Protocol Title: Post-Marketing Observational Surveillance Study to Evaluate the Incidence of New-Onset Immune-mediated Diseases, Herpes Zoster, and Anaphylaxis in Adults 18 Years of Age and Older Who Receive HEPLISAV-B® Compared with Another Hepatitis B Vaccine

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Sponsor:
Randall N. Hyer MD, PhD, MPH
VP of Clinical Development and Medical Affairs
Dynavax Technologies Corporation
2929 Seventh Street, Suite 100
Berkeley, CA 94710
Phone: 510-665-0451
Email: rhyer@dynavax.com

Principal Investigator:
Steven J. Jacobsen, MD, PhD
Senior Director of Research
Kaiser Permanente Southern California
100 S. Los Robles, 6th Floor
Pasadena, CA 91101
Phone: 626-564-3478
Email: steven.j.jacobsen@kp.org

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1.0 ABBREVIATIONS

Abbreviation or Term	Definition
ACIP	Advisory Committee on Immunization Practices
ED	emergency department
FDA	Food and Drug Administration
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IPTW	inverse probability of treatment weighting
IRB	Institutional Review Board
KPSC	Kaiser Permanente Southern California
MedDRA	Medical Dictionary for Regulatory Activities
MMRV	measles, mumps, rubella and varicella vaccine
RDW	Research Data Warehouse
RIPC	Regional Immunization Practice Committee
SD	standard deviation
STD	sexually transmitted disease
VSD	Vaccine Safety Datalink

2.0 STUDY SUMMARY

Hepatitis B is a vaccine-preventable viral infection causing substantial morbidity and mortality. In 2015, there were an estimated 21,900 new acute cases and up to 2.2 million people living with chronic hepatitis B disease in the U.S.[1]. Hepatitis B vaccination is recommended for adults at risk through sexual exposure, percutaneous or mucosal exposure, travelers, and those with hepatitis C infection, HIV infection, or diabetes mellitus [2, 3]. Available hepatitis B vaccines require 3 doses over 6 months, but coverage has been low (e.g., <25% of persons with diabetes in 2015) [4].

HEPLISAV-B® is a hepatitis B vaccine developed by Dynavax, comprised of recombinant yeast cell-derived hepatitis B surface antigen (HBsAg) and a proprietary 22-mer phosphorothioate oligodeoxynucleotide adjuvant, 1018 [5]. HEPLISAV-B vaccine is approved for prevention of hepatitis B virus infection in adults aged 18 years and older. HEPLISAV-B induced higher and earlier seroprotection than comparator vaccine Engerix-B in Phase 3 trials, and requires only 2 doses over 1 month. In pre-licensure clinical trials, the rates of serious adverse events and events leading to study discontinuations were similar between HEPLISAV-B and Engerix-B. Rates of the medically-attended adverse event of herpes zoster were higher in the HEPLISAV-B group compared to the Engerix-B group in a single trial, HBV-23 (HEPLISAV-B: 0.7% [n = 38]; Engerix-B: 0.3% [n = 9]). Confirmed new-onset immune-mediated events occurring in more than one HEPLISAV-B subject were balanced between treatment groups. All other immune-mediated events occurred in a single subject and were distinct pathophysiologic entities [6].

This observational surveillance study will take place at Kaiser Permanente Southern California (KPSC), a large integrated health care organization serving approximately 4.4 million highly diverse members. KPSC has extensive experience in vaccine safety and effectiveness studies. In this non-randomized cluster design, HEPLISAV-B will be used exclusively at approximately 7 medical centers while another hepatitis B vaccine will be used exclusively at 8 other medical centers. Approximately 30,000 adult patients will receive HEPLISAV-B and approximately 30,000 adult patients will receive the comparator vaccine. Patients will be followed through their electronic health records for 90 days.

The incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis will be described in patients who receive at least 1 dose of HEPLISAV-B and in patients who receive at least 1 dose of the comparator hepatitis B vaccine. For new-onset herpes zoster and anaphylaxis, and new-onset immune-mediated outcomes where there is at least 80% power to detect a relative risk of 3, primary analysis will be based on Poisson regression employing inverse probability of treatment weighting (IPTW). Potential confounding factors will be adjusted for in data analyses. The incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis in patients who receive at least 2 doses of HEPLISAV-B will be described in secondary analyses.

3.0 INTRODUCTION

Hepatitis B is a viral infection causing substantial morbidity and mortality. In 2015, there were an estimated 21,900 new acute cases, and an estimated 850,000 to 2.2 million people living with chronic hepatitis B disease in the U.S., with many unaware of infection [1]. The risk of developing chronic disease after infection is 90% in infants, 25-50% in children, and 6-10% in adults [7, 8]. Asian Americans and Pacific Islanders comprise more than half of Americans living with chronic hepatitis B. Approximately 1% of acute hepatitis B infections result in liver failure and death, and of those with chronic disease, 15-25% are at risk of death from cirrhosis or hepatocellular carcinoma [9-12].

Most new infections of hepatitis B are in adults ages 30 years and older, as the younger population has been largely protected since 1991 with universal hepatitis B vaccination of infants and catch up vaccination of adolescents [1, 13]. Hepatitis B vaccination has been recommended since 1981 for adults at higher risk of exposure, including sexual exposure (unprotected sex with an infected partner, multiple sexual partners, men who have sex with men); percutaneous or mucosal exposure (injection drug use, chronic kidney disease, healthcare workers); travelers to countries with a high prevalence of hepatitis B; and persons with chronic liver disease, hepatitis C, or human immunodeficiency virus [2]. As persons with diabetes mellitus have an increased risk of exposure if diabetes-care equipment is shared, they should be vaccinated for hepatitis B if younger than 60 years of age [3, 4].

Other approved single-antigen hepatitis B vaccines for adults include Recombivax HB (Merck) [14] and Engerix-B (GlaxoSmithKline) [15]. These are comprised of recombinant hepatitis B surface antigen (HBsAg) with an aluminum salt adjuvant and require 3 doses over 6 months. Coverage of hepatitis B vaccination has remained low in adults. In 2015, 24.6% of adults age 19 years or older were vaccinated with at least 3 doses. Among persons with diabetes ages 19 to 59 years of age, 24.4% were vaccinated with at least 3 doses [16, 17].

Dynavax has developed HEPLISAV-B for hepatitis B vaccination of adults. HEPLISAV-B is a hepatitis B vaccine comprised of recombinant yeast cell-derived HBsAg and a proprietary 22-mer phosphorothioate oligodeoxynucleotide adjuvant, 1018 [5]. Two doses of HEPLISAV-B are required, with the second dose 1 month after the first. Furthermore, HEPLISAV-B has demonstrated significantly greater and earlier seroprotection compared to Engerix-B, including in persons with diabetes.

Safety data from adults who received at least 1 dose of HEPLISAV-B in pre-licensure clinical trials have demonstrated a similar safety profile when compared to Engerix-B. Adverse events were generally mild and infrequent. The rates of serious adverse events and events leading to study discontinuations were also similar between HEPLISAV-B and Engerix-B. Rates of the medically-attended adverse event of herpes zoster were higher in the HEPLISAV-B group compared to the Engerix-B group in a single trial, HBV-23 (HEPLISAV-B: 0.7% [n = 38];

Engerix-B: 0.3% [n = 9]). Confirmed new-onset immune-mediated events occurring in more than one HEPLISAV-B subject were balanced between treatment groups. All other immune-mediated events occurred in a single subject and were distinct pathophysiologic entities [6].

4.0 OBJECTIVE

The primary objective of this post-marketing observational surveillance study is to describe and compare the incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis in recipients of HEPLISAV-B with recipients of another hepatitis B vaccine.

5.0 STUDY DESIGN

5.1 Study setting

This study will be conducted by Kaiser Permanente Southern California (KPSC). KPSC is a large integrated health care organization and represents the largest Kaiser Permanente region in the U.S. KPSC spans a vast geographic area, covering a distance of over 230 miles between Bakersfield in the north and San Diego in the south. KPSC has over 7,000 physicians, 15 hospitals and 225 medical offices and serves approximately 4.4 million members with diverse ethnic and socioeconomic backgrounds largely representative of the underlying population [18]. Health plan members enroll through their employer or a family member's employer, through individual and family plans, or through state or federal programs. KPSC utilizes a comprehensive electronic health record system to track members' healthcare encounters.

The KPSC Center for Vaccine Safety and Effectiveness Research conducts research with real-world implications. In partnership with clinicians, academics, federal funders (e.g., the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration (FDA), and the National Institutes of Health), and industry sponsors, investigators conduct a wide range of studies, from the incidence and outcomes of vaccine-preventable disease to the safety and effectiveness of vaccines. Published studies include the post-licensure safety of measles, mumps, rubella, varicella vaccine (MMRV) [19], autoimmune conditions following quadrivalent human papillomavirus vaccine [20], safety of quadrivalent meningococcal conjugate vaccine [21], safety of zoster vaccine in the Vaccine Safety Datalink (VSD) [22], and hepatitis B testing and vaccination [23]. In addition, KPSC has used a modern advanced method, inverse probability of treatment weighted (IPTW) estimation, to adjust for potential selection bias in observational studies, including a study of the safety of testosterone replacement based on cardiovascular outcomes [24] and an evaluation of the safety of seasonal influenza vaccine among hospitalized surgical patients [25].

The KPSC Regional Immunization Practice Committee (RIPC) makes recommendations to ensure appropriate use of vaccination and implementation of new Advisory Committee on Immunization Practices (ACIP) recommendations within medical centers. KPSC has a proactive immunization program that includes: 1) alerts on the electronic health record that indicate which vaccines are due, 2) a policy of vaccinating at all visits, not just well visit or physical exam appointments, and 3) giving recommended immunizations on a walk-in basis without appointment at no-cost nurse visits. Since all ACIP-recommended immunizations are free to members at any visit regardless of co-pay status, there is an incentive to receive immunizations within the KPSC system.

KPSC maintains comprehensive electronic health records to integrate medical information including diagnosis and procedure codes, immunizations, medications and laboratory results from outpatient, emergency department (ED), and inpatient settings within the KPSC network. All details of a patient encounter are entered into the electronic health record at the point of care. Events are coded using standard *International Classification of Diseases* (ICD) codes. Events occurring in the outpatient setting are captured directly from provider input. Those in the emergency department and inpatient settings are coded by professional coders, based on review of the health record. There is strong incentive for KPSC members to seek care within the health plan system; however, members may seek emergency medical care from outside healthcare providers. For outside facilities to be reimbursed, claims must include documentation substantiating a clinical diagnosis, which is entered into administrative data systems. In addition, KPSC is part of the Care Everywhere Network, which facilitates sharing of health records between organizations using the Epic electronic health record system. Thus, the capture of care delivered to KPSC members by electronic data is comprehensive.

5.2 Overview of study design

This is an observational surveillance study of adults aged 18 years and older who are enrolled in KPSC and receive a hepatitis B vaccination during the study period. This design will provide real world evidence on the risk of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis in a highly diverse population vaccinated with HEPLISAV-B. Approximately 30,000 patients will receive HEPLISAV-B and approximately 30,000 patients will receive another hepatitis B vaccine according to a non-randomized cluster design. HEPLISAV-B will be used exclusively at approximately 7 medical centers in family practice and internal medicine departments, while another hepatitis B vaccine will be used exclusively at the other 8 medical centers in family practice and internal medicine departments. For each patient, the index dose is defined as the first dose of HEPLISAV-B during the study vaccination period given in family practice and internal medicine departments at medical centers assigned to the HEPLISAV-B cohort, or the first dose of hepatitis B comparator vaccine (non-dialysis formulation) during the study vaccination period given in family practice and internal medicine departments at medical centers assigned to the comparator cohort. Each individual patient will be passively followed through their electronic health records for 90 days after the index vaccine dose during the study

period. Incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis will be described in patients who receive at least 1 dose of HEPLISAV-B at the medical centers in the HEPLISAV-B arm and patients who receive at least 1 dose of another hepatitis B comparator vaccine at medical facilities in the comparison arm. Cases of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis based on *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) predefined codes (Appendix 1) will be identified from electronic health records.

5.3 Selection of target medical centers

To reduce potential selection bias resulting from physician's or patient's decisions based on a patient's risk profile, HEPLISAV-B will be provided to selected medical centers as the sole vaccine for adult use in routine clinical care in family practice and internal medicine departments. Thus, providers and patients will rarely have a choice of hepatitis B vaccines, emulating a non-randomized clustered design. HEPLISAV-B will be provided exclusively to approximately 7 medical centers for adult use in their affiliated family practice and internal medicine departments. The remaining 8 medical centers and affiliated family practice and internal medicine departments will continue to use their current hepatitis B vaccine exclusively.

Site selection for the study is based on clustering of medical centers and logistics. The electronic health record in KPSC is supported in clusters of medical centers. Each medical center consists of a hospital and associated medical office buildings. When alerts or order sets are created or modified in the electronic health record, they are usually done across all clusters. In the case of this study, changes will be made in select clusters but not others, with the order sets for adult hepatitis B vaccine for family practice and internal medicine departments changed from the current vaccine to HEPLISAV-B. Target medical centers are also selected based on their proximity to our regional research headquarters in Pasadena, since study staff will need to travel to train and monitor clinic staff in vaccine management activities. We will also select the medical centers in which our clinical investigators work so that they can serve as advocates and points of contact for clinical staff.

Overall, the characteristics of adult hepatitis B vaccine recipients at the target medical centers and comparator medical centers were similar. In 2016, recipients at target and comparator medical centers were similar in terms of age distribution and sex. The recipients in both the target and comparator medical centers had similar risk of new-onset immune-mediated disease, herpes zoster, and anaphylaxis in the 90 days following the first hepatitis B vaccination in 2016 (Table 5-1).

Table 5-1: Frequency of new-onset immune-mediated events, herpes zoster, and anaphylaxis in adults following hepatitis B vaccine in 2016 by target (HEPLISAV-B®) and comparator medical centers

	Comparator Medical Center[1]	Target Medical Center[1]	Total
N	40,720	38,730	79,450
Age (years)			
Mean (SD)	47.9 (11.42)	48.0 (11.47)	48.0 (11.44)
Sex	n (%)	n (%)	n (%)
Female	19,460 (47.79%)	18,776 (48.48%)	38,236 (48.13%)
Male	21,260 (52.21%)	19,954 (51.52%)	41,214 (51.87%)
Primary systemic vasculitides	n (%)	n (%)	n (%)
No	40,720 (100%)	38,725 (99.99%)	79,445 (99.99%)
Yes	0 (0%)	5 (0.01%)	5 (0.01%)
Alopecia areata	n (%)	n (%)	n (%)
No	40,706 (99.97%)	38,721 (99.98%)	79,427 (99.97%)
Yes	14 (0.03%)	9 (0.02%)	23 (0.03%)
Basedow's (Graves) Disease	n (%)	n (%)	n (%)
No	40,710 (99.98%)	38,715 (99.96%)	79,425 (99.97%)
Yes	10 (0.02%)	15 (0.04%)	25 (0.03%)
Bell's palsy	n (%)	n (%)	n (%)
No	40,678 (99.9%)	38,693 (99.9%)	79,371 (99.9%)
Yes	42 (0.1%)	37 (0.1%)	79 (0.1%)
Erythema nodosum	n (%)	n (%)	n (%)
No	40,719 (100%)	38,729 (100%)	79,448 (100%)
Yes	1 (0%)	1 (0%)	2 (0%)
Giant cell arteritis	n (%)	n (%)	n (%)
No	40,720 (100%)	38,730 (100%)	79,450 (100%)
Guillain-Barre syndrome	n (%)	n (%)	n (%)
No	40,719 (100%)	38,730 (100%)	79,449 (100%)
Yes	1 (0%)	0 (0%)	1 (0%)
Lichen planus	n (%)	n (%)	n (%)
No	40,717 (99.99%)	38,724 (99.98%)	79,441 (99.99%)
Yes	3 (0.01%)	6 (0.02%)	9 (0.01%)
Polyarteritis nodosa	n (%)	n (%)	n (%)
No	40,720 (100%)	38,730 (100%)	79,450 (100%)
Polymyalgia rheumatica	n (%)	n (%)	n (%)
No	40,719 (100%)	38,729 (100%)	79,448 (100%)
Yes	1 (0%)	1 (0%)	2 (0%)

Table 5-1: Frequency of new-onset immune-mediated events, herpes zoster, and anaphylaxis in adults following hepatitis B vaccine in 2016 by target (HEPLISAV-B®) and comparator medical centers (Contd)

	Comparator Medical Center[1]	Target Medical Center[1]	Total
N	40,720	38,730	79,450
Age (years)			
Mean (SD)	47.9 (11.42)	48.0 (11.47)	48.0 (11.44)
Sex	n (%)	n (%)	n (%)
Female	19,460 (47.79%)	18,776 (48.48%)	38,236 (48.13%)
Male	21,260 (52.21%)	19,954 (51.52%)	41,214 (51.87%)
Rheumatoid arthritis	n (%)	n (%)	n (%)
No	40,698 (99.95%)	38,709 (99.95%)	79,407 (99.95%)
Yes	22 (0.05%)	21 (0.05%)	43 (0.05%)
Scleroderma	n (%)	n (%)	n (%)
No	40,717 (99.99%)	38,728 (99.99%)	79,445 (99.99%)
Yes	3 (0.01%)	2 (0.01%)	5 (0.01%)
Systemic lupus erythematosus	n (%)	n (%)	n (%)
No	40,717 (99.99%)	38,725 (99.99%)	79,442 (99.99%)
Yes	3 (0.01%)	5 (0.01%)	8 (0.01%)
Takayasu's arteritis	n (%)	n (%)	n (%)
No	40,720 (100%)	38,730 (100%)	79,450 (100%)
Ulcerative colitis	n (%)	n (%)	n (%)
No	40,707 (99.97%)	38,722 (99.98%)	79,429 (99.97%)
Yes	13 (0.03%)	8 (0.02%)	21 (0.03%)
Tolosa Hunt syndrome	n (%)	n (%)	n (%)
No	40,720 (100%)	38,730 (100%)	79,450 (100%)
Vitiligo	n (%)	n (%)	n (%)
No	40,705 (99.96%)	38,717 (99.97%)	79,422 (99.96%)
Yes	15 (0.04%)	13 (0.03%)	28 (0.04%)
Anaphylaxis	n (%)	n (%)	n (%)
No	40,720 (100%)	38,730 (100%)	79,450 (100%)
Herpes Zoster	n (%)	n (%)	n (%)
No	40,621 (99.76%)	38,645 (99.78%)	79,266 (99.77%)
Yes	99 (0.24%)	85 (0.22%)	184 (0.23%)

[1] Conditions were identified using ICD codes in all care settings (inpatient, outpatient, and emergency department) for patients who were KPSC members on day of index vaccination. Immune-mediated diseases and herpes zoster were identified within 0 to 90 days of index vaccination, and anaphylaxis was identified within 0 to 1 days of index vaccination. Pre-existing conditions (i.e., same diagnosis within one year prior to the index date) were not considered new-onset.

5.4 Study period

The study will begin with administration of the first dose of HEPLISAV-B and is contingent upon ACIP and RIPC recommendation of HEPLISAV-B. The study vaccination period will occur until 30,000 patients have received at least 1 dose of HEPLISAV-B, expected to take approximately 12 months based on historical vaccination trends. Each patient will be followed until the earliest of disenrollment from KPSC (not due to death and allowing for a 31-day gap in membership), death from any cause, or the end of the 90-day follow-up period after the index dose given during the vaccination period.

6.0 STUDY POPULATION

6.1 Recommendations for vaccination

The ACIP recommends hepatitis B vaccination for adults at increased risk of hepatitis B through sexual exposure, percutaneous or mucosal exposure, and travelers to countries with high or intermediate prevalence of hepatitis B [2-4]. Universal vaccination is recommended in settings in which a high proportion of persons are likely to be at risk (e.g., STD/HIV testing and treatment facilities, drug abuse treatment and prevention facilities, etc.). Persons with diabetes mellitus are also recommended for vaccination if age 19 to 59 years, or if age 60 years or older at the discretion of the health provider.

6.2 Study inclusion and exclusion criteria

6.2.1 Inclusion criteria

1. Received at least 1 dose of hepatitis B vaccine (either HEPLISAV-B in HEPLISAV-B arm, or non-dialysis formulation hepatitis B comparator vaccine in comparator arm) at KPSC during study vaccination period
2. Enrolled as a KPSC member at time of hepatitis B vaccination during the study vaccination period
3. Age 18 years or older at time of hepatitis B vaccination during study vaccination period
4. Received hepatitis B vaccine at KPSC family practice or internal medicine departments, or in urgent care or nurse clinics affiliated with those departments

6.2.2 Exclusion criteria

1. Received peritoneal dialysis or chronic hemodialysis (more than 9 dialysis sessions in the past 3 months) prior to index hepatitis B vaccination
2. Received all doses of their hepatitis B vaccine series in KPSC departments other than family practice or internal medicine or their affiliated departments as described above

6.3 Number of subjects

HEPLISAV-B recipients: 30,000 patients

Other hepatitis B vaccine recipients: approximately 30,000 patients

The number of subjects includes 25,000 patients in each arm who will also be included in DV2-HBV-25. The exact number of recipients will depend on the number of patients vaccinated with hepatitis B vaccine at the target and other medical centers during the study period.

7.0 STUDY METHODS

7.1 Exposure of interest

The exposure of interest for this study is the index dose of hepatitis B vaccine (Section 5.2).

Hepatitis B vaccine exposure will be assigned at the cluster level. At target medical centers, providers in family practice and internal medicine departments will only be able to order HEPLISAV-B for hepatitis B vaccination of adult patients not on dialysis. Patients receiving an index dose of HEPLISAV-B in family practice or internal medicine departments will be included in the HEPLISAV-B cohort. Adults vaccinated with one or more doses of comparator hepatitis B vaccine prior to study initiation who did not complete the full 3-dose regimen may be given HEPLISAV-B if they receive care at a HEPLISAV-B target medical center.

At non-target medical centers, providers in family practice or internal medicine departments will only be able to order a hepatitis B comparator vaccine other than HEPLISAV-B. Only patients receiving an index dose of comparator vaccine in family practice or internal medicine departments will be included in the comparator cohort. In recent years at KPSC, Engerix-B has been used for routine vaccination, while Recombivax-HB (Dialysis Formulation) has been used for dialysis patients. As dialysis patients are not included in this study, the comparator is expected to be Engerix-B.

While providers are advised to follow ACIP and RIPC recommendations, decisions regarding the appropriateness of administering a hepatitis B vaccination and the vaccination schedule will be determined by the healthcare providers and patients. Vaccine exposure will be identified retrospectively from the electronic health records, including vaccine, dose, manufacturer, and lot number entered at the time of vaccination. Data on vaccine exposure will be checked using quality control procedures described in Section 9.2 below.

7.2 Outcome of interest

The outcome of interest is incidence of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis following the index dose of hepatitis B vaccine. New-onset immune-mediated diseases of interest in this study are: primary systemic vasculitides, alopecia areata, Basedow's (Graves) Disease, Bell's palsy, erythema nodosum, giant cell arteritis, Guillain-Barre syndrome, lichen planus, polyarteritis nodosa, polymyalgia rheumatica, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Takayasu's arteritis, ulcerative colitis, Tolosa Hunt syndrome, and vitiligo.

Events will be identified from electronic health records from inpatient, outpatient, and emergency department (ED) encounters. ICD-10-CM codes for each condition are specified in Appendix 1. Events that occur in individuals with a diagnosis of the same condition in the 12 months prior to the index dose will be excluded.

Selection of follow-up periods are based on several considerations. First, extending the follow-up period past the true risk window could result in an artificially decreased relative risk estimate and decreased power to detect differences, while too short of a follow-up period would not bias the estimate but would potentially result in a loss of power. Therefore, it is best to set the follow-up period as close as possible to the period of time corresponding to elevated risk. Secondly, biological plausibility and review of relevant literature suggests that the risk windows for events associated with vaccination are likely less than 90 days [20, 21, 26-33]. Thirdly, we have previously conducted a post-licensure safety surveillance study for similar outcomes with 84-day and 42-day follow-up periods [21].

Based on these considerations, we propose a follow-up period for new-onset immune-mediated disease and herpes zoster of 1 to 90 days following index vaccination; a sensitivity analysis will be conducted with a follow-up period of 1 to 42 days (Section 8.5). The follow-up period for anaphylaxis will be 0 to 1 days following index vaccination.

7.3 Covariates

Patient characteristics will be identified through electronic health records. Covariates to be considered may include:

1. Age, sex, race / ethnicity, socioeconomic status
2. Duration of membership prior to index dose of hepatitis B vaccine
3. Conditions included in the Charlson co-morbidity index in year prior to index dose of hepatitis B vaccine
4. Healthcare utilization in year prior to index dose of hepatitis B vaccine
5. Hepatitis B vaccination in year prior to index dose of hepatitis B vaccine
6. Zoster vaccine in year prior to index dose of hepatitis B vaccine
7. Concomitant receipt of other vaccines, e.g., influenza or pneumococcal

As these covariates are comprised of basic characteristics, risk factors, and important co-morbidities that are usually captured during healthcare encounters, and patients have strong incentive to obtain care within KPSC, it is expected that data will be reasonably complete.

7.4 Data sources and claims

The study will be conducted using the KPSC Research Data Warehouse (RDW) which supports external and internal research projects conducted in the KPSC Department of Research and Evaluation as well as patient care management programs. The data warehouse is an integrated and comprehensive resource of electronic health records. It contains information as far back as 1980, including records related to membership, benefits, utilization, pharmacy, vital signs, laboratory, vaccines, geocoding, mortality, and procedures. Data are linked through a unique medical record number assigned to each member of the health plan.

Care received outside of KPSC, including emergency care, is integrated into the RDW. If a patient is transferred to KPSC, then records for care at the outside facility are usually transferred and incorporated into the patient's health records. Patients who are not transferred often have documentation incorporated as part of the claims process or through Care Everywhere.

Because claims can take several months to be incorporated into electronic health records, a 3-month lag period will be used to allow for data settling. The 3-month lag is essential to avoid bias in the number of events, as there may be differences between target and comparator medical centers in the proportion of events derived from claims.

8.0 STATISTICAL ANALYSES & CONSIDERATIONS

8.1 Power for primary analysis

Analyses will be determined based on power, underlying rates, and the number of events in each arm (Table 8-1). Power to detect a relative risk of 3 would be approximately 80% for conditions with an underlying event rate of 0.25 per 1000. This would be a total of 30 events (7.5 + (7.5*3)) across both cohorts (n=60,000). For conditions where power is less than approximately 80%, descriptive analyses only will be conducted.

Table 8-1: Power to detect a relative risk in the HEPLISAV-B immune-mediated diseases, herpes zoster, and anaphylaxis study, by underlying event rate

Underlying event rate (per 1000)	**# events in comparison group**	**Relative Risk**				
		1.5	**2**	**3**	**4**	**5**
		power	power	power	power	power
0.1	**3**	0.085	0.17	0.41	0.642	0.808
0.25	**7.5**	0.139	0.353	0.782	0.957	0.994
0.5	**15**	0.232	0.609	0.972	0.999	1.000
0.75	**22.5**	0.323	0.782	0.997	1.000	1.000
1	**30**	0.41	0.886	1.000	1.000	1.000
2.5	**75**	0.783	0.999	1.000	1.000	1.000
5	**150**	0.973	1.000	1.000	1.000	1.000
Assumes 30,000 individuals in each group.						

8.2 Descriptive analysis

A descriptive analysis of baseline characteristics will be conducted comparing recipients of at least 1 dose of HEPLISAV-B and receipients of at least 1 dose of comparator vaccine. Variables described in Section 7.3 will be extracted from electronic health records. Categorical variables will be presented as absolute numbers and percentages with p-values for the χ^2 test. Continuous variables such as age in years will be presented as the mean with standard deviation and interquartile ranges, with p-values for the two-sample t-test or Wilcoxon rank-sum test, as appropriate. The incidence rates of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis during the study period among HEPLISAV-B recipients and comparator vaccine recipients will be described.

8.3 Primary analysis

Incidence rates of new-onset herpes zoster and anaphylaxis in HEPLISAV-B and comparator vaccine recipients will be compared using Poisson regression models employing inverse probability of treatment weighting (IPTW) [34]. For new-onset immune-mediated diseases, Poisson regression with IPTW will be conducted where there is at least 80% power to detect a relative risk of 3. Censoring events will include end of study, disenrollment from Kaiser Foundation Health Plan (allowing for a 31-day gap in membership), and death. Relative risks, adjusted for potential confounding factors, and associated 95% confidence intervals will be reported.

The IPTW provides an assessment of the closeness of match in the weighted analysis across all variables, providing a sense of the degree of control of imbalance between the vaccine exposure groups. Two tables will be created comparing the cohort of HEPLISAV-B recipients to the cohort of recipients of the comparator vaccine. The first table will be unweighted, showing the true distribution of recipient characteristics. The second table will be weighted by the inverse probability of treatment as estimated by a propensity score model. Standardized difference scores will be used to assess whether balance of covariates is achieved between the cohorts. These tables will show the effectiveness of the weighting at reducing effective differences between the cohorts. Variables to consider in the propensity model are listed in Section 7.3.

8.4 Investigation of significantly elevated risks

An investigation will be conducted if results of the primary analysis indicate a significantly increased risk of a new-onset immune-mediated disease, herpes zoster, or anaphylaxis. This will involve stratifying results by length of membership prior to the index dose (≥ 1 year and <1 year) and investigating temporal relationships between date of hepatitis B vaccination exposure and date of outcome diagnosis. Specific outcome codes and vaccinations given during the risk window after the index dose of hepatitis B vaccine may also be examined.

8.5 Sensitivity analysis

A sensitivity analysis will be conducted using a 42-day follow-up period for new-onset immune-mediated diseases and herpes zoster. Incidence rates among HEPLISAV-B recipients and comparator vaccine recipients will be described. For new-onset herpes zoster or immune-mediated diseases where there is at least 80% power to detect a relative risk of 3, Poisson regression with IPTW will be used to compare incidence rates among HEPLISAV-B recipients and comparator vaccine recipients, as described above (Section 8.3).

8.6 Secondary analysis

A secondary analysis will be conducted to examine any differential effect on study outcomes associated with the number of doses of HEPLISAV-B vaccine. Incidence rates of new-onset immune-mediated diseases, herpes zoster, and anaphylaxis will be described for recipients of only 1 dose of HEPLISAV-B, recipients of 2 or more doses of HEPLISAV-B, and recipients of at least 1 dose of comparator vaccine during the study period. For outcomes where analysis was triggered in the primary analyses (Section 8.3), Poisson regression with IPTW will also be employed in secondary analyses to compare incidence rates among (a) recipients of only 1 dose of HEPLISAV-B and recipients of at least 1 dose of comparator vaccine, and (b) recipients of 2 or more doses of HEPLISAV-B and recipients of at least 1 dose of comparator vaccine.

8.7 Model selection rationale

Potential confounders to include in the propensity score model are listed in Section 8.3. These covariates will be assessed for their availability and ability for adjusting crude results, including an examination of their distributions and missingness. Potential confounders will be selected based on a combination of a priori decisions and a qualitative assessment of the empirical relationships between potential confounders and exposure. Note that we will not use an algorithmic backward, forward or stepwise process, and that the results of the multivariable model should corroborate the knowledge gained during the model-building process.

9.0 DATA MANAGEMENT

9.1 Data processing

Electronic health record data are extracted and maintained securely in the electronic RDW database at KPSC. The database is regularly supported with appropriate backup and recovery options. Only authorized study personnel with passwords can access the database.

Data processing in this study will be performed by programmers and analysts at KPSC using SAS (version 9.3 or higher; SAS Institute, Cary, NC). No imputation for missing data will be performed. We expect there to be a very low rate of missing data in the electronic health records. Any loss to follow-up due to leaving the KPSC health plan (Section 8.3) will be addressed in data analysis by the truncation of person-time in the event rate calculations.

9.2 Data quality

Quality control of data will include range and consistency checks for all study variables, with additional consistency checks for hepatitis B vaccine exposure. For example, discordant records (e.g., vaccine name with wrong manufacturer or invalid lot number), HEPLISAV-B administrations in non-target medical centers, and comparator vaccine administrations in target medical centers will trigger a review of the medical records. Double programming will be conducted for assignment of the cohort (vaccine group) and outcomes, and all source code will be reviewed by a second analyst.

10.0 REGULATORY AND ETHICAL CONSIDERATIONS

The protocol will be reviewed and approved by the KPSC Institutional Review Board (IRB). All study staff with access to protected health information are trained in procedures to protect the confidentiality of subject data. Informed consent is not needed for HEPLISAV-B vaccination, as the vaccine is approved by the U.S. FDA and recommended for eligible KPSC members as part of routine clinical care. Individual written Health Insurance Portability and Accountability Act (HIPAA) authorizations will not be required prior to initiating data collection using electronic health records. Adverse event reporting is not required, as this is a non-interventional study based on secondary use of KPSC electronic health records. Adverse events cannot be identified spontaneously under the current methodology, so there will not be individual reporting of adverse events. The study will be conducted in accordance with the protocol, applicable regulatory requirements, and good pharmacoepidemiologic practice.

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APPENDIX 1: INTERNATIONAL CLASSIFICATION OF DISEASES, 10TH REVISION, CLINICAL MODIFICATION (ICD-10-CM) PRE-DEFINED CODES FOR OUTCOMES OF INTEREST

Condition	ICD-10	ICD10 description
Primary systemic vasculitides (antineutrophil cytoplasmic antibody [ANCA] positive) • **Microscopic polyangiitis (MPA)** • **Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis [EGPA])** • **Granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis)**	I77.6	Arteritis, unspecified. Synonyms: ANCA positive vasculitis; Glomerulonephritis due to ANCA; vasculitis, ANCA positive
		Vasculitis, ANCA positive; Vasculitis, ANCA positive with glomerulonephritis
	M31.7	Microscopic polyangiitis, excludes polyarteritis nodosa
	M30.1	Polyarteritis with lung involvement (Churg-Strauss)
		Allergic granulomatous angiitis
	M1.3, M31.30, M31.31	Wegener's granulomatosis, Wegener's granulomatosis without renal involvement, Granulomatosis with polyangiitis, Wegener's granulomatosis with renal involvement
Alopecia areata	L63.9	Alopecia areata
Basedow's (Graves') Disease (primary code)	E05.0	Thyrotoxicosis with diffuse goiter, Exophthalmic or toxic goiter not otherwise specified (NOS), Grave's disease, Toxic diffuse goiter
	E05.00	Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm; Graves' Disease, Graves' Disease with restrictive strabismus
	E05.01	Thyrotoxicosis with diffuse goiter with thyrotoxic crisis or storm
Bell's palsy	G51.0	Bell's palsy
Erythema nodosum	L52	Erythema nodosum
Giant cell arteritis	M31.5	Giant cell arteritis with polymyalgia rheumatica
	M31.6	Other giant cell arteritis
		Giant cell arteritis, Temporal arteritis, cranial arteritis
Guillain-Barre syndrome (GBS)	G61.0	Guillain-Barre Syndrome, Miller-Fisher variant of GBS
Lichen planus	L43.9	Lichen planus, lichen planus unspecified
	L43.8	Lichen planus annularis, lichen planus not elsewhere classified (NEC)
		Benign lichenoid keratosis

Condition	ICD-10	ICD10 description
	L43.1	lichen planus bullous
	L43.0	lichen planus hypertrophic
	L43.3	lichen planus subacute
Polyarteritis nodosa	M30.0	Polyarteritis nodosa, excludes M31.7
	M30.8	Polyarteritis related condition NEC
Polymyalgia rheumatica	M35.3	Polymyalgia rheumatica
Rheumatoid arthritis (RA)	M06.9	RA, unspecified
	M06.xyz, x=0-4,8,9	RA, specific sites, laterality, uveitis RA syndrome, etc.
	M05.9	RA, with rheumatoid factor
	M05.xyz, x=0-9	M05=RA with RF; M05.0yz=Felty's Syndrome (RA, splenomegaly, granulocytopenia) various sites, laterality; M05.1yz=Rheumatoid lung disease with RA various sites, laterality; M05.2yz=Rheumatoid vasculitis with RA various sites, laterality, etc.
Scleroderma	L94.0	Localized scleroderma
	L94.1	Linear scleroderma
	M34	Systemic sclerosis (scleroderma)
	M34.0	Progressive systemic sclerosis
	M34.1	Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome
	M34.2	Systemic sclerosis induced by drug and chemical
	M34.8	Other forms of systemic sclerosis
	M34.81	Systemic sclerosis with lung involvement
	M34.82	Systemic sclerosis with myopathy
	M34.83	Systemic sclerosis with polyneuropathy
	M34.89	Other systemic sclerosis
		Scleroderma renal crisis
	M34.9	Systemic sclerosis, unspecified
		Scleredema, Scleredema with glomerulonephritis, Scleredema Buschkes
Systemic lupus erythematosus (SLE)	M32	SLE
	M32.0	Drug-induced SLE

Condition	ICD-10	ICD10 description
		Drug-induced SLE, hydralazine
	M32.1	Systemic lupus erythematosus with organ or system involvement;
	M32.10	Systemic lupus erythematosus with organ or system involvement, unspecified
	M32.11	Endocarditis in SLE
	M32.12	Pericarditis in SLE
	M32.13	Lung involvement in SLE
	M32.14	Glomerular disease in SLE
	M32.15	Tubulo-interstitial nephropathy in SLE
	M32.19	Other organ or system involvement in SLE
		Inflammatory myopathy due to SLE, central nervous system (CNS) lupus
	M32.8	Other forms of SLE
	M32.9	SLE, unspecified
	L93.0, H01.12x	Discoid lupus erythematosus (H codes specify eyelid)
Takayasu's arteritis	M31.4	Takayasu's disease (Aortic arch syndrome, pulseless disease)
Ulcerative colitis	K51	Ulcerative colitis
	K51.00	Chronic ulcerative pancolitis
	K51.011	Chronic ulcerative colitis pancolitis with rectal bleed
	K51.012	Chronic ulcerative colitis pancolitis with obstruction
	K51.013	Chronic ulcerative colitis pancolitis with fistula
	K51.014	Chronic ulcerative colitis pancolitis with abscess
	K51.019	Chronic ulcerative colitis pancolitis with complication
	K51.2	Ulcerative proctitis
	K51.20, 51.211, K51.212, K51.213, K51.214, K51.219	Uncomplicated to with various complications
	K51.20	Ulcerative proctitis
	K51.211	Ulcerative proctitis w/ rectal bleeding
	K51.212	Ulcerative proctitis w/ obstruction
	K51.213	Ulcerative proctitis w/ fistula
	K51.214	Ulcerative proctitis w/ abscess

Condition	ICD-10	ICD10 description
	K51.219	Ulcerative proctitis w/ complication
	K51.3	Ulcerative rectosigmoiditis
	K51.30, K51.311, K51.312, K51.313, K51.314, K51.319	Uncomplicated to with various complications
	K51.30	Proctocolitis
	K51.311	Chronic ulcerative colitis w/ rectosigmoiditis w/ rectal bleeding
	K51.312	Chronic ulcerative colitis w/ rectosigmoiditis w/ obstruction
	K51.313	Chronic ulcerative colitis w/ rectosigmoiditis w/ fistula
	K51.314	Chronic ulcerative colitis w/ rectosigmoiditis w/ abscess
	K51.319	Chronic ulcerative colitis w/ rectosigmoiditis w/ complication
	K51.40	Inflammatory polyps of colon
		Colonic pseudopolyp
	K51.411	Colonic pseudopolyp w/ rectal bleeding
	K51.412	Colonic pseudopolyp w/ obstruction
	K51.413	Colonic pseudopolyp w/ fistula
	K51.414	Colonic pseudopolyp w/ abscess
	K51.419	Colonic pseudopolyp w/ complication
	K51.5	Left-sided ulcerative colitis
	K51.5yz; y=0,1; z=1-4,8,9	Uncomplicated to with various complications
	K51.50	Chronic left-sided ulcerative colitis
	K51.511	Chronic left-sided ulcerative colitis w/ rectal bleeding
	K51.512	Chronic left-sided ulcerative colitis w/ obstruction
	K51.513	Chronic left-sided ulcerative colitis w/ fistula
	K51.514	Chronic left-sided ulcerative colitis w/ abscess
	K51.519	Chronic left-sided ulcerative colitis w/ complication
	K51	Ulcerative colitis
	K51.0	Ulcerative pancolitis
	K51.0yz; y=0,1; z=1-4,8,9	Uncomplicated to with various complications
	K51.00	Chronic ulcerative colitis enterocolitis, chronic ulcerative colitis pancolitis
	K51.011	Chronic ulcerative pancolitis with rectal bleeding

Condition	ICD-10	ICD10 description
	K51.012	Chronic ulcerative pancolitis with obstruction
	K51.013	Chronic ulcerative pancolitis with fistula
	K51.014	Chronic ulcerative pancolitis with abscess
	K51.019	chronic ulcerative pancolitis with complication
	K51.80	eosinophilic ulcerative colitis
	K51.90	Ulcerative colitis, unspecified, without complications
	K51.911	Ulcerative colitis with rectal bleeding
	K51.912	Ulcerative colitis with obstruction
	K51.913	Ulcerative colitis with fistula
	K51.914	Ulcerative colitis with abscess
	K51.919	Ulcerative colitis with complication
Tolosa Hunt syndrome	H49.40	Tolosa Hunt Syndrome, progressive external ophthalmoplegia, unspecified eye
	H49.41	Right Tolosa Hunt Syndrome, right progressive external ophthalmoplegia
	H49.42	Left Tolosa Hunt Syndrome. Left progressive external ophthalmoplegia
	H49.43	Bilateral Tolosa Hunt Syndrome, bilateral progressive external ophthalmoplegia
Vitiligo	L80	Vitiligo
	A67.2	Vitiligo of pinta
	H02.731	Vitiligo, left eyelid and periocular area
	H02.732	Vitiligo, left lower eyelid and periocular area
	H02.733	Vitiligo, left upper eyelid and periocular area
	H02.734	Vitiligo, right eyelid and periocular area
	H02.735	Vitiligo, right lower eyelid and periocular area
	H02.736	Vitiligo, right upper eyelid and periocular area
Anaphylaxis	T78.2XXA	Anaphylactic shock, unspecified, initial encounter
	T88.6XXA	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter

Condition	ICD-10	ICD10 description
	T80.52XA	Anaphylactic reaction due to vaccination, initial encounter
Herpes Zoster (HZ)	B02	HZ
	B02.0	Zoster encephalitis
	B02.2x	Zoster with other nervous system involvement
	B02.1	Zoster meningitis
	B02.3x	Zoster ocular disease
	H35.729	HZ retinal pigment epithelium detachment
	B02.7	Disseminated zoster
	B02.8	Zoster with other complications
	B02.9	Zoster without complications