DV2-HBV-24

STATISTICAL ANALYSIS PLAN

An Open-label, Single Arm Study, Evaluating the Immunogenicity and Safety of HEPLISAV-B® in Adults With End-Stage Renal Disease Undergoing Hemodialysis

NCT03934736

Amendment 2: Version 2.1: 15 September 2020
Amendment 1: Version 2: 02 September 2020
Original Version: Version 1: 25 February 2020

Dynavax Technologies Corporation

STATISTICAL ANALYSIS PLAN

Study Title:	An Open-label, Single Arm Study, Evaluating the Immunogenicity and Safety of HEPLISAV-B® in Adults with End-Stage Renal Disease Undergoing Hemodialysis
Protocol Identifier:	DV2-HBV-24
Phase	Phase 1
Investigational Product:	HEPLISAV-B®
Indication:	Prevention of Hepatitis B Virus Infection
Sponsor:	Dynavax Technologies Corporation 2100 Powell Street Suite 900 Emeryville, CA 94608 United States of America
Reference Numbers:	United States IND 12692

Amendment 2:	Version 2.1: 15 September 2020
Based on Protocol Version:	Amendment 4: 17 April 2020
Amendment 1:	Version 2: 02 September 2020
Original Version:	Version 1: 25 February 2020

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND TERMS

Abbreviation or Term	Definition
AE	adverse event
AESI	adverse event of special interest
AMI	acute myocardial infarction
anti-HBs	antibodies against hepatitis B surface antigen
ATC	anatomical therapeutic chemical
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
eCRF	electronic case report form
EOS	End of Study (visit)
FDA	United States Food and Drug Administration
GMC	geometric mean concentration
GRF	glomerular filtration rate
HBV	hepatitis B virus
MAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat (population)
ODS	output delivery system
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System of Organ Class
SPR	seroprotection rate
TEMAE	treatment emergent medically-attended adverse event
TFL	tables, figures, listings

Abbreviation or Term	Definition
WHO	World Health Organization

1.0 INTRODUCTION

This statistical analysis plan contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the safety and immunogenicity in patients on hemodialysis as described in Protocol DV2-HBV-24 (Amendment 4: 17 April 2020): "An Open-label, Single Arm Study, Evaluating the Immunogenicity and Safety of HEPLISAV-B® in Adults With End-Stage Renal Disease Undergoing Hemodialysis".

2.0 STUDY OVERVIEW

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

In this study, the safety and immunogenicity in patients on hemodialysis will be evaluated further to investigate an optimal dosing regimen for this patient population. An optimal dosing regimen for HEPLISAV B that induces higher rates of protection, earlier onset of protective immunity, and longer duration of protection in hemodialysis patients would be an important advance in vaccine development given the ongoing risk of HBV infection in the hemodialysis setting and consequences of HBV infection in this highly compromised patient population.

This study will consist of a 4-injection (0.5 mL per injection) regimen of HEPLISAV-B at Weeks 0, 4, 8, and 16. It is anticipated that a fourth dose of HEPLISAV-B will provide improved seroprotection [redacted] for hemodialysis patients. Eligible subjects will receive HEPLISAV-B at Weeks 0, 4, 8 and 16 and will be followed through Week 68 (Figure 2-1). The study is designed to evaluate the immunogenicity over the 20-week period and safety over the 68-week period.

Figure 2-1: Study Flow Diagram

	Screening	HEPLISAV-B Treatment				Follow-Up			
Day:	-28	1	29	57	113	141	197	295	477
Week:	-4	0	4	8	16	20	28	42	68
	N = 100	**X**	**X**	**X**	**X**				

X = study injection

For the primary immunogenicity endpoint, SPR will be evaluated at Week 20, 4 weeks after the last injection, [redacted]

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

- To evaluate the safety of HEPLISAV-B with respect to clinically significant adverse events
- To evaluate the immunogenicity induced by HEPLISAV B at Week 20 as measured by the seroprotection rate (SPR)

3.2 Secondary Objectives

- To evaluate the immunogenicity of HEPLISAV-B as measured by the percentage of subjects with anti-HBs concentration ≥100 mIU/mL
- To evaluate the immunogenicity of HEPLISAV-B as measured by the anti HBs geometric mean concentration (GMC)
- To evaluate the immunogenicity of HEPLISAV-B at each study visit through 20 weeks after the first dose of study vaccine as measured by the SPR

4.0 ANALYSIS VARIABLES

Primary Endpoints

- Proportion of subjects with treatment-emergent MAEs
- Proportion of subjects with treatment-emergent SAEs, acute myocardial infarctions (AMIs), or deaths
- Proportion of subjects with treatment-emergent immune-mediated adverse events of special interest (AESIs)
- SPR at Week 20

Secondary Endpoints

- Proportion of subjects with anti-HBs concentration ≥100 mIU/mL
- Anti-HBs geometric mean concentration (GMC)
- SPR at each study visit through 20 weeks after the first dose of study vaccine

5.0 SAMPLE SIZE CONSIDERATIONS

The sample size calculation is based on approximately 100 subjects in the per-protocol population. With an expected 15% loss to follow up prior to week 20, approximately 115 subjects will be enrolled. This sample size would allow estimating immunogenicity response at the following accuracy levels depending on the observed immunogenicity responses (Table 5-1).

Table 5-1: Sample Size Estimates

N	If Observed Immunogenicity Response is	Width of the Resulting 95% Confidence Interval[a]	Lower Limit of the Resulting 95% Confidence Interval[a]
100	80.0%	0.165	70.8%
100	86.0%	0.145	77.6%
100	90.0%	0.127	82.4%
100	95.0%	0.096	88.7%

N = number of subjects

[a] Calculation based on exact method (Clopper-Pearson)

Note: Approximately 115 subjects will be enrolled to meet the N of 100 evaluable subjects in the per-protocol population.

6.0 ANALYSIS POPULATIONS

6.1 Enrolled Population

The enrolled population is defined as all patients who enrolled in the study.

6.2 Safety Population

The safety population will comprise all subjects who received at least 1 study injection, excluding subjects who have no on-study safety data.

6.3 Efficacy Population

The per-protocol (PP) population for the immunogenicity analysis will comprise all subjects who receive all study injections, have no major protocol deviations (see Section 9.2), and have anti-HBs levels obtained within the study visit window at Week 20. PP population is defined for Week 20 visit, but will be used in analyses at other visits where applicable.

The modified intent-to-treat (mITT) population for the immunogenicity analysis will comprise all eligible subjects who receive at least 1 study injection and have at least 1 post-injection immunogenicity evaluation.

7.0 DEFINITIONS, COMPUTATIONS, AND CONVENTIONS

7.1 Definitions and Computations

Study Day

Study day will be calculated in reference to the date of first injection (Day 1). For visits conducted on or after the first injection date, study day is calculated as (visit date – first injection date + 1). For visits conducted before the first injection date, study day is calculated as (visit date – first injection date). There will be no Day 0.

Date of First Injection and Date of Last Injection of Study Vaccine

The date of the first injection of study vaccine is defined as the date a patient receives the first injection of the study vaccine. The date of the last injection of study vaccine is the date a patient receives the last injection of the study vaccine.

Treatment-Emergent Period

In this trial, only medically attended adverse events (MAEs), AEs for which a subject seeks medical attention at a doctor's office, clinic, study site, emergency room, or is hospitalized, will be collected.

The reporting period for all non-serious MAEs begins at the time of the first study injection (Day 1) through EOS Visit. All MAEs will be captured on the MAE eCRF.

Any SAE that occurs from the time the consent is signed through EOS Visit, whether or not the SAE is related to the study treatment, must be reported.

The treatment-emergent period is defined as time from the first study injection through EOS visit.

7.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated by the following SAS code:

  If only year of birth is given, then Age = (Year of Screening – Year of Birth). Otherwise

  ```
  age = floor ((intck('month', birth_date, consent_date) -
  (day(consent_date) < day(birth_date))) / 12);
  ```

- 1 pound = 0.454 kg
- 1 inch = 2.54 cm
- Missing safety data will not be imputed unless otherwise specified.
- For immunogenicity results, anti-HBs concentrations, are obtained using the Elecsys Anti-HBs II assay. For concentration reported as <value, half of the value will be used in calculation. For concentration reported as >value, value+1 will be used in calculation.
- For safety analyses, percentages will be calculated based on the number of patients in the analysis population.

- For by-visit observed data analyses, percentages will be calculated based on the number of patients with nonmissing data as the denominator unless otherwise specified.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, and range (minimum and maximum).
- For categorical endpoints, the summary statistics will include counts and percentages.
- MAEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17 or higher.
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

7.3 Rules for Missing Data

Missing data will not be imputed, except for missing date information for AEs and concomitant medications. The imputed dates will be used to determine the treatment-emergent period. For AEs with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the AE will be considered treatment emergent by default.
The following rules will be applied to impute partial dates for AEs:

- If start date of an AE is completely or partially missing, impute as follows:
  - If both month and day are missing and year = year of first dose date, then set to first dose date.
  - If both month and day are missing and year ≠ year of first dose date, then set to January 1.
  - If day is missing and month and year = month and year of first dose date, then set to first dose date.
  - If day is missing and month and year ≠ month and year of first dose date, then set to first of the month.
  - If start date is completely missing and AE end date is on or after the first dose date, set to first dose date.
  - If start date is completely missing and AE end date is prior to the first dose date, do not impute an AE start date.
- If end date of an AE is partially missing, impute as follows:
  - If both month and day are missing, then set to December 31.
  - If only day is missing, then set to last day of the month.
  - If end date is completely missing, do not impute.

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

- If start date of a medication is partially missing, impute as follows:
  - If both month and day are missing, then set to January 1.
  - If only day is missing, then set to the first of the month.
- If end date of a medication is partially missing, impute as follows:
  - If both month and day are missing, then set to December 31.
  - If only day is missing, then set to last day of the month.
- If start date or end date of a medication is completely missing, do not impute.

Listings will show the original date information without imputation, but derived parameters (TEAE indicator and duration of AE) will be flagged to indicate the type of imputation performed.

8.0 TIMING OF ANALYSES

A preliminary analysis may be performed to assess the primary immunogenicity objective of the SPR at Week 20 after approximately 50 subjects have completed their Week 20 visit (see Section 9.9).

A final immunogenicity report with data up to Week 20 will be produced including demographics, baseline characteristics, medical history, vaccine exposures, immunogenicity data and post-injection reaction data. These data will be verified as complete and final following database lock process, and major protocol deviations up to Week 20 have been identified. Safety analysis of MAEs and concomitant medications with non-fully validated and non-final data will be included in this report. Status of these data will be footnoted where applicable.

Final analyses will be carried out after the last participant has completed their last study visit, the study database has been authorized by Dynavax as complete and final, and major protocol deviations have been identified. Any changes to the frozen data in the final immunogenicity report with data up to Week 20 will follow post database lock change process according to BRK-SOP[redacted] Clinical Study Database Lock-Unlock Authorization.

9.0 STATISTICAL METHODS

This is an open-label, single arm study, evaluating the immunogenicity and safety of HEPLISAV-B® in adults with end-stage renal disease undergoing hemodialysis. No pre-specified hypothesis testing will be performed. All analyses of demographics and baseline

characteristics, medical history, vaccine exposure, immunogenicity and safety will be summarized in a descriptive manner.

All confidence intervals are two-sided 95% confidence intervals unless otherwise specified.

In general, continuous variables will be summarized by sample size, mean, standard deviation, median, quartiles, minimum and maximum, and categorical variables will be summarized by counts and percentages. All data processing, summarization, and analyses will be performed using SAS Version 9.3 or higher. Specifications for tables, graphs, and data listings will be provided in the tables, figures, listings (TFL) specifications document if needed.

9.1 Patient Disposition

Patient disposition will be summarized for all enrolled patients including patients in the safety, PP and mITT populations and patients discontinuing the study along with the reasons for discontinuation (as documented on the case report form Study Completion).

A listing of patients discontinuing the study after enrollment will be produced.

9.2 Protocol Deviations

For the purpose of selecting subjects for the per-protocol population, a major protocol deviation is defined as one of the following:

- not meeting one or more enrollment criteria,
- anti-HBs serum sample obtained outside protocol specified visit window 4 weeks following the fourth study injection (Week 20 ± 7 days)
- 28 days prior to Injection 1 and through Week 20: received prohibited concomitant medications comprising systemic corticosteroids, other immunomodulators or immune suppressive medications (with the exception of inhaled steroids), immunoglobulin, DNA plasmids or oligonucleotides, or any other investigational medication.

A listing of patients with major protocol deviations will be provided describing their deviations. Any exclusions from analysis populations due to protocol deviations and other reasons will also be listed.

9.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed by subject and summarized. Descriptive summary statistics (sample size, mean, median, SD, and range, when appropriate) will be provided for the continuous variables such as age, weight, height and BMI. Count and percentage will be reported for categorical variables such as sex, race, and ethnicity.

Listings will be provided for these parameters for all patients.

9.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Version 201506 or higher). Prior medications are drugs and therapies used before the first dose date. Medications or therapies are considered concomitant if exposure occurs after the first dose date. The number and percentage of patients with concomitant medications will be presented alphabetically by anatomical therapeutic chemical (ATC) class and by decreasing order of frequency of preferred terms within each ATC class for the safety population. Patients taking the same medication multiple times will be counted once per medication.

All medications recorded on the case report form will be listed.

9.5 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA V17.0 or higher). Medical history will be summarized by System of Organ Class (SOC) and Preferred Term (PT) for safety population. All medical history data will be provided in a listing.

9.6 Immunogenicity Analyses

Immunogenicity data will be analyzed based on the PP population by visit for all visits through 20 weeks with immunogenicity data collected.

The SPR will be estimated. The associated 2-sided 95% confidence interval will be calculated using the Clopper-Pearson method.

Proportion of subjects with anti-HBs concentration ≥100 mIU/mL and associated 2-sided 95% confidence interval will also be calculated using Clopper-Pearson methods.

Anti-HBs geometric mean concentration (GMC) and associated 2-sided 95% confidence interval will be calculated by exponentiating the mean and confidence interval in log10 of the anti-HBs concentration assuming Normal distribution.

Analyses based on the mITT population may also be conducted.

9.7 Safety Analyses

Vaccine exposure and compliance will be summarized descriptively for safety population.

Safety data will be analyzed descriptively and will be based on the safety population. The most important safety parameters will be presented for all sites combined. Summary statistics will be used to describe the incidence of all post-injection reactions and MAEs (including SAEs, deaths, AMIs, and AESIs; further details regarding safety reporting of AMIs and AESIs are provided in Protocol Section 9.4.7.2). The incidence and proportion of post-

injection reactions and MAEs will be summarized. MAEs will be coded using the MedDRA SOC and PT.

The incidence of AMIs and major adverse cardiovascular events will be analyzed in subjects initiating hemodialysis after enrollment in the study and in subjects undergoing hemodialysis at the time of enrollment in the study.

The treatment-emergent period is defined in Section 7.1.

Local and systemic post-injection reactions are to be recorded on the subject diary. If they persist longer than 7 days (i.e., 8 days or longer) and are medically attended (i.e., subject seeks medical attention), they should also be recorded and reported as MAEs, per protocol Section 10.2. The severity of the post-injection reactions will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Local reactions include redness, swelling and pain, and systemic reactions include malaise (not feeling well), headache, myalgia (body aches) and fatigue (feeling tired).

Post-injection reactions reported from day 1 to day 7 will be summarized by maximal severity and by vaccine group. The severity of local reactions, including redness and swelling will be categorized as none, 1 to ≤10mm, >10mm to ≤25mm, >25 to ≤50mm, >50 to ≤100mm and >100mm (severe local reactions).

The severity of pain and systemic reactions including malaise, headache, myalgia and fatigue occurring up to 7 days after each vaccination will be categorized as none, mild (no interference with activity), moderate (some interference with activity), severe (significant, prevents daily activity).

Temperature will be categorized as <38°C (no fever), 38-38.4°C, 38.5-38.9°C, 39-40°C and >40°C.

Each local and systemic reaction will also be categorized as none vs. any.

All MAEs will be coded to preferred term and system organ class using MedDRA 17.0 or higher. An MAE that started or increased in severity during the treatment-emergent period will be considered a TEMAE. Severity of TEMAEs and laboratory abnormalities will be graded based on the United States Food and Drug Administration's (FDA) Guidance for Industry: Center for Biologics Evaluation and Research (CBER) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (with the exception of malaise, which will be graded per CTCAE v4.03), with the modification that, by convention, all fatal MAEs will be graded as Grade 5 (Fatal). All MAEs not listed in the CBER toxicity grading scale will be graded as shown in Table 9-1.

Table 9-1: Grading Scale for Medically-Attended Adverse Events Not Included in the CBER Guidance on Toxicity Grading for Healthy Volunteers in Vaccine Clinical Trials

MAE Severity	Definition
Grade 1 – Mild	No interference with activity
Grade 2 – Moderate	Some interference with activity, not requiring medical intervention
Grade 3 – Severe	Prevents daily activity and requires medical intervention
Grade 4 – Potentially life-threatening	Emergency room visit or hospitalization
Grade 5	Death

A study vaccine-related TEMAE is defined as any TEMAE with at least a possible relationship to the study vaccine as assessed by the investigator or that is missing the assessment of causal relationship whose relationship to the study vaccine could not be ruled out.

Patients with multiple occurrences of events for a given preferred term, system organ class, or overall will only be counted once at the worst severity and strongest relationship to study vaccine for each preferred term, system organ class, and overall, respectively. MAEs that are continuous but change in grade, relationship, or seriousness will be counted as 1 event. TEMAEs of unknown severity will be categorized separately. A TEMAE of unknown relationship will be considered to be probably related to study vaccine.

Incidences and percentages of subjects experiencing each reaction will be presented by severity. Summary tables showing the occurrence of any local or systemic reaction overall and at each time point will also be presented.

Tabular summaries including numbers and percentages of the following adverse events will be provided:

- All TEMAEs
- TEMAEs of Grade 3 or above
- All treatment-related MAEs
- Treatment-related MAEs of Grade 3 or above
- All treatment-emergent SAEs
- All treatment-related SAEs
- All TEMAEs leading to premature discontinuation of HEPLISAV
- All SAEs leading to death
- All AMI

- All AESI

Listings will be provided for all TEAEs.

9.8 Other Analyses

No other analyses are planned.

9.9 Interim Analysis

A preliminary analysis may be performed to assess the primary immunogenicity objective of the SPR at Week 20 after approximately 50 subjects have completed their Week 20 visit. The scope of the analysis is limited to the estimates of the SPR at Week 20. Limited demographic and safety data may be presented along with the SPR estimates. The list of analyses for this interim analysis will be highlighted in the Table of Contents of Tables, Figures and Listings document.

9.10 Reporting Output

All outputs will be produced using SAS® version 9.3 or later. The REPORT procedure will be used to produce all tables and listings whenever possible. The SGPLOT procedure will be used to produce all figures whenever possible. All statistical appendices (supportive SAS output) will be output directly from the appropriate SAS procedure.

Post-text tables, listings, and statistical appendices will be produced as RTF files using output delivery system (ODS) and Times New Roman or a similar font size 8 or larger. Data will be presented in RTF tables with data in individual cells. Figures will be produced as RTF files using ODS and simplex font. For all outputs, the page numbering will be applied to ensure that when the RTF files are combined, the page numbering remains fixed.

All tables, listings and statistical appendices will be produced to landscape orientation and will be incorporated into a Word 2010 or later document (margins: top 1.5”, left, right and bottom 1”) using 8pt font or larger.

Vaccine name for tables and figures will be as follows:

- HEPLISAV-B

10.0 REVISION HISTORY

Version	Date	Author	Comments/Rationale for Revision
1.0	25FEB2020	[redacted]	New Document
2.0	02SEP2020	[redacted]	Update for Protocol Amendment 4
2.1	15SEP2020	[redacted]	COVID-19 Specific Update [1] on Major Protocol Deviations/PP Population definition: "vaccine given outside protocol specified visit window at Weeks 4, 8 and 16 (± 7 days)" are not Considered as Major Protocol Deviations for PP Population Exclusion Purpose.

11.0 REFERENCES

[1] FDA Guidance for Industry: Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, June 2020
https://www.fda.gov/media/139145/download

12.0 LIST OF TABLES

List of tables will be provided in a separate Table of Contents of Tables, Figures and Listings document.

13.0 LIST OF FIGURES

List of figures will be provided in a separate Table of Contents of Tables, Figures and Listings document.

14.0 LIST OF PATIENT DATA LISTINGS

List of listings will be provided in a separate Table of Contents of Tables, Figures and Listings document.