NCT04456504

HepB-CpG series for healthcare workers who are hepatitis B vaccine nonresponders

6/11/2020

Protocol Number: UW HSC-IRB #2020-0631
Principal Investigator: Mary S. Hayney, PharmD, MPH

Dynavax is supplying Heplisav-B™ for this study.

Protocol Version History

Protocol Version	Version Date	Summary of Revisions Made	Rationale
1.0	05/28/2020	Initial version	
2.0	6/11/2020	Edits regarding AE notification and added Data collection form	Required elements

REMINDER: update the Table of Contents before considering the document or draft final. To update the Table of Contents, right click anywhere below and then select "Update Field."

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1.0 STATEMENT OF COMPLIANCE

I confirm that I have read this protocol. I will comply with the IRB-approved protocol, and applicable regulations, guidelines, laws, and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

Name	**Signature**	**Date**
Mary S. Hayney, PharmD, MPH		
Principal investigator		

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event
antiHBs	Antibody to the hepatitis B surface antigen
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMB	Data & Safety Monitoring Board
DSMC	Data & Safety Monitoring Committee
DSMP	Data & Safety Monitoring Plan
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HepB-CpG	Hepatitis B vaccine with CpG adjuvant (Heplisav-B™)
HIPAA	Health Insurance Portability and Accountability Act
ICTR	Institute for Clinical and Translational Research
IND	Investigational New Drug Application
IRB	Institutional Review Board
MOP	Manual of Procedures
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
POC	Point of Contact
PRC	Pharmaceutical Research Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sIRB	single IRB
SMART IRB	Streamlined, Multisite, Accelerated Resources for Trials IRB
SMC	Safety Monitoring Committee
SMP	Study Monitoring Plan
SMS	Study Monitoring Service
UP	Unanticipated Problem

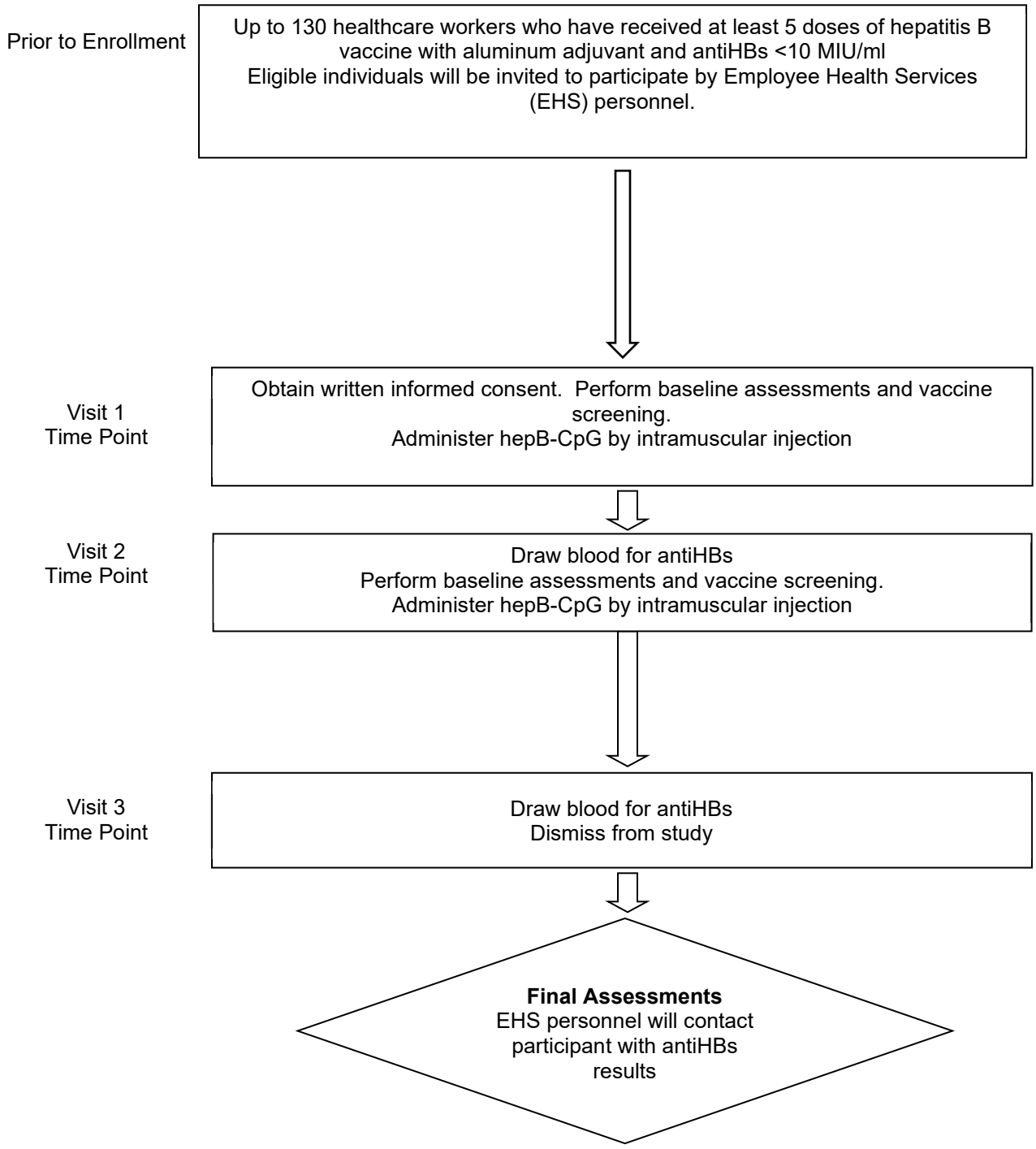
3.0 STUDY SUMMARY

3.1 Synopsis

Full Title	HepB-CpG series for healthcare workers who are hepatitis B vaccine nonresponders
Short Title	Vaccination for healthcare worker hepatitis B vaccine nonresponders
Protocol Number	[HS IRB 2020-0631]
ClinicalTrials.gov Identifier & Summary	pending This study is being done to determine if healthcare workers who have previously failed to respond to hepatitis B vaccine series will respond to a hepatitis B with CpG adjuvant (hepB-CpG) (Heplisav-B)
Number of Site(s)	The study will be conducted at UWHealth Employee Health Services
Phase	Phase 4
Main Inclusion Criteria	• Healthcare worker who has previously received at least 5 doses of hepatitis B vaccine with aluminum adjuvant (Recombivax B or Engerix B) and has an antibody to the hepatitis B surface antigen (antiHBs) that is less than 10 mIU/ml. • English-speaking (able to provide consent)
Main Exclusion Criteria	• Allergy to hepB-CpG or a component
Objective(s)	Primary Objective • To measure the number of healthcare workers who failed to respond to 5 or more doses of hepatitis B vaccine with aluminum adjuvant who will respond to hepatitis B vaccine with CpG adjuvant series. Secondary Objectives • To measure the number of healthcare workers who respond to a single dose of hepB-CpG • To determine risk factors associated with hepatitis B vaccine nonresponse, including age, smoking status, sex, diabetes, immunosuppression
Endpoints	Primary Endpoint • AntiHBs >10 mIU/ml following two doses of hepB-CpG Secondary Endpoint • AntiHBs >10 mIU/ml following a single dose of hepB-CpG • Measure effect of known hepatitis B vaccine nonresponse risk factors on response in this population
Study Design	Open label
IND or IDE Number	Not applicable

Study Intervention	Each individual who has completed at least 5 doses hepB vaccine with aluminum adjuvant series but is anti-HBs negative will be contacted by EHS staff and invited to receive the hepB-CpG two dose series on a 0 and 1 month schedule. Antibody to the surface antigen will be measured after the first dose during the visit for the administration of the second dose. One month after completion of the series, each immunized individual will have another anti-HBs measured.
Total Number of Subjects	Up to 130 individuals will be recruited and enrolled.
Study Population	Healthcare workers who have received at least 5 doses of hepatitis B vaccine with aluminum adjuvant and have antiHBs < 10mIU/ml.
Statistical Methodology	We will count the number of individuals who seroconvert and have anti-HBs >10 mIU/ml and report a ratio with the total number immunized as the denominator. We will develop a multivariate model to predict hepB-CpG response which will include age, sex, smoking status, diabetes, and immunosuppression as variables.
Estimated Subject Duration	The duration of the study for each subject is approximately 8 weeks.
Estimated Enrollment Period & Study Duration	Study enrollment and follow-up will occur over 12 months.

3.2 Schematic of Study Design



4.0 KEY ROLES

The following is a list of all key personnel and roles:

Principal Investigator	Mary S. Hayney, PharmD, MPH Professor of Pharmacy University of Wisconsin School of Pharmacy 777 Highland Avenue, Madison, WI 53705 608-265-4666
Participating Site(s)	UWHealth Employee Health Services 700 University Bay Drive Madison, WI 53705
Local Laboratory Services	UWHealth Clinical Laboratory 601 Highland Avenue Madison, WI 53792
Funding Sponsor (Supplying vaccine only)	Dynavax 2100 Powell Street, Suite 900 Emeryville, CA 94608

5.0 INTRODUCTION

5.1 Disease Background

Although the recombinant hepatitis B (hepB) vaccine with aluminum adjuvant as a three dose series induces seroprotection in about 95% of individuals, a small number of healthy individuals fail to mount an immune response. Increasing age is an important risk factor for hepB vaccine response. 1 Healthcare personnel are among the individuals for whom protection from hepatitis B infection is very important. Employee Health Service (EHS) at the University of Wisconsin Hospital and Clinics screens employees with documented history of completion of the hepB vaccine 3-dose series for antibody to the hepatitis B surface antigen (anti-HBs) at time of hire. Those who are found to have anti-HBs less than 10 mIU/ml receive a challenge dose. 2 If the anti-HBs remains less than 10 mIU/ml, two more doses of vaccine are administered. Among the 15,000 employees, about 100 individuals have completed two hepB vaccine with aluminum adjuvant series but remain vaccine non-responders. Heplisav-B (hepB-CpG) is a recently licensed hepB vaccine with a new adjuvant that is more immunogenic in the general adult population and patients with chronic kidney disease or diabetes.3-5 Given the superior immunogenicity of hepB-CpG in these individuals who were difficult to induce seroprotection, we hypothesize that 70% of the 101 non-responders will mount an immune response to two doses of hepB-CpG.

5.2 Current Standard of Care

With the recent licensure of hepatitis B vaccine with CpG antigen, the Advisory Committee on Immunization Practices (ACIP) has recommended this vaccine series as a vaccine that can be used for adults for whom hepatitis B immunization is recommended. This vaccine series is more immunogenic in the general adult population and patients with chronic kidney disease or diabetes. The ACIP has listed hepB-CpG as a vaccine that can be used for revaccination.

5.3 Investigational Treatment

Although reimmunization is recommended for individuals at high risk of bloodborne pathogen exposure, including healthcare workers, we are prospectively using hepB-CpG series and measuring the vaccine response. Each healthcare worker who wishes to receive the hepB-CpG series on a 0 and 1 month schedule will be asked for written informed consent and will have blood drawn for antiHBs one month after dose 1 and prior to administration of dose 2 and one month after the second dose.

5.4 Rationale

The response rate to hepB-CpG series in healthcare workers who failed to respond to at least 5 doses of hepatitis B vaccine with aluminum adjuvant is not known. If healthcare workers respond to this vaccine series, it may become the standard of care rather than an option among all hepatitis B vaccine preparations.

6.0 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To measure the number of healthcare workers who failed to respond to 5 or more doses of hepatitis B vaccine with aluminum adjuvant who will respond to hepatitis B vaccine with CpG adjuvant series	antiHBs > 10mIU/ml after completion of the series
Secondary	
To measure the number of healthcare workers who respond to a single dose of hepB-CpG	antiHBs > 10mIU/ml after one dose of hepB-CpG
To determine risk factors associated with hepatitis B vaccine nonresponse, including age, smoking status, sex, diabetes, immunosuppression	Proportion of participants who are nonresponders with each risk factor and develop a multivariate model

7.0 STUDY DESIGN

7.1 General Design

This Phase 4 single center, open label study will measure the response rate to hepB-CpG series in healthcare workers who have received at least 5 doses of hepatitis B vaccine with aluminum adjuvant and have antiHBs < 10mIU/ml.

The study population will consist of 130 healthcare workers who have received at least 5 doses of hepatitis B vaccine with aluminum adjuvant and have antiHBs < 10mIU/ml.

All study visits will be done at Employee Health Services. During visit 1, written informed consent for participation will be obtained. Each participant will be screened for vaccine contraindications. Participants

will be briefly interviewed for known hepatitis B vaccine nonresponse risk factors—age, sex, smoking status, diabetes, and immunosuppression.

Each participant will receive hepB-CpG intramuscularly at visit 1 and at visit 2 will have a blood draw for antiHBs and receive hepB-CpG dose 2 intramuscularly. A blood draw for antiHBs will be done at visit 3 one month following dose 2. The vaccine administration will be documented in the Wisconsin Immunization Registry (the WIR) and the antiHBs results will be retained in the Employee Health electronic medical record (Agility).

Subject accrual will occur over 6 months at UWHealth Employee Health Services. Subjects will complete 3 study visits over the course of approximately 8 weeks. Each subject will contribute 2.

7.2 End of Study Definition

A subject is considered to have completed the study if they receive both doses of hepB-CpG and the blood draw one month after the second dose.

8.0 SUBJECT SELECTION

8.1 Inclusion & Exclusion Criteria

Eligibility will be determined by inclusion and exclusion criteria below.

Inclusion Criteria
1. Willing to provide informed consent.
2. Willing to comply with all study procedures and be available for the duration of the study.
3. healthcare workers who have received at least 5 doses of hepatitis B vaccine with aluminum adjuvant and have antiHBs < 10mIU/ml
4. Individuals at least 18 years of age.
5. Females of childbearing potential will be asked about the possibility of pregnancy as is the standard of care for immunization services. If a female indicates that she may be pregnant, study participation will be postponed until pregnancy is completed or the female reports that she is not pregnant.

Exclusion Criteria
1. Women who are pregnant or planning on becoming pregnant during the study.
2. Allergy to the vaccine or a component of the vaccine
3. Not suitable for study participation due to other reasons, such as inability or unwillingness to comply with the study procedures, at the discretion of the investigators.

8.2 Subject Identification

8.2.1 Electronic Medical Record (EMR) Query

Potential subjects will be identified via Agility (the EMR used by EHS) query. Eligible individuals are flagged in the system as they require special prophylaxis following bloodborne pathogen exposures. The research team will conduct further prescreening of individual records to further refine the list of potential subjects.

8.3 Subject Recruitment

Up to 130 subjects will be recruited from UWHealth. Specific recruitment strategies are as follows (non-comprehensive list):

8.3.1 Recruitment through Employee Health Practice

If the potential subject is agreeable, they will be provided contact information for the study team or the research team will initiate contact.

8.3.2 Email

An email invitation from EHS staff describing the study will be sent to eligible individuals.

8.3.3 Telephone Recruitment

When potential subjects contact the study team, a brief description of the study's purpose and participation requirements will be reviewed. This must also include a statement that participation is voluntary. The screener will ask the caller if s/he has any questions and about interest in participating. After all questions have been answered, the study team member will ask if the potential subject is interested in proceeding to the next step in recruitment for the study (e.g., scheduling a visit to learn more and go through the consent process, or answering some screening questions).]

8.4 Retention Strategies

Strategies for retention include:

- Appointment for the next visit will be set at the end of each visit
- Email visit reminder 3 days prior to visit and day prior if appointment is before 10am or day of visit if visit is at 10am or later.
- Recall reminders for missed appointment. Each participant will be contacted three times by email and then with two phone calls at least 2 days apart.
- Flexible study visit windows and be used with the following limits to accommodate subject schedules.

Time between visits 1 and 2	Not less than 28 days and not more than 60 days
Time between visits 2 and 3	Not less than 28 days and not more than 60 days

8.5 Early Termination and Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

The Principal Investigator (PI) may discontinue or withdraw a subject from the study for the following reasons at her discretion:

- Pregnancy
- Subject non-compliance with study requirements (e.g., study intervention non-compliance)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- If the subject is no longer an appropriate candidate for participation

The following actions must be taken if a subject withdraws, or fails to return for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit by email and phone as in 8.4 above and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject as described in 8.4 above. These contact attempts shall be documented the study file.
- If the subject continues to be unreachable, s/he will be considered to have withdrawn from the study with a primary reason of lost to follow-up. The withdrawn date is the last day of attempted contact.

9.0 STUDY AGENT (STUDY DRUG, DEVICE, BIOLOGIC, VACCINE, ETC.) AND/OR PROCEDURAL INTERVENTION

9.1 Study Agent and Control Description

Study Product

Recombinant hepatitis B vaccine with CpG adjuvant (Heplisav-B, Dynavax)

9.1.1 Source

All study drug will be provided free of charge by Dynavax, Emeryville, CA during the treatment phase.

Dynavax, Emeryville, CA will distribute hepB-CpG to UWHealth PRC. Each shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit, as well as a packing slip. On delivery of the product to the site, the person in charge of product receipt will use departmental procedures for unpacking and storing the vaccine, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature indicator). The contents of the shipment will then be reviewed and verified against the packing slip, and will be documented as instructed at the initiation visit.

If the temperature-monitoring indicator reflects that the cold chain has been broken, the entire shipment must be immediately quarantined. The principal investigator will contact Dynavax for instructions.

9.1.2 Packaging and Labeling

- The vaccine will be supplied as the commercial product and labeled as such.

9.1.3 Preparation

The vaccine will be supplied as a single-dose prefilled syringe.

9.1.4 Storage and Stability

Storage Conditions

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
Do not freeze; discard if the vaccine has been frozen.

9.1.5 Dosing and Administration

HepB-CpG will be supplied as 0.5 mL single-dose, pre-filled syringes. No preparation is required. Administer as follows:

- Visually inspect the syringe for particulate matter and/or discoloration prior to administration. If either of these conditions exist, do not administer
- Gently shake the prefilled syringe
- Identify the deltoid muscle (upper arm) and cleanse the injection site with alcohol
- Insert needle (22 to 25 -gauge 1-inch needle recommended; 1 ½ inch needle recommended for those with BMI ≥ 30) at a 90 degree angle to the skin and inject entire contents of the syringe

intramuscularly. Do not inject the vaccine subcutaneously or intravenously. Care should be taken to avoid administering the injection into or near blood vessels and nerves.
- Monitor the subject for at least 15 minutes post administration]

10.0 STUDY VISITS AND PROCEDURES

10.1 Study Calendar

The procedures performed at each study visit are listed in the table below.

Procedure	Visit 1	Visit 2	Visit 3 End of study/early withdrawal
Visit Window	**Day 0**	**Day 28- 42**	**Day 28-42 following visit 2**
Informed Consent	X		
Review Eligibility Criteria	X		
Demographics[1]	X		
Obtain Medical History[2]	X		
Vital Signs[3]	X	X	X
Vaccine screening	X	X	
Vaccine administration	X	X	
Blood draw		X	X
Adverse Events Review/Assessment		X	X

[1] Age, sex, dates of previous hepatitis B vaccine doses and antiHBs
[2] Self-reported smoking history, diabetes, immunosuppression
[3] vitals as standard of practice at EHS for immunization visit

10.2 Screening and Enrollment

The Screening and Enrollment visits and procedures are described in detail below.

10.2.1 Pre-screening

Potential participants will be identified and invited to participate by EHS staff. Potential participant are UWHealth healthcare workers who have received at least 5 doses of hepatitis B vaccine with aluminum adjuvant and have antiHBs < 10mIU/ml

10.2.2 Informed Consent

Preliminarily eligible subjects will be invited to EHS for informed consent and formal screening. The informed consent process will be conducted following all federal and institutional regulations relating to informed consent. Informed consent will be obtained prior to conducting any study-related activities.

The informed consent process will be performed as follows:
- The principal investigator or a co-investigator will review the informed consent form and discuss the study in detail with the potential research subject.

- The principal investigator or a co-investigator will explain the study, its risks and benefits, what would be required of the research subject, and alternatives to participation.
- The research subject will be given the opportunity to take the informed consent form home so that s/he may discuss it with family members, friends, clergy or others when possible.
- The subject will have the opportunity to ask questions and have all questions answered by the principal investigator or a co-investigator.
- The informed consent document must be signed and dated by the research subject.
- The principal investigator or a co-investigator will review the informed consent document to ensure that all fields that require a response are complete (i.e., checkbox marked yes or no, etc.) as applicable.
- The research subject will be given a copy of the signed and dated informed consent form. The original signed informed consent form is kept the study binder.

10.2.3 Enrollment

A research subject will be defined as “enrolled” in the study when they meet the following criteria:

- The subject has been consented by study staff.
- The subject and study staff have completed all screening documentation.
- The study staff has verified that the subject meets all of the inclusion criteria.
- The study staff has verified that subject meets none of the exclusion criteria.
- The subject has been assigned to the protocol by study staff.
- The subject has scheduled a study visit which can follow the informed consent process described above.

10.2.4 Screen Failure and Re-enrollment

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a possible pregnancy may be rescreened. Rescreened subjects should be assigned a new subject ID number when they are re-screened.

10.3 On-Study/Follow-up Visits

After subjects have been enrolled, the On-Study/Follow-up visit and the procedures performed at each visit are described in detail below.

10.3.1 Visit Number 1

The following activities will be done during visit 1 which can directly follow the informed consent and enrollment phases.

- Limited interview for medical history to collect age, sex, race, ethnicity, and self-reported smoking history, diabetes and immunosuppression. Hepatitis B vaccine history and antiHBs dates, UWHealth department and location will be collected from Agility, the EHS EMR. (research)
- Vitals (per EHS routine)
- Vaccine screening (research)
- Vaccine administration and aftercare (research)

Visit 1 is expected to take about 45 minutes.

10.3.2 Visit Number 2

The following activities will be done during visit 2 which is done 28-42 days after visit 1.

- Vitals (per EHS routine)
- Ask about adverse events following hepB-CpG. Report to VAERS if appropriate (routine)
- Blood draw for antiHBs (research)
- Vaccine screening (research)
- Vaccine administration and aftercare (research)

Visit 2 is expected to take about 30 minutes.

10.3.3 Visit Number 3

The following activities will be done during visit 3 which is done 28-42 days after visit 3.

- Vitals (per EHS routine)
- Ask about adverse events following hepB-CpG. Report to VAERS if appropriate (routine)
- Blood draw for antiHBs (research)
- Dismiss from study participation with information that EHS employee will contact with antiHBs results (research)

Visit 3 is expected to take about 15 minutes.

10.4 Unscheduled Visits

Unscheduled visits will not occur for this study.

10.5 Early Termination/Withdrawal Visit

Subjects who are either withdrawn or terminated early from the study will have one final visit to to follow up regarding adverse events.

11.0 CORRELATIVE | SPECIAL STUDIES

11.1 Biospecimen Collection Guidelines

Standard phlebotomy procedures to collect 3ml in red top with yellow ring and sent to the UWHealth Clinical Lab for antiHBs.

11.2 Assay Methodology

The UWHealth Clinical Laboratory uses a chemiluminescent immunoassay to measure antiHBs.

12.0 DATA COLLECTION, HANDLING, SHARING, AND RECORD KEEPING

12.1 Data Collection

12.1.1 Data Collection Forms

Standardized data collection forms (e.g., source documents, case report forms, standardized assessment forms, etc.) are used to ensure data collected are consistent and compliant with the protocol and IRB application.

Data collection is the responsibility of study team members under the supervision of the Principal Investigator (PI). The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the recorded and reported data. Data will be collected from the participant and the EHS EMR as described in Section 10.

All data collection forms must be completed in a legible manner; any missing data will be explained. Data entry errors will be corrected with a single line through the incorrect entry and the correct data is entered above/near the correction. All changes will be initialed and dated.

Data collection forms are maintained in the subject files and retained as described in Section 12.3: Records Retention.

12.2 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating investigators and their staff. The sponsor will have no access to the study data. This confidentiality is extended to cover testing of biological samples and to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

All study staff engaged in the conduct of this project have completed training on the protection of human subjects and the Health Insurance Portability and Accountability (HIPAA) Privacy Rule. In addition, all key personnel (i.e.., Principal Investigator, individuals involved in identifying/recruiting subjects, obtaining informed consent, or interacting and intervening with subjects) have undergone Good Clinical Practice (GCP) training.

Information about study subjects will be kept confidential and managed according to HIPAA requirements. All subjects will a combined informed consent and HIPAA authorization form that includes specific privacy and confidentiality rights. Study data will be maintained per federal, state, and institutional data policies.

The investigator(s) will ensure that the identities of subjects are protected by using coded subject information. The log of subject identifying information that links subjects to their study-specific identification number will be maintained by the investigator. The log and all study records will be maintained in locked rooms and access will be limited to essential study personnel. Electronic study records/files will be stored on a School of Pharmacy server and accessed via networked computers that are password-protected with access provided only to authorized study personnel.

Authorized representatives of the following groups may need to review this research as part of their responsibilities to protect research subjects: representatives of the IRB and federal oversight agencies, such as the Food and Drug Administration (FDA). The clinical study site will permit access to such records.

Study staff may use e-mail to communicate with research subjects, if the subject has agreed to using email in the Informed Consent form. The information contained in emails will be limited to study visit time and date information and general questions. All emails to subjects will be sent from UW/wisc.edu or uwhealth accounts; personal, home or Gmail email accounts will not be used.

12.3 Records Retention

It is the investigator’s responsibility to retain study essential documents for a minimum period of 7 years following completion of the study per UW-Madison institutional policy, or at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever comes last.

12.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or investigational plan requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the Principal Investigator and study staff to use continuous vigilance to identify and report deviations. The Principal Investigator is responsible for assessing whether the deviation constitutes noncompliance as defined by the reviewing IRB and will report the deviation within the timeframes posted on the HS IRB website of the discovery.

12.5 Publication and Data Sharing Policy

The Principal Investigators will work with the co-investigators to draft a manuscript for publication regarding the findings of this study. All precautions will be taken to avoid identification of an research participant in the publication.

13.0 STUDY ANALYSIS

13.1 Statistical Hypotheses

- **Primary Efficacy Endpoint(s):**
  AntiHBs >10 mIU/ml following two doses of hepB-CpG
  Descriptive statistics will be used to report the result, including number of responders and ratio of responders.

- **Secondary Efficacy Endpoint(s):**
  AntiHBs >10 mIU/ml following two doses of hepB-CpG
  Descriptive statistics will be used to report the result, including number of responders and ratio of responders.

  Proportion of participants who are nonresponders with each risk factor and develop a multivariate model
  Descriptive statistics will be used to report the result for each risk factor, including number of responders and ratio of responders. Multivariate analysis will be used to develop a model.

13.2 Sample Size Justification

In an effort to be fair to all potentially eligible UWHC healthcare workers, we want to offer the hepB-CpG vaccine series to all known eligible individuals (those who have failed to respond to at least 5 doses of hepatitis B vaccine with aluminum adjuvant).

13.3 Subject Population(s) for Analysis

Analyses will include all individuals who received at least one dose of hepB-CpG. We will also do a per-protocol analysis for hepB-CpG one dose and two doses.

13.4 Statistical Methods

Descriptive statistics will be used to report the number and ratio of vaccine responders to both doses and one dose and with regard to known risk factors for hepatitis B vaccine nonresponse. A multivariate model with the risk factors will be developed.

14.0 RISK/BENEFIT ASSESSMENT

14.1 Potential Benefits to the Subjects

The potential benefits to research subjects associated with this study include participants' safety as healthcare providers should they be converted to hepatitis B vaccine responders.

If hepB-CpG has a high response rate, this vaccine could become the preferred vaccine series for nonresponders.

14.2 Known Potential Risks

14.2.1 Known Procedural Risks

Procedure: Risk description(s)

- Blood Draw: The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.

14.2.2 Known Interventional Risks

- HepB-CpG: Risks of hepatitis B immunization include soreness at the injection site, fever, or fainting. Anaphylaxis occurs very rarely. No information regarding hepB-CpG during pregnancy is available.

Hepatitis B immunization is recommended for all healthcare workers at risk for bloodborne pathogens exposure. Repeated series, including the use of hepB-CpG series, is one strategy to convert nonresponders to responders so participation in this study conforms with current immunization recommendations for healthcare providers. (Heplisav-B package insert, Vaccine Information Statement published by the CDC)

15.0 DATA AND SAFETY MONITORING

15.1 Adverse Event (AE) Definition

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

15.2 Serious Adverse Event (SAE) Definition

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it meets any of the following criteria:

- Results in death

- Is life-threatening
- Requires an inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity.
- Results in a congenital anomaly/birth defect.
- A medical event, based on appropriate medical judgment, that is believed to jeopardize the subject and/or requires medical or surgical intervention to prevent one of the outcomes defining a SAE. For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that may not result in hospitalization

15.3 Classification of an Adverse Event

15.3.1 Severity of Event

All AEs will be assessed by the clinician using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, each event searchable using the Safety Profiler website (https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx). For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

Mild (Grade 1)	Events require minimal or no treatment and do not interfere with the subject's daily activities.
Moderate (Grade 2)	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe (Grade 3)	Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
Life Threatening (Grade 4)	The subject was at risk of death at the time of the event.
Fatal (Grade 5)	The event caused death.

15.3.2 Relationship to Study, Study Procedure(s) and/or Study Intervention(s)

For all collected AEs, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related	Clearly related to the study procedures/intervention and other possible contributing factors can be ruled out.
Probably Related	Likely related to the study procedures/intervention and the influence of other factors is unlikely.
Possibly Related	Possibly related to the study procedures/intervention and there are other factors that could be equally likely.
Unlikely to be related	Doubtfully related to the study procedures/intervention and there is another likely cause.
Unrelated	Clearly not related to the study procedures/intervention and/or evidence exists that the event is definitely related to another cause.

15.3.3 Expectedness for Study, Study Procedure(s) and/or Study Intervention(s)

The PI will be responsible for determining whether an AE is expected or unexpected in relation to the study procedures and intervention(s) (as applicable).

For studies not evaluating an investigational drug: An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the clinical protocol, the IRB application, or the informed consent document. The expectedness could be based on study procedures or the characteristics of the patient population.

15.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. AEs will be reported to the Vaccine Adverse Event Reporting System (VAERS) as this is the standard of practice.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after the administration of the study drug and for up to 30 days after the date of the last dose of study drug or at Visit 3. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution, stabilization, or completion of study participation.

15.5 Reporting AEs and SAEs

15.5.1 Reporting AEs

The Principal Investigator will be notified regarding any AE reported by a participant. AEs will be reported to the Vaccine Adverse Event Reporting System (VAERS) as this is the standard of practice.

15.5.2 Reporting SAEs

The investigator will i report to the IRB any SAE, whether or not considered study intervention-related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. The report will be made within the timeframes posted on the HS IRB website.

All SAEs will be followed until satisfactory resolution or until the principal investigator deems the event to be chronic or the subject is stable.

The investigator will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible and within the timeframes posted on the HS IRB website after the investigator's initial receipt of the information.

15.6 Unanticipated Problems

An unanticipated problem (UP), as defined by the DHHS Office for Human Research Protection (OHRP), is any incident, experience, or outcome that meets all of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the informed consent documents) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents, product labeling, or package insert.
- The incidence, experience, or outcome is related or probably related to participation in the research study. “Probably related” means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

The investigator will report UPs to the reviewing IRB within the timeframe posted on the HS IRB website. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol, informed consent documents, or other corrective actions that have been taken or are proposed in response to the UP.

15.7 Protocol Deviations

Refer to section 12.4.

15.8 Data Safety Monitoring Plan

The study involves a small number of participants, is conducted at only one site, and/or the range of possible study events having an important impact on risks and benefits to participants is narrow, the principal investigator (PI) will perform the monitoring functions.

The type of data or events to be captured under the monitoring plan: Reported adverse events by participants at visits 2 and 3. Study accruals, protocol deviations, protocol violations, and unanticipated problems will also be monitored.

The name(s) of the person(s) who will be responsible for monitoring the data collected (i.e. study accruals, protocol deviations, protocol violations, unanticipated problems, adverse events) and their respective roles (e.g. investigators, research sponsor): Mary Hayney, Principal Investigator, is responsible.

The frequency of assessments/analysis of data or events captured by the monitoring plan (e.g. a periodic time interval or after a specific number of participants are enrolled): Monitoring will be done monthly.

The time frame for reporting unanticipated problems, adverse events, protocol deviations, and protocol violations. These will be reported by study personnel to the PI as they are discovered. The PI will report them to the IRB as within the timeframes posted on the HS IRB website. Reports to VAERS or FDA will be done at the same time.

Plans to monitor adherence to the IRB-approved protocol and assure the validity and integrity of data: The data collection forms and adverse event descriptions will be reviewed by the PI monthly.

16.0 Economic Burden to Subjects

Subjects will not have to pay for study procedures. The subject will not be billed by the healthcare system or their health insurance company for any costs related to a study procedure.

16.1Facilities and Locations

Study visits will take place at Employee Health Services.

16.2 Feasibility of Recruiting the Required Number of Subjects

Employee Health Services has responsibility for the occupational health and safety of the over 15,000 UWHealth employees. The staff estimates that about 100 individuals will qualify for this study.

16.3 Principal Investigator Considerations

15.8.1 Time Devoted to Conducting the Research

The Principal Investigator is a professor in the School of Pharmacy. She has dedicated time for research and is committed to completing this research study.

16.4 Process for Informing Study Teams

The study team has completed three research studies already. They have a history of efficient conduct of research studies. The Principal Investigator will provide the protocol and in-person training or training via video conference on the protocol and the consent process. A review of all study procedures will be included in the training.

16.5Availability of Medical or Psychological Resources

Not applicable

17.0 REFERENCES

1. Jackson S, Lentino J, Kopp J, et al. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. Vaccine. 2018;36(5):668-674.
2. Hyer RN, Janssen RS. Immunogenicity and safety of a 2-dose hepatitis B vaccine, HBsAg/CpG 1018, in persons with diabetes mellitus aged 60–70 years. Vaccine. 2019;37(39):5854-5861.
3. Janssen RS, Mangoo-Karim R, Pergola PE, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a

licensed hepatitis B vaccine in patients with chronic kidney disease. Vaccine. 2013;31(46):5306-5313
4. Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2018;67(RR No.-1):1-31.

16.0 18.0 APPENDICES

18.1 Data collection form (appendix A)

Data Collection Form
Subject ID
Date of birth
UWH Dept
UWH location
Sex
Race
Ethnicity
Diabetes yes/no
Smoking yes/no/past
Immunosuppression yes/no
HepB dose 1
HepB dose 2
HepB dose 3
antiHBs date
antiHBs result
HepB dose 4
antiHBs date
antiHBs result
HepB dose 5
HepB dose 6
antiHBs date
antiHBs result
HepB-CpG dose 1
antiHBs date
antiHBs result
HepB-CpG dose 2
antiHBs date
antiHBs result