >6.0 and Incidence $\geq$ 1/1000

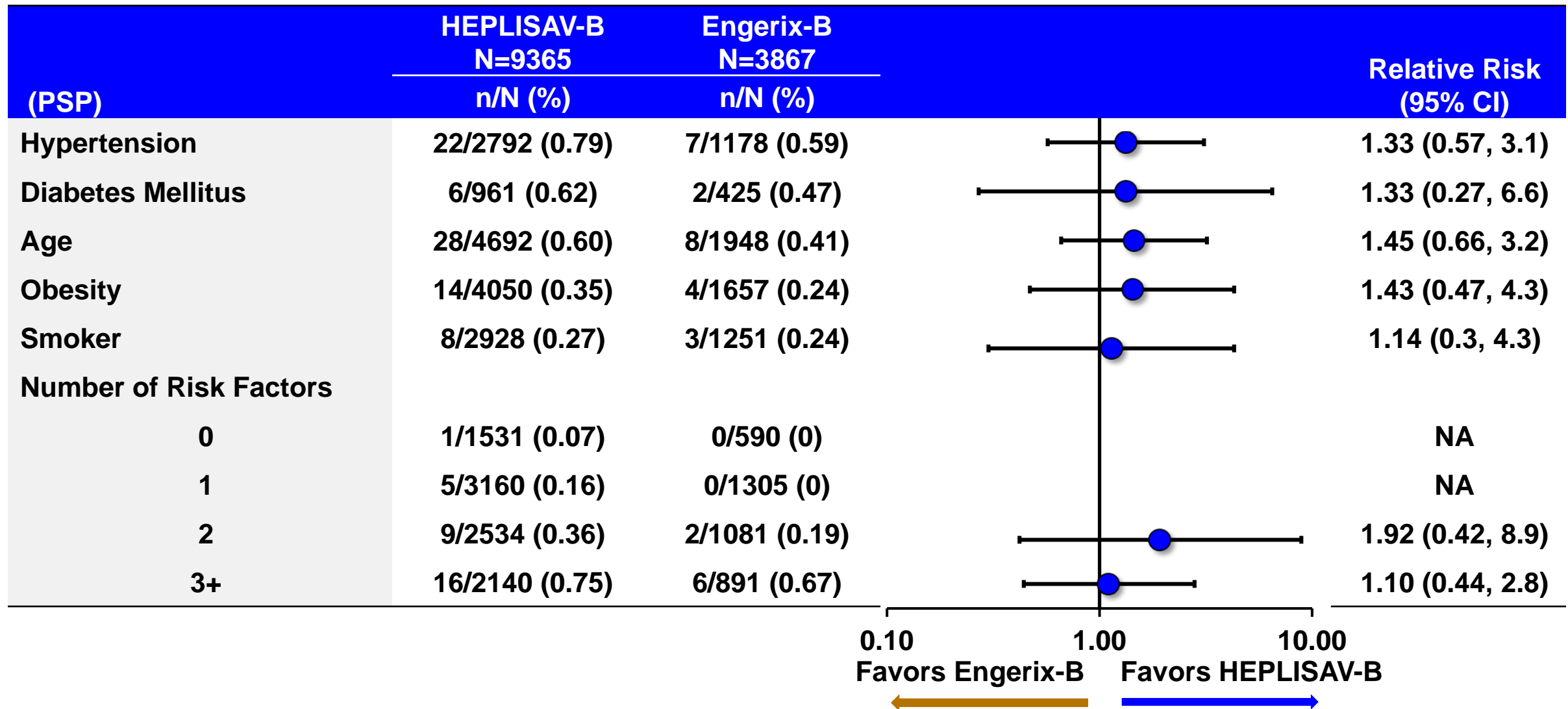
	HEPLISAV-B N=5,587		Engerix-B N=2,781		Relative Risk	95% CI
	n	%	n	%		
<b>HEP-B/Eng-B</b>						
Excoriation	10	0.18	0	0	10.45	(0.61 – 178)
Wound	9	0.16	0	0	9.46	(0.55 – 163)
Lipoma	8	0.14	0	0	8.46	(0.49 – 146)
Acute myocardial infarction	14	0.25	1	0.04	6.97	(0.92 – 53.0)
Bipolar I disorder	6	0.11	0	0	6.47	(0.36 – 115)
<b>Eng-B/HEP-B</b>						
Adenomyosis	0	0	3	0.11	14.1	(0.73 – 272)
Acute cholecystitis	0	0	3	0.11	14.1	(0.73 – 272)
Muscle rupture	0	0	3	0.11	14.1	(0.73 – 272)
Oral herpes	0	0	3	0.11	14.1	(0.73 – 272)
Irritable bowel syndrome	1	0.02	4	0.14	8.04	(0.90 – 71.9)
Oral candidiasis	1	0.02	4	0.14	8.04	(0.90 – 71.9)

# Potential Myocardial Infarctions from SMQ

PSP (HBV-10, HBV-16 and HBV-23) Preferred Term	HEPLISAV-B N=9,365		Engerix-B N=3,867	
	n	%	n	%
<b>Subjects with <math>\geq 1</math> qualifying AE</b>	<b>21</b>	<b>0.22</b>	<b>4</b>	<b>0.10</b>
Acute coronary syndrome	1	0.01	0	0
Acute myocardial infarction	16	0.17	2	0.05
Angina unstable	1	0.01	1	0.03
Coronary artery occlusion	1	0.01	1	0.03
Myocardial infarction	2	0.02	1	0.03



# MACE by Cardiovascular Risk Factors

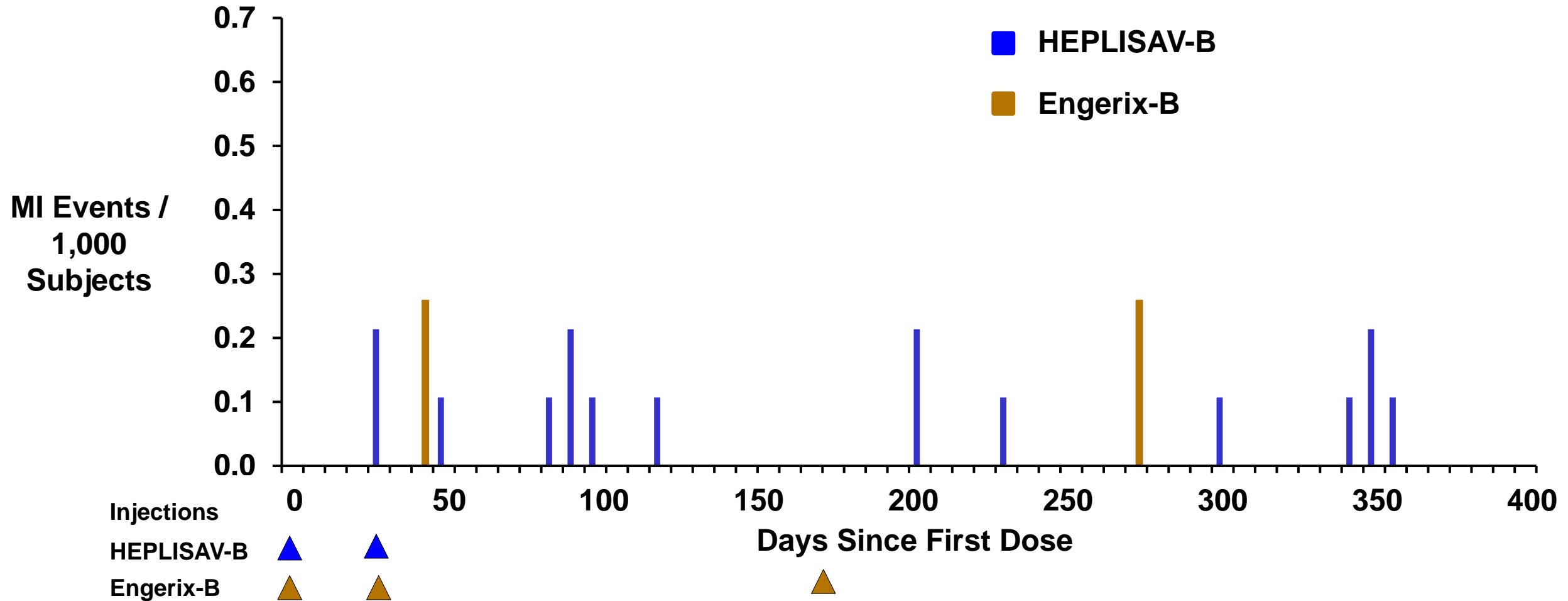


# Findings from Blinded Review of Clinical Summaries and Cardiac Catheterization Results

---

- Typical coronary event in nearly all cases
  - “Culprit” lesion
  - Advanced, multi-vessel obstructive disease
- No evidence of inflammation or immune cause
  - No vasculitis
  - No aneurysmal disease, dissection, vasospasm
  - No embolism / *in situ* thrombosis
  - No myocarditis
- No evidence of myocardial supply / demand mismatch

# Confirmed MI Events Occurred Throughout Trials



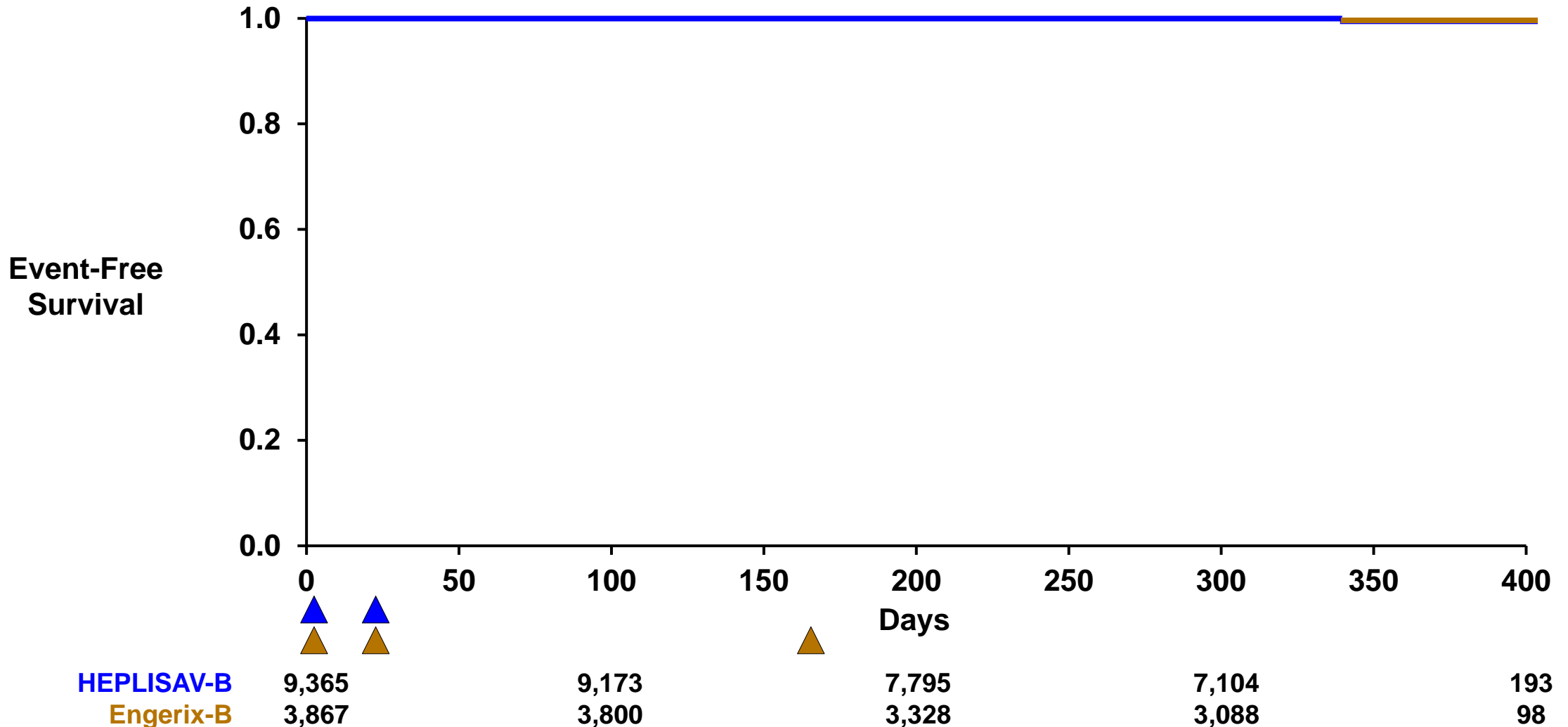
Injections

HEPLISAV-B

Engerix-B

Primary safety population

# MACE Similar Between Groups Following Injections – Full Scale



Primary safety population