U.S. FOOD & DRUG ADMINISTRATION

## Vaccines and Related Biological Products Advisory Committee Meeting

# Hepatitis B Vaccine (Recombinant), Adjuvanted (Heplisav-B): Review of Safety

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# Presentation Outline

- Background
  - Overview of clinical trials
  - Regulatory history
- Summary of data previously presented
- Safety data from Phase 3 trial DV2-HBV-23
- Integrated analysis of safety in Phase 3 trials
- Summary of safety
- Pharmacovigilance plan proposed by Dynavax

# Heplisav-B

- Product
  - 20 µg recombinant Hepatitis B surface antigen
  - 3000 µg 1018, a novel cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate adjuvant
- Proposed Indication and Usage
  - For immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older
- Dosage and Administration
  - Two 0.5 mL doses administered four weeks apart

# Heplisav-B Safety Population

| Studies | Number of Heplisav-B Recipients | Number of Engerix-B Recipients |
|---|---|---|
| **DV2-HBV-10** | 1810 | 605 |
| **DV2-HBV-16** | 1968 | 481 |
| **DV2-HBV-23** | 5587 | 2781 |
| **Phase 3 Trials** | **9365** | **3867** |
| **Uncontrolled trials using final formulation and schedule** | 232 | 0 |
| **Total** | 9597 | 3867 |
| **Additional studies** | 441 | 333 |

# Phase 3 Trials: Safety Follow-Up Periods Post-Dose 1

- Adverse Events (AEs)
  - Solicited AEs HBV-10 and HBV-16: 7 days
  - Unsolicited AEs HBV-10 and HBV-16: 28 weeks
- Medically Attended Adverse Events (MAEs)
  - HBV-23: 56 weeks
- Serious Adverse Events (SAEs)
  - HBV-10: 28 weeks
  - HBV-16: 52 weeks
  - HBV-23: 56 weeks

# Phase 3 Trials: Safety Follow-Up Periods Post-Dose 1

- Adverse Events of Special Interest (AESIs)
  - HBV-16: 52 weeks
  - HBV-23: 56 weeks
- Subjects in both treatment groups were monitored for the same total length of time from dose 1.
  - Engerix-B subjects were monitored for a shorter length of time following the last active dose (6 months vs. 1 year for Heplisav-B).

# Summary Data from Previously Presented Studies: Solicited Adverse Reactions

| Solicited AE | Heplisav-B Dose 1 % | Engerix-B Dose 1 % | Heplisav-B Dose 2 % | Engerix-B Dose 2 % | Engerix-B Dose 3 % |
|---|---|---|---|---|---|
| **Local** | N = 3761 | N = 1083 | N = 3694 | N = 1067 | N = 1038 |
| Pain | 30.8 | 26.9 | 28.6 | 20.8 | 17.5 |
| Redness | 2.5 | 0.6 | 1.8 | 0.5 | 0.4 |
| Swelling | 1.6 | 0.6 | 1.0 | 0.4 | 0.3 |
| **Systemic** | | | | | |
| Fatigue | 14.9 | 15.0 | 12.3 | 12.1 | 9.8 |
| Headache | 14.2 | 16.1 | 10.4 | 11.2 | 9.2 |
| Malaise | 8.4 | 8.8 | 7.3 | 6.7 | 5.9 |
| | N = 3706 | N = 1069 | N = 3651 | N = 1050 | N = 999 |
| Fever | 0.8 | 1.3 | 1.0 | 1.4 | 1.3 |

# Summary Data from Previously Presented Studies: AEs, SAEs, and Deaths

- HBV-10
  - Unsolicited AEs: 60.5% of Heplisav-B, 62.0% Engerix-B recipients
  - SAEs: 1.5% of Heplisav-B, 2.1% of Engerix-B recipients
  - No deaths
- HBV-16
  - Unsolicited AEs: 51% Heplisav-B, 53% Engerix-B recipients
  - SAEs: 3.9% Heplisav-B, 4.8% Engerix-B recipients
  - Deaths:
    - Heplisav-B: 46 year-old male with no medical history had fatal PE 7 weeks after dose 2
    - Engerix-B: 64 year-old male with medical history that included hypertension and gout hospitalized for acute myocardial infarction within 7 weeks after dose 2. Died of cardiac arrest on 2nd day of hospitalization
- Adverse events of special interest (AESIs) were observed in both studies

# Regulatory History

# HEPLISAV-B: Regulatory History

- A VRBPAC Meeting was held in November 2012 to discuss the immunogenicity and safety of the vaccine in adults 18 through 70 years of age
  - HBV-10 and -16
- Members voted 13:1 that the immunogenicity data were adequate to support effectiveness
- Members voted 8:5, with one abstention, that the available data were not adequate to support safety
  - In view of the novel adjuvant, members recommended a larger pre-licensure safety database

# Clinical Study HBV-23

# HBV-23: Study Design

- Phase 3, observer-blinded, active-controlled, multicenter U.S. trial
- Randomized 2:1 (Heplisav-B:Engerix-B)
- Adults 18 – 70 years old
- Primary Safety Objective
  - Evaluate the overall safety of Heplisav-B with respect to clinically significant AEs

# HBV-23: Safety Assessments

- Safety assessments and evaluation period post-dose 1
  - MAEs: 56 weeks
  - SAEs: 56 weeks
  - AESIs: 56 weeks
    - AESIs referred to Safety Evaluation and Adjudication Committee (SEAC) for review
  - Laboratory sub-study (N = 309)
    - Subset of subjects had serum chemistry, hematology, urinalysis, clotting assessment, and thrombotic assessment: baseline, 4, 8, 24, 56 weeks

# HBV-23: Safety Population

- Safety population
  - Received ≥ 1 study injection
  - Had any on-study safety data
- 8368 subjects vaccinated
  - Heplisav-B: N = 5587
  - Engerix-B: N = 2781

# HBV-23: Safety Population Demographics

| Demographic | Subgroup | Heplisav-B N = 5587 % | Engerix-B N = 2781 % |
|---|---|---|---|
| **Age** | Mean (SD) | 50.36 (11.74) | 50.37 (11.68) |
| | 18 – 29 years | 4.7 | 4.7 |
| | 30 – 39 years | 15.6 | 15.5 |
| | 40 – 49 years | 22.7 | 22.7 |
| | 50 – 59 years | 31.6 | 32.2 |
| | ≥ 60 years | 25.4 | 24.9 |
| **Gender** | Male | 50.9 | 50.0 |
| | Female | 49.1 | 50.0 |
| **Race** | White | 71.0 | 72.2 |
| | Black or African American | 26.1 | 25.0 |
| | Asian | 1.0 | 1.4 |
| | American Indian or Alaska Native | 1.1 | 0.9 |
| | Native Hawaiian or Other Pacific Islander | 0.3 | 0.3 |
| | Other | 0.4 | 0.3 |
| | Unknown | 0.0 | 0.0 |
| **Ethnicity** | Hispanic or Latino | 9.3 | 8.6 |
| | Not Hispanic or Latino | 90.6 | 91.4 |
| | Unknown | 0.1 | 0.0 |

# HBV-23: Safety Population Baseline Risk Factors for Cardiovascular Disease

| Condition or characteristic | Heplisav-B N=5587 % | Engerix-B N=2781 % |
|---|---|---|
| At least one baseline medical diagnosis of cardiac ischemia | 3.8 | 3.6 |
| Type 2 Diabetes | 13.6 | 13.7 |
| Hypertension | 36.2 | 35.2 |
| Hyperlipidemia | 31.4 | 31.6 |
| Smoking within 1 year | 33.0 | 32.7 |
| Obesity: BMI ≥ 30 | 48.8 | 46.2 |

# HBV-23: Medically-Attended Adverse Events

- Heplisav-B
  - 46.0% of subjects reported ≥ 1 MAE
  - 16.1% of subjects reported a severe event
  - 1.0% of subjects reported an MAE assessed by the investigator as related
- Engerix-B
  - 46.2% of subjects reported ≥ 1 MAE
  - 15.2% of subjects reported a severe event
  - 1.6% of subjects reported an MAE assessed by the investigator as related

# HBV-23: Medically-Attended Adverse Events

- MAEs reported in at least 0.5% of either treatment group and at at least twice the frequency in one treatment group compared to the other
  - Heplisav-B
    - Herpes zoster: 0.7% of Heplisav-B, 0.3% of Engerix-B recipients
  - Engerix-B
    - Tooth infection: 0.3% Heplisav, 0.6% Engerix-B recipients
    - Exostosis: 0.1% of Heplisav, 0.5% of Engerix-B recipients

# HBV-23: Nonfatal SAEs

- Heplisav-B
  - 5.8% of subjects reported ≥ 1 non-fatal SAE
- Engerix-B
  - 5.1% of subjects reported ≥ 1 non-fatal SAE

# HBV-23: Cardiac SAEs (Fatal and Nonfatal) by MedDRA* SOC** and PT***

- SAEs in the Cardiac Disorders SOC
  - Heplisav-B
    - 51 subjects (0.9%) reported ≥ 1 SAE
    - 14 subjects (0.25%) reported an SAE with a PT of acute myocardial infarction
  - Engerix-B
    - 15 subjects (0.5%) reported ≥ 1 SAE
    - 1 subject (0.04%) reported SAE with a PT of acute myocardial infarction

* MedDRA: Medical Dictionary for Regulatory Activities
**SOC: System Organ Class
*** PT: preferred term

# HBV-23: SAEs with PTs in the SMQ* Narrow for Myocardial Infarction (MI)

| MedDRA Preferred Term | Heplisav-B N = 5587 n (%) | Engerix-B N = 2781 n (%) |
|---|---|---|
| Acute coronary syndrome | 1 (0.02) | 0 |
| Acute myocardial infarction (AMI) | 14 (0.25) | 1 (0.04) |
| Angina unstable | 1 (0.02) | 0 |
| Coronary artery occlusion | 1 (0.02) | 1 (0.04) |
| Myocardial infarction (MI) | 2 (0.04) | 1 (0.04) |
| Total Subjects with ≥ 1 SAE with PT in the SMQ for MI | 19 (0.34) | 3 (0.11) |

*SMQ: Standardized MedDRA Query

# HBV-23: SAEs with Preferred Terms in the SMQ for Myocardial Infarction

- Heplisav-B (n = 19)
  - 13 males and 6 females
  - Mean age:  59.2 years (SD +/- 2.1)
  - Median days since last active dose: 96 (3 – 329)
  - Mean: 2.9 baseline risk factors*
  - 31.6% (n=6) had a history of ischemic heart disease

*Risk factors = diabetes, smoking, hypertension, dyslipidemia, obesity, ischemic heart disease

# HBV-23: SAEs with Preferred Terms in the SMQ for Myocardial Infarction

- Engerix-B (n = 3)
  - All males
  - Mean age: 57 years (SD +/- 4.0)
  - Median days since last active dose: 115 days (13 – 203)
  - Mean: 3 baseline risk factors
  - All had a history of ischemic heart disease

# HBV-23: Major Adverse Cardiovascular Events (MACE) Analysis

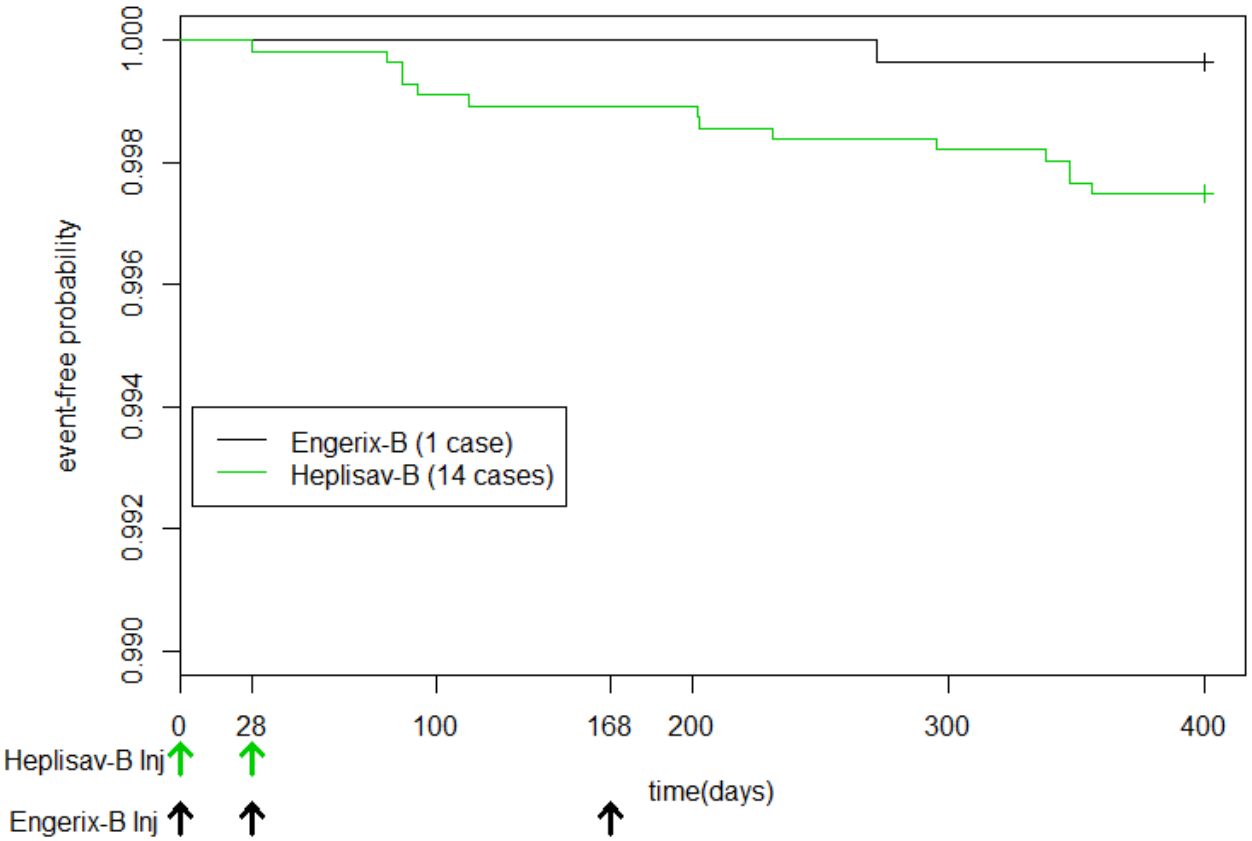
- MACE composite endpoint defined as events of cardiac death, non-fatal myocardial infarction, or non-fatal stroke
- Preferred terms selected to identify potential MACE outcomes were chosen in a blinded manner by Dynavax's consulting cardiologist.
- Dynavax's external consultants performed independent and blinded post-hoc adjudication of all potential MACE events, categorizing events as

    1) MACE event
    2) Not a MACE event, or
    3) Insufficient information to make a determination

# HBV-23: MACE Analysis

- Adjudicated SAEs of MI
  - Heplisav-B: 14 subjects (0.25%)
  - Engerix-B: 1 subject (0.04%)

# HBV-23: Kaplan-Meier Curve for Adjudicated Myocardial Infarctions



# HBV-23: Deaths

- Heplisav-B
  - 0.45% of subjects (25 subjects) died
  - 0.29% of subjects (16 subjects) cause of death not attributable to injury or illicit drug overdose
- Engerix-B
  - 0.25% of subjects (7 subjects) died
  - 0.14% of subjects (4 subjects) cause of death not attributable to injury or illicit drug overdose
- No deaths deemed related to study vaccine by investigator

# HBV-23: Deaths

- Adjudication results for cardiovascular death

| | Heplisav-B N = 5587 | Engerix-B N = 2781 |
|---|---|---|
| **Total Deaths Selected for Adjudication** | 11 | 3 |
| **Adjudicated as Cardiovascular Death** | 3 | 1 |
| **Adjudicated as Non-Cardiovascular Death** | 1 | 2 |
| **Adjudicated as Unknown Cause of Death** | 7 | 0 |

# HBV-23: Cardiac SAEs Summary

- Imbalance in SAEs (fatal plus non-fatal) considered Cardiac disorders: Heplisav-B 0.9%, Engerix-B 0.5%
- Imbalance in SAEs of Acute myocardial infarction
  - By standardized PT search: Heplisav-B 0.34%, Engerix-B 0.11%
  - By adjudication: Heplisav-B 0.25%, Engerix-B 0.04%
- All subjects with MIs had risk factor(s) for cardiovascular disease
- Baseline risk factors for cardiovascular disease were balanced between treatment groups
- The difference between treatment groups is first noted at 3 months after dose 1 and persists through the 1-year study follow-up
- Imbalance in deaths
  - Adjudicated cardiovascular deaths: Heplisav-B 0.05%, Engerix-B 0.04%
  - Deaths lacking sufficient information to determine the cause of death: Heplisav-B 0.13%, Engerix-B 0%

# Heplisav-B: Definition of Categories of Immune-mediated Events in Studies

- HBV-23
  - AESIs: Pre-specified by a CBER-generated list of potentially immune-mediated conditions
  - AIAEs: MAEs/SAEs not on the list of AESIs, but that SEAC adjudicates as autoimmune
- HBV-16
  - AIAE: collected prospectively, list of AESIs provided to investigators
- HBV-10
  - Not prospectively collected, defined

# Heplisav-B: Definition of Categories of Potentially Immune-mediated Events

- AESI
  - AE/MAE/SAE that is potentially immune-mediated, identified prospectively or retrospectively, may or may not be on a CBER-generated list of potentially immune-mediated conditions
- Potential AESI
  - HBV-16, HBV-23: AE/MAE/SAE suspected by the investigator to be an AESI and referred to a specialist and/or SEAC

# HBV-23: AESI Evaluation

- Subjects monitored for AESIs through 56 weeks following the first vaccination
- Subjects with “potential autoimmune” MAEs (AESIs) were referred to a specialist and to a Safety Evaluation and Adjudication Committee (SEAC)

# HBV-23: SEAC Adjudication

- SEAC
  - Composed of one infectious disease and two autoimmune experts external to Dynavax
- Assessment questions
  - Is the event an autoimmune disorder?
    - Not all AESIs were considered autoimmune
  - If autoimmune, is the event a new-onset autoimmune disorder?
  - If autoimmune, is the event related to study vaccine?

# HBV-23: AESIs

- Potential AESIs
  - Heplisav-B: 39 subjects (0.7%) reported MAEs referred to SEAC
  - Engerix-B: 22 subjects (0.8%) reported MAEs referred to SEAC

# HBV-23: AESIs

- SEAC-adjudicated autoimmune event
  - Heplisav-B: 17 subjects, 0.3%
  - Engerix-B: 12 subjects, 0.4%
- New-onset autoimmune event
  - Heplisav-B: 4 subjects, 0.07%
  - Engerix-B: 0 subjects
- The SEAC did not adjudicate any events as related to study vaccines

# HBV-23: SEAC-Adjudicated New-onset Autoimmune Events (Heplisav-B)

| Age/ Sex | AESI | Last Active Dose | Days After Last Active Dose | Related (Investigator) |
|---|---|---|---|---|
| 52 F | Alopecia areata | 2 | 229 | Possibly |
| 46 F | Ulcerative colitis* | 2 | 221 | Not |
| 68 M | Polymyalgia rheumatica | 2 | 292 | Possibly |
| 60 F | Hypothyroidism** | 2 | 246 | Not |

* SAE
** Alternative plausible cause
No events were assessed by the SEAC as related to study vaccine

# HBV-23: AESIs Adjudicated by the SEAC as Not Autoimmune (Heplisav-B)

| Age/ Sex | AESI | Last Active Dose | Days After Last Active Dose | Related (Investigator) |
|---|---|---|---|---|
| 49 M | Bell's palsy | 1 | 10 | Possibly |
| 52 M | Bell's palsy | 2 | 256 | Not |
| 31 F | Bell's palsy | 2 | 170 | Not |
| 49 F | Bell's palsy | 2 | 1 | Not |
| 49 M | Bell's palsy<br>Diplopia (IIIrd nerve palsy)* | 2<br>2 | 172<br>101 | Not<br>Not |
| 49 M | VIth nerve paralysis* | 2 | 159 | Possibly |
| 49 M | Takayasu arteritis** | 2 | 61 | Not |
| 43 F | Granulomatous dermatitis*** | 2 | 70 | Possibly |

* Alternative plausible cause
** Assessed as pre-existing by FDA consultants
*** Assessed by FDA as new-onset AESI, not SEAC or Applicant

# HBV-23: AESIs Adjudicated by the SEAC as Not Autoimmune (Engerix-B)

| Age/ Sex | AESI | Last Active Dose | Days After Last Active Dose | Related (Investigator) |
|---|---|---|---|---|
| 29 M | Bell's palsy | 3 | 27 | Possibly |

# HBV-23: AESIs

- New-onset AESI
  - Heplisav-B: 11 subjects (0.20%)
  - Engerix-B: 1 subject (0.04%)
- New-onset AESI (excluding events with an alternative plausible cause)
  - Heplisav-B: 9 subjects (0.16%)
    - Bell's palsy, n = 5
    - Alopecia areata
    - Polymyalgia rheumatica
    - Ulcerative colitis
    - Granulomatous dermatitis
  - Engerix-B: 1 subject (0.04%)
    - Bell's palsy

# HBV-23: Safety Summary

- Overall, non-fatal SAEs and MAEs occurred at similar frequencies between study groups
- SAEs of Myocardial infarction
  - Standardized PT query: 0.34% Heplisav-B, 0.11% of Engerix-B
  - Adjudicated MI: 0.25% Heplisav-B, 0.04% Engerix-B
- Deaths: 0.29% of Heplisav-B and 0.14% of Engerix-B recipients died, not attributable to injury or illicit drug overdose
- AESIs: 0.16% Heplisav-B recipients and 0.03% Engerix-B recipients reported a new-onset AESI with no alternative plausible cause

# Integrated Analysis of Safety (IAS)

# Overview of Safety Follow-Up Periods

| | AE | MAE | SAE | AESI |
|---|---|---|---|---|
| **HBV-10** | 28 weeks | -- | 28 weeks | -- |
| **HBV-16** | 28 weeks | -- | 52 weeks | 52 weeks |
| **HBV-23** | -- | 56 weeks | 56 weeks | 56 weeks |
| | | | | |
| **Supportive studies using final formulation (uncontrolled)** | 12 or 28 weeks | -- | 28 or 56 weeks | 0 or 56 weeks |
| **Supportive studies using prior formulations or schedules** | 4-62 weeks | -- | 32-62 weeks | -- |

# IAS: Safety Populations

- 6-month Primary Safety Population (6-month PSP)
  - Pivotal trials that monitored subjects for at least 6 months
    - HBV-10, HBV-16, HBV-23
  - SAEs reported within 28 weeks of first vaccination were evaluated.
- 1-year PSP
  - Pivotal trials that monitored subjects for one year
    - HBV-16, HBV-23
  - All SAEs reported were evaluated.
- Modified Total Safety Population (mTSP)
  - Studies that utilized the final formulation of Heplisav-B
    - HBV-10, HBV-14, HBV-16, HBV-22, and HBV-23
  - SAEs reported within 28 weeks of first vaccination were evaluated.

# IAS: Safety Population

| Studies | Number of Heplisav-B Recipients | Number of Engerix-B Recipients |
|---|---|---|
| **HBV-16** | 1968 | 481 |
| **HBV-23** | 5587 | 2781 |
| **1-year PSP** | **7555** | **3262** |
| **HBV-10** | 1810 | 605 |
| **6-month PSP** | **9365** | **3867** |
| **Supportive trials using final formulation and schedule** | 232 | 0 |
| **mTSP** | 9597 | 3867 |

# IAS: Demographics of Safety Population

- 6-month PSP
  - Mean age of Heplisav-B recipients was 49.1 (SD 11.61), Engerix-B recipients was 49.2 (11.65)
  - 50.5% Heplisav-B, 51.2% Engerix-B recipients were female
  - 78% of Heplisav-B, 77% of Engerix-B recipients were of white race
  - 93% of Heplisav-B, 92% of Engerix-B recipients were of non-Hispanic ethnicity
- 1-year PSP
  - Mean age of Heplisav-B recipients was 51.3 (SD 10.99), Engerix-B recipients was 50.9 (11.26)
  - 49.9% Heplisav-B, 50.1% Engerix-B recipients were female
  - 74% of Heplisav-B and Engerix-B recipients were of white race
  - 92% of Heplisav-B and Engerix-B recipients were of non-Hispanic ethnicity

# IAS: Selected Baseline Characteristics of Safety Populations

| Condition or characteristic | HBV-23 Heplisav-B N=5587 % | HBV-23 Engerix-B N=2781 % | HBV-16 Heplisav-B N=1968 % | HBV-16 Engerix-B N=481 % | HBV-10* Heplisav-B N = 1810 % | HBV-10* Engerix-B N = 605 % |
|---|---|---|---|---|---|---|
| At least one baseline medical diagnosis of cardiac ischemia | 3.8 | 3.6 | 2.5 | 3.1 | 0.7 | 0.3 |
| Type 2 Diabetes | 13.6 | 13.7 | 8.0 | 6.9 | 2.3 | 1.8 |
| Hypertension* | 36.2 | 35.2 | 29.4 | 29.7 | 10.7 | 9.4 |
| Hyperlipidemia/ Dyslipidemia* | 31.4 | 31.6 | 29.8 | 31.6 | 8.1 | 7.8 |
| Smoking within 1 year | 33.0 | 32.7 | 21.9 | 24.5 | 36.1 | 37.0 |
| Obesity: BMI ≥ 30 | 48.8 | 46.2 | 43.9 | 42.6 | 25.6 | 27.6 |

* FDA Analysis

# IAS: Limitations of Pooling Studies HBV-10 and HBV-16 with HBV-23

- Differences in study populations
  - Higher cardiovascular risk in HBV-23
- Differences in study design
  - Randomization ratios
    - HBV-10: 3 to 1
    - HBV-16: 4 to 1
    - HBV-23: 2 to 1

→ Pooling adds disproportionately more low-risk subjects to the Heplisav-B group

# Integrated Analysis of Safety: Results

# IAS: Deaths & SAEs

- **SAEs**

| Event | 6 mo PSP Heplisav-B N = 9365 % | 6 mo PSP Engerix-B N = 3867 % | 1 yr PSP Heplisav-B N = 7555 % | 1 yr PSP Engerix-B N = 3262 % |
|---|---|---|---|---|
| ≥ 1 SAE | 2.89 | 2.95 | 5.57 | 5.24 |
| ≥ 1 non-fatal SAE | 2.78 | 2.82 | 5.29 | 1111 |

- **Deaths**

| | 6 mo PSP Heplisav-B N = 9365 n (%) | 6 mo PSP Engerix-B N = 3867 n (%) | 1 yr PSP Heplisav-B N = 7555 n (%) | 1 yr PSP Engerix-B N = 3262 n (%) |
|---|---|---|---|---|
| Deaths | 15 (0.16) | 5 (0.13) | 26 (0.34) | 8 (0.25) |
| Deaths not due to overdose or injury | 9 (0.10) | 3 (0.08) | 17 (0.23) | 5 (0.15) |
| Expected based on randomization and Engerix-B rate | 7 | n/a | 12 | n/a |

# IAS: SAEs with Preferred Terms in the SMQ Narrow for Myocardial Infarction

| MedDRA Preferred Term | HBV-23 Heplisav-B N = 5587 n (%) | HBV-23 Engerix-B N = 2781 n (%) | HBV-16 Heplisav-B N = 1968 n (%) | HBV-16 Engerix-B N = 481 n (%) | HBV-10 Heplisav-B N = 1810 n (%) | HBV-10 Engerix-B N = 605 n (%) |
|---|---|---|---|---|---|---|
| Acute coronary syndrome | 1 (0.02) | 0 | 0 | 0 | 0 | 0 |
| Acute myocardial infarction | 14 (0.25) | 1 (0.04) | 2 (0.10) | 1 (0.21) | 0 | 0 |
| Angina unstable | 1 (0.02) | 0 | 0 | 1 (0.21) | 0 | 0 |
| Coronary artery occlusion | 1 (0.02) | 1 (0.04) | 0 | 0 | 0 | 0 |
| Myocardial infarction | 2 (0.04) | 1 (0.04) | 0 | 0 | 0 | 0 |
| **Subjects with ≥ 1 SAE of MI** | **19 (0.34)** | **3 (0.11)** | **2 (0.10)** | **1 (0.21)** | **0** | **0** |

# IAS: Major Adverse Cardiovascular Events (MACE) Analysis

| Adjudicated MACE Outcome | HBV-23 Heplisav-B N=5587 n (%) | HBV-23 Engerix-B N=2781 n (%) | HBV-23 Relative Risk (95% CI)[a] (95% CI)[b] | HBV-16 Heplisav-B N=1968 n (%) | HBV-16 Engerix-B N=481 n (%) | HBV-16 Relative Risk (95% CI)[a] (95% CI)[b] |
|---|---|---|---|---|---|---|
| Composite 3-point MACE events | 28 (0.50) | 6 (0.22) | 2.32 (0.96, 5.60) (0.99, 5.46) | 3 (0.15) | 2 (0.42) | 0.37 (0.06, 2.19) (0.07, 1.83) |
| Cardiovascular death | 3 (0.05) | 1 (0.04) | 1.49 (0.16, 14.35) (0.21, 10.42) | 1 (0.05) | 1 (0.21) | 0.24 (0.02, 3.9) (0.01, 4.09) |
| Myocardial infarction | 14 (0.25) | 1 (0.04) | 6.97 (0.92, 52.97) (1.17, 41.44) | 2 (0.10) | 1 (0.21) | 0.49 (0.04, 5.38) (0.06, 3.73) |
| Stroke | 11 (0.20) | 4 (0.14) | 1.37 (0.44, 4.30) (0.46, 4.07) | 0 | 0 | - |

[a] 95% Wald confidence interval (Dynavax analysis)
[b] 95% Koopman score confidence interval (FDA analysis)

# IAS: Cardiovascular Events Analysis Considerations

- Higher rate in the Heplisav-B group
  - Dynavax assessment
    - Bradford-Hill criteria do not support causality
    - Lower observed rate than expected in the Engerix-B group based on population-based data and risk prediction models
  - However,
    - Study was a randomized controlled trial, so the most valid comparison is to Engerix-B
    - RR for MI in HBV-23 is 6.97

# Key Points from Cardiology Consult 1

- Imbalance of MI in HBV-23, with more events in Heplisav-B
- Imbalance in MI was not observed in previous studies. But, HBV-23 had a larger sample size and higher % cardiac risk factors compared to HBV-16
- Adjudicated stroke and cardiovascular (CV) deaths showed a similar direction as the MI imbalance. But, there were few adjudicated CV deaths and the RR was not robust.
- Kaplan-Meier curves for MACE separate after 100 days post-first dose – no close temporal relationship

# Key Points from Cardiology Consult 1 (cont.)

- Non-clinical and clinical studies failed to reveal a plausible mechanism for MI. The risk of MI could result from accelerated atherosclerosis, sustained increase in blood pressure, or some prothrombotic state. None of these is in evidence.
- The assessment that the event rate in the control is spuriously low is plausible. It is also plausible the between-group difference is spurious.
- Low likelihood of a reliable finding and low absolute risk

# Key Points from Cardiology Consult 2

- The numerical imbalance in MI events between Heplisav-B and Engerix-B is moderately concerning.
- While the finding could be attributable to chance, cannot confidently say that there is no increased cardiovascular risk with Heplisav-B.
- Thus, believes that further evaluation is warranted.
- The Applicant's analyses are a reasonable first step, but their conclusions largely hinge on the low ratio of observed to expected events with Engerix-B in the phase 3 trials.
  - That analysis has several limitations
  - Difficult to place more weight on a comparison with externally-derived event rates (observed vs expected) than on the internal comparison (between study arms)

# Key Points from Cardiology Consult 3

- The sponsor has observed an imbalance of ischemic cardiac events (mostly MI) associated with use of its vaccine compared with an active control vaccine in a large randomized clinical trial.
- The trial was not prospectively designed to optimally identify suspected ischemic events, to have appropriately collected supporting materials on these events, nor to prospectively adjudicate suspected events.
- The trial did enroll a group of patients at increased risk of cardiac events based on entry cardiac risk factor profiles.
- The sponsor has performed a very reasonable series of analyses intended to “explain” or to minimize this infrequent, but troubling, difference in cardiac risk.

# Key Points from Cardiology Consult 3 (cont.)

- The observation is consistent across several cardiac events, including unexplained death and MI.
- In Study HBV-23, the comparison of the MACE composite does not meet conventional statistical significance.
- The sponsor cannot/does not fully eliminate the notion that this is a “real” observation worth further investigation. The consultant agrees.
- Further insights into possible cardiac risk associated with Heplisav-B require randomized comparisons and/or large post market observational studies with appropriate collection of suspected events, ECGs, biomarkers and other records needed for event adjudication.

# IAS: Unsolicited AEs

- Prior review: overall incidence similar between treatment groups
  - Heplisav-B: 55%, Engerix-B: 58%
  - Most mild-moderate in intensity
- Herpes Zoster
  - HBV-10 and HBV-16
    - Heplisav-B: 7 subjects (N=3778) 0.2%
    - Engerix-B: 1 subject (N=1086) 0.1%

# IAS: AESIs

- Prospective collection of AESIs
  - Pivotal studies HBV-16 and HBV-23
  - Supportive, uncontrolled study HBV-22 (N = 25)

- New-onset AESIs (excluding events with an alternative plausible cause)
  - Heplisav-B: 15 subjects (N=7580) 0.20%
  - Engerix-B: 1 subject (N=3262) 0.03%

# AESI: New-onset AESIs Identified in Studies that Prospectively Monitored AESIs

| Study | Treatment Arm | Age Sex | AE | Last Active Dose | Days After Last Active Dose | AI SEAC | Background incidence/yr |
|---|---|---|---|---|---|---|---|
| HBV-23 | Heplisav-B | 52 F | Alopecia areata | 2 | 229 | Yes | 8.8-29.3/100,000 |
| | Heplisav-B | 46 F | Ulcerative colitis | 2 | 221 | Yes | 2.2-14.3/100,000 |
| | Heplisav-B | 68 M | Polymyalgia rheumatica | 2 | 292 | Yes | 52.5/100,000 (adults 50 years and older) |
| | Heplisav-B | 49 M | Bell's Palsy | 1 | 10 | No | 13-34/100,000 |
| | Heplisav-B | 52 M | Bell's Palsy | 2 | 256 | No | 13-34/100,000 |
| | Heplisav-B | 31 F | Bell's Palsy | 2 | 169 | No | 13-34/100,000 |
| | Heplisav-B | 49 F | Bell's Palsy | 2 | 1 | No | 13-34/100,000 |
| | Heplisav-B | 49 M | Bell's Palsy | 1 | 172 | No | 13-34/100,000 |
| | Heplisav-B | 43 F | Granulomatous dermatitis | 2 | 70 | No | Unknown |
| | Engerix-B | 29 M | Bell's Palsy | 3 | 27 | No | 13-34/100,000 |

# AESI: New-onset AESIs Identified in Studies that Prospectively Monitored AESIs

| Study | Treatment Arm | Age/ Sex | AE | Last Active Dose | Days After Last Active Dose | AI SEAC | Background incidence/yr |
|---|---|---|---|---|---|---|---|
| HBV-16 | Heplisav-B | 68 M | Tolosa-Hunt syndrome | 2 | 292 | Yes | 1/1,000,000 |
| | Heplisav-B | 58 F | Hypothyroidism | 1 | 27 | Yes | 0.3-1.5/1,000 |
| | Heplisav-B | 52 F | Hypothyroidism | 2 | 30 | Yes | 0.3-1.5/1,000 |
| | Heplisav-B | 62 M | Erythema Nodosum* | 2 | 20 | No | 1-5/100,000 |
| | Heplisav-B | 59 M | Bell's Palsy | 2 | 271 | No | 13-34/100,000 |
| | Heplisav-B | 69 M | Vitiligo** | 2 | 2 | Yes | 0.14 - 8.8/100 |

* Vaccine-related per SEAC

** Past medical history of another autoimmune disease

# IAS: AESIs

- Retrospective AESIs
  - Dynavax searched safety database for PTs from the list of AESIs used in the studies that prospectively collected AESIs
  - Includes studies that did not use the final formulation
- New-onset AESIs
  - Heplisav-B: 6 subjects (N=2458) 0.2%
  - Engerix-B: 5 subjects (N=938) 0.5%

# IAS: New-onset AESIs Identified in Studies without Prospective Collection of AESIs

| Study | Arm | Age Sex | AE | Last Active Dose | Days after Last Active Dose | Related by Investigator |
|---|---|---|---|---|---|---|
| HBV-10 | Heplisav-B | 24 F | Granulomatosis with polyangiitis | 2 | 73 | Possibly |
| HBV-10 | Heplisav-B | 35 F | Guillain-Barré syndrome | 2 | 111 | Probably not |
| HBV-10 | Heplisav-B | 41 F | Basedow's (Grave's) disease | 2 | 44 | Probably not |
| HBV-10 | Heplisav-B | 48 F | Lichen planus | 2 | 26 | Probably not |
| HBV-04 | Heplisav-B | 53 F | Bell's palsy | 1 | 16 | Probably not |
| HBV-04 | Heplisav-B | 59 F | Uveitis | 3 | 23 | No |
| HBV-10 | Engerix-B | 44 F | p-ANCA positive vasculitis* | 2 | 127 | No |
| HBV-10 | Engerix-B | 34 M | Bell's palsy | 2 | 122 | No |
| HBV-10 | Engerix-B | 30 F | Grave's disease | 2 | 78 | No |
| HBV-10 | Engerix-B | 46 M | Raynaud's Phenomena | 3 | 33 | No |
| HBV-04 | Engerix-B | 56 M | Rheumatoid arthritis | 1 | 21 | No |

* Past medical history of another autoimmune disease

# IAS: Granulomatosis with Polyangiitis (Heplisav-B)

- 55 year-old woman with no significant medical history
  - 18 days after dose 1: dose 2 as scheduled
  - ~1.5 months after dose 2: Recurrent sinusitis
  - ~6 months after dose 2: Pulmonary infiltrates, pleural/pericardial effusions, and glomerulonephritis
    - Wegener's granulomatosis (currently known as GPA) diagnosed
  - Serum retrospectively analyzed for ANCA
    - Screening visit: ANCA negative
    - 4 weeks after Dose 1: Proteinase 3 (PR3) ANCA weakly positive
    - 8 weeks after Dose 1, 4 weeks after Dose 2: PR3 ANCA weakly positive
    - 12 weeks after Dose 1: PR3 ANCA positive
    - 23 and 28 weeks after Dose 1: PR3 ANCA strongly positive
  - Investigator's assessment: possibly related to study treatment

# IAS: p-ANCA + Vasculitis (Engerix-B)

- 44 year-old woman with medical history that included mixed connective tissue disease (MCTD), osteoarthritis, food allergy, and headache
  - History of MCTD undisclosed at enrollment
  - ~3 months after dose 2: Fever and malaise, treated for PNA
  - ~4 months after dose 2: Pulmonary hemorrhage, positive p-ANCA leading to diagnosis
  - ANCA testing of banked serum negative until time of diagnosis
  - Baseline ANA >1:5120
  - Investigator's assessment: not related to study treatment

# IAS: Tolosa-Hunt Syndrome (Heplisav-B)

- 68 year-old man with HTN, GERD, ruptured cervical disc, back surgery, gun shot wound in the left chest
  - ~5 months after dose 2: decreased visual acuity
  - ~7 months after dose 2: severe left frontal headaches
  - ~9 months after dose 2: hospitalized with double vision, headache, left facial numbness, left ptosis, photophobia, deficits of cranial nerves $V_1$ and VI on the left
  - Responded to high dose steroids, resolved in 6 weeks
  - Imaging studies: non-confirmatory
  - Diagnosis: Tolosa-Hunt syndrome (THS), captured as cavernous sinus syndrome
    - THS: Rare syndrome of painful ophthalmoplegia, caused by idiopathic granulomatous inflammation of the cavernous sinus
    - No tissue diagnosis of granuloma in this case
  - Investigator's assessment: not related to study treatment

# IAS: FDA Consultations

- 4 specialist consultations were obtained
  - All four consultants agreed that the case was THS
  - Of the three consultants that commented, two did not believe that there was evidence of overlap between THS and GPA. One consultant noted that there can be overlap, but that this case of THS did not have features expected if it were GPA.
  - Of the three consultants that commented, none endorsed a causal association between the vaccine and the adverse event.

# IAS: Laboratory Investigations

- Hematology, serum chemistries, ANA, anti-dsDNA, ANCAs*, complement components C3 and C4, erythrocyte sedimentation rate (ESR) and urinalyses were evaluated
- No clinically significant trends were identified post-vaccination

* Retrospectively evaluated in Studies HBV-10 and HBV-14 (uncontrolled supportive trial using final formulation/schedule)

# Integrated Analysis of Safety: Summary

# IAS: Summary of Solicited AEs and Labs

- Prior review of local & systemic solicited AEs & laboratory investigations did not reveal any clinically significant differences between recipients of Heplisav-B and Engerix-B

# IAS: Summary of SAEs and Deaths

- Overall, nonfatal SAEs occurred with similar frequencies between treatment groups
- Numerical imbalance in the incidence of deaths and deaths not attributable to illicit drug overdose or injury in the six-month and one-year PSPs

# IAS: Summary of MIs

- Imbalance in SAEs of Myocardial infarction noted in HBV-23
- MACE Analysis performed for the 3 pivotal trials
  - Blinded adjudication of events of CV death, MI, and stroke by the Applicant's consultants
- In Study HBV-23, there were more subjects with adjudicated events of MI and a trend toward more subjects with adjudicated stroke in the Heplisav-B group

# IAS: Summary of MIs

- Imbalance in MI was not observed in other trials with study populations with lower prevalence of known risk factors for cardiovascular disease
- The difference in risk noted at approximately month 3 and persisted throughout the study follow-up periods
- All subjects who reported myocardial infarctions had one or more risk factors for cardiovascular disease
- Reported risk factors for cardiovascular disease were similar between treatment groups at baseline within each study
- Dynavax attributes their finding that there was a lower than expected rate of MI in the Engerix-B group to chance

# IAS: Summary of AESIs

- AESIs were evaluated prospectively in pivotal studies HBV-16 and HBV-23, and in supportive study HBV-22
  - 15 (0.2%) new-onset AESIs in the Heplisav-B groups and 1 (0.03%) new-onset AESI in the Engerix-B group
- AESIs were reviewed retrospectively across other trials
  - By selected MedDRA preferred term (PT), the incidence of AESIs was greater in the Engerix-B group

# IAS: Summary of AESIs

- Rare serious events reported among Heplisav-B recipients
  - Granulomatosis with polyangiitis
  - Tolosa-Hunt syndrome
  - Guillain-Barré syndrome
- Rare serious events reported among Engerix-B recipients
  - p-ANCA positive vasculitis in a subject with pre-existing mixed connective tissue disorder

# IAS: Limitations

- Pooling
  - Study populations with different baseline characteristics and cardiovascular risk factors
  - AESIs: Differences in defining, collecting, evaluating
- Lack of prospective monitoring of events
  - Potential under-ascertainment of events
    - For example, no EKG monitoring = no silent MIs captured
- Rare events
  - Autoimmune diseases require large sample sizes necessary for statistically robust assessment of risk

# Post-Licensure Pharmacovigilance Plan Proposed by Dynavax

# Cohort study in Kaiser California

- Retrospective cohort study
- Electronic healthcare databases
- 20,000 HEPLISAV-B recipients: 20,000 other HepB vaccine recipients
- Follow-up: 13 months following first dose vaccination

# Cohort study in Kaiser:

## Important potential risks. Applicant's power calculations

| Major Adverse Cardiovascular Events (MACE) | Pre-specified immune-mediated diseases | Herpes zoster |
|---|---|---|
| • BIR (MACE): 6/1,000 py<br>• 99% power*<br>• 2-fold increased risk | • BIR: 1/1,000 py<br>• 87% power<br>• 2.5-fold increased risk | • BIR: 4/1,000 py<br>• 99% power*<br>• 2-fold increased risk |
| • BIR (acute myocardial infarction): ≈2/1,000 py<br>• 87% power*<br>• 2-fold increased risk** | • BIR (Granulomatosis with polyangiitis: ≈0.8-1/100,000 py)<br>• BIR (Tolosa-Hunt syndrome): ≈1-2/1,000,000 py | |

BIR: Background incidence rate; py: person-years; *2 year after study start



References: Anderson JL et al NEJM, 2017; Kubaisi B et al. Intractable&Rare Diseases Research 2016; Iaconetta G et al. Cephalalgia 2006

# Questions to the Committee

# Questions to the Committee

1. Do the available data support the safety of Heplisav-B when administered to adults 18 years and older?

   **Please vote Yes or No**

If yes,

2. Please comment on the proposed pharmacovigilance plan.

# Questions to the Committee

If no,

3. Do the presented data support usage in a more specific subpopulation?

   **Please vote Yes or No**

4. What additional studies (pre- and post-licensure) are needed to further evaluate the safety of Heplisav-B in the general adult population and/or in specific subpopulations?