**Date:** April 20, 2020

**Title:** Response to the HEPLISAV-B Hepatitis B Vaccine in Chronic Lymphocytic Leukemia (CLL) Patients that are Treatment Naïve or Receiving Bruton's-tyrosine Kinase Inhibitor (BTK-I) Therapy

Other identifying words: Hepatitis B vaccine, CLL, BTK-inhibitor, Ibrutinib, Acalabrutinib

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| Subjects of Study: | Number | Sex | Age range |
|---|---|---|---|
| Subjects: | 108 | Either | Ages 18 and older |

| | |
|---|---|
| Project involves ionizing radiation? | No |
| Off-site project? | No |
| Multi-institutional project? | No |
| DSMB involvement? | Yes |

## 1. PRÉCIS

This study aims to determine the HEPLISAV-B hepatitis B vaccine efficacy in chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) patients that are treatment naïve or receiving Bruton's-tyrosine kinase inhibitor (BTK-I) therapy. (Note: Since CLL and SLL are considered the same disease, CLL/SLL will be referred to as CLL hereafter, unless otherwise specified).

**Key Eligibility Criteria:**

a. Diagnosis of CLL

b. Cohort 1: Treatment naïve CLL or SLL patients

c. Cohort 2: Subjects must be receiving ibrutinib monotherapy for at least 6 months prior to administration of the first vaccine dose

d. Cohort 3: Subjects must be receiving acalabrutinib monotherapy for at least 6 months prior to administration of the first vaccine dose

e. No known active or past hepatitis B infection

f. No history of prior hepatitis B virus vaccination (approved or investigational)

g. Age greater ≥18 years.

h. ECOG performance status of 0-1

**Design:**

Patients with CLL will enroll on the study for the purpose of determining the HEPLISAV-B vaccine efficacy in patients who are treatment naïve ore receiving BTK-I therapy. A series of 2 doses of HEPLISAV-B will be given on a 0- and 3- month schedule by intramuscular injection. Subjects will be followed at regular intervals and receive serologic response assessment following completion of the HEPLISAV-B vaccine series (6 months after the first vaccine administration).

**Study Objectives:**

**Primary Objective:**

a) Determine the rate of hepatitis B seroprotective titer achievement (anti-HBs ≥10mIU/mL) following completion of the HEPLISAV-B 2-dose vaccine series (6 months after the first vaccine administration) in the following populations:

- CLL patients who are treatment naïve (n=54)
- CLL patients receiving treatment with ibrutinib (n=27)
- CLL patients receiving treatment with acalabrutinib (n=27)

**Secondary Objective:**

a) Determine the safety and tolerability of the HEPLISAV-B vaccine among CLL patients who are treatment naïve or receiving BTK-Is (ibrutinib or acalabrutinib).

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## 2. OBJECTIVES

**Primary Objective:**

a) Determine the rate of hepatitis B seroprotective titer achievement (anti-HBs ≥10mIU/mL) following completion of the HEPLISAV-B 2-dose vaccine series (6 months after the first vaccine administration) in the following populations:
   - Chronic Lymphocytic Leukemia (CLL) patients who are treatment naïve (n=54)
   - CLL patients receiving treatment with ibrutinib (n=27)
   - CLL patients receiving treatment with acalabrutinib (n=27)

**Secondary Objective:**

a) Determine the safety and tolerability of the HEPLISAV-B vaccine among CLL patients who are treatment naïve or receiving a Bruton's-tyrosine kinase inhibitor (BTK-I) (ibrutinib or acalabrutinib).

**Exploratory Objectives:**

a) Compare HEPLISAV-B vaccine response rates in patients on BTK-I treatment (ibrutinib and acalabrutinib) to response rates in treatment naïve CLL patients.
b) Compare HEPLISAV-B vaccine response rates between patients on ibrutinib and patients on acalabrutinib.
**c)** Determine the kinetics of vaccine response by assessing serologic response at two different time points (3- and 6- months following the first vaccination).

## 3. BACKGROUND

### 3.1. Clinical Background

This study aims to determine the HEPLISAV-B hepatitis B vaccine efficacy in CLL/SLL patients that are treatment naïve or receiving BTK-I therapy.

Immune dysregulation is a hallmark of CLL, making these patients particularly vulnerable to infectious complications. CLL-related complications (infections and second cancers) remain a major cause of death in patients with CLL.[1] The implementation of vaccination strategies provides the opportunity to deliver high-value, cost-effective care interventions. Surprisingly, to date there is little evidence available to guide vaccination in immunocompromised individuals with cancer. Published reports advocate for the administration of the hepatitis B vaccine series to patients with hematologic malignancies[2,3], however it is unknown how effective the vaccine

is in protecting immunocompromised patients with CLL against hepatitis. Looking at other vaccines, the influenza vaccine has previously been studied in CLL, however reported vaccine response rates (VRRs) vary widely with 15-63% of patients achieving seroprotective titers following vaccination.[4,5] Moreover, influenza is a unique vaccine owing to the fact that it is given annually to patients. Despite frequent iterations to the influenza vaccine based on which strains are projected to be most prevalent in any given year, subjects may have pre-existing immunity due to previous exposure and/or vaccination. Serologic responses following influenza vaccine administration may therefore be a reflection of an anamnestic 'recall' effect rather than development of de-novo immunity. The hepatitis B vaccine was FDA approved in 1981[6], thus many patients with CLL born prior to 1981 have not yet been exposed to the vaccine. The hepatitis B vaccine is therefore an ideal candidate to study vaccine immune responses in CLL patients.

The advent of BTK-Is (ibrutinib and acalabrutinib) has revolutionized the treatment of CLL in recent years, providing a targeted treatment approach that improves long-term outcomes and limits toxicities for these patients.[7] Unlike chemo-immunotherapy that is given for a limited amount of time, CLL patients typically remain on daily BTK-I therapy for many months or even years.[7] Ibrutinib results in partial reconstitution of humoral immunity in patients with CLL, however it targets B cell receptor (BCR) signaling that is critical in normal B lymphopoiesis and serum immunoglobulin G levels remain decreased during treatment.[8] Seroconversion and subsequent host immunity after vaccine administration is reliant on an effective B-cell response and it is uncertain whether BTK-Is interfere with vaccine responses. Our group conducted a study investigating the influenza vaccine in 19 CLL patients treated with ibrutinib, demonstrating that mounting an immune response to the influenza vaccine is possible with BTK-I treatment (VRR 26%).[9] Some aspects of humoral immunity appear to be positively affected by ibrutinib therapy. A consistent increase in IgA has been observed in clinical trials of ibrutinib.[10] The change in IgA appears to be clinically relevant in a phase 2 study, patients with greater improvements in IgA developed fewer infections.[11] In addition, preclinical studies have demonstrated that BTK-Is may improve immune function and surveillance by polarizing T cells towards a Th1 predominant phenotype. This Th1 polarization is accompanied by an increase in Th1-mediated cytokines (e.g. IFN-$\gamma$). Additionally, BTK-Is attenuate the expression of T cell activation and pseudoexhaustion markers (HLA-DR and CD39) on T cells, conceivably causing a shift toward healthier effector T cells.[12] Taken together, these effects may not only decrease infection risk, but may also enhance the efficacy of vaccines and immunotherapies to treat CLL.[13-15]

This study will determine the HEPLISAV-B vaccine response rate in two large and clinically relevant CLL patient populations, including subjects who are (1) treatment naïve and (2) treated with a BTK-I. The resulting clinical findings have the potential to inform patients and clinicians about the yield and ideal timing of vaccine administration (prior to, or during BTK-I therapy) and may therefore change clinical practice of hepatitis B vaccine administration to CLL patients.

### 3.2. Indications for Hepatitis B Vaccination

The most recent guidelines from the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) recommend providing information to all adults regarding the health benefits of hepatitis B vaccination, including risk factors for HBV infection and persons for whom vaccination is recommended. The recommendation from the ACIP is to vaccinate all adults who report risks for HBV infection and to vaccinate all adults requesting protection from HBV infection, without requiring them to acknowledge a specific risk factor.[2] HEPLISAV-B is approved for adults age 18 or older. Although the vaccine is not specifically studied in immunocompromised patients there is no contraindication. HEPLISAV-B will be provided with a modified dosing schedule at 0 and 3 months (as compared to 0 and 1 months listed in the package insert). The modified dosing schedule is not expected to compromise safety or efficacy of the vaccine. Please refer to section 14.2 for more details and regulatory considerations.

Current indications for the Hepatitis B vaccine in adults ≥18 years of age include[2]:

- Sexually active individuals with multiple sex partners and homosexual or bisexual males
- Household contacts of patients with hepatitis B
- Injection drug users
- Health care workers
- Patients on chronic hemodialysis
- Patients with chronic liver disease
- Patients with HIV
- Patients with diabetes
- Individuals traveling to areas with intermediate to high levels of HBV infection

### 3.3. Summary of Clinical Safety

A brief summary of safety data from the HEPLISAV-B (Hepatitis B Vaccine [Recombinant], adjuvanted) vaccine is provided in the table below. A large Phase III, multicenter, randomized double-blinded trial has already established safety as well as superior vaccine response rates of HEPLISAV-B compared to Engerix-B, another licensed Hepatitis B vaccine, in healthy adults.[16] Most solicited local adverse reactions and systemic adverse events seen with HEPLISAV-B were considered by the subjects as mild and self-limiting and did not last more than 7 days. There rate of serious adverse events (SAEs) (prevents daily activity and requires treatment) was 3.9% with no reported vaccine-related SAE in a large trial investigating the safety of HEPLISAV-B.[16] The most frequently reported vaccine related adverse events (VRAEs) in subjects receiving HEPLISAV-B are listed in the following table[16,17]:

| Rates of Local and Systemic Adverse Reactions within 7 days of receiving HEPLISAV-B | | |
|---|---|---|
| **Local** | **Dose 1 (n=1952) (%)** | **Dose 2 (n=1905) (%)** |
| Soreness | 23.7 | 22.8 |
| Redness | 0.9 | 0.7 |
| Swelling | 0.9 | 0.6 |
| **Systemic** | | |
| Fatigue | 12.6 | 10.8 |
| Headache | 11.8 | 8.1 |
| Malaise | 7.7 | 7 |
| Myalgia | 8.5 | 6.4 |
| Fever | 0.6 | 0.6 |

### 3.4. Clinical and Scientific Justification

This study aims to provide critical information to clinicians and patients about the utility and feasibility of the hepatitis B vaccine series administration in CLL patients who are treatment naïve or receiving BTK-I therapy.

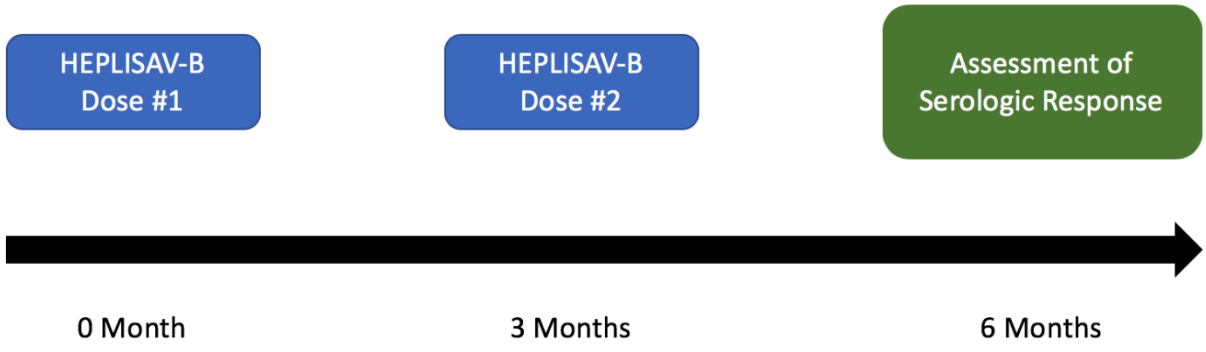
Although the hepatitis B vaccine is not directly indicated for patients with CLL, high-risk patients (including immunocompromised patients with HIV, diabetes mellitus and chronic liver disease)

should receive hepatitis B vaccination.[2] Immune dysregulation is a hallmark of CLL and these patients are therefore considered immunosuppressed. One could argue that unvaccinated CLL patients are likely to benefit from protection against hepatitis B. Additionally, the CDC ACIP recommends vaccination for all adults requesting protection from HBV infection, without requiring them to acknowledge a specific risk factor.[2] In summary, vaccination of CLL patients against hepatitis B can be considered as part of supportive care.

Finally, the search for a cure of CLL has sparked interest in combining BTK-Is with immunotherapies. While clinical trials combining BTK-Is and immune checkpoint inhibitors are ongoing, little is known about the impact of BTK-I therapy on immune responses. Vaccination with the hepatitis B vaccine therefore not only provides a means to reduce infectious complications but also add to the scientific basis for immunotherapy approaches in combination with kinase inhibitors.

## 4. STUDY DESIGN

Patients with CLL will enroll on the study for the purpose of determining the HEPLISAV-B vaccine efficacy in patients who are treatment naïve or receiving BTK-I therapy. A series of 2 doses of HEPLISAV-B will be given on a 0 and 3 month (+/- 15-days window) schedule by intramuscular injection. Subjects will be followed for a total of 6 months and receive assessment of serologic response 6 months (- 15-day s, +180 days window) following the first HEPLISAV-B vaccine dose.




## 5. ELIGIBILITY ASSESSMENT and ENROLLMENT

### 5.1. Inclusion Criteria

a. Diagnosis of CLL/SLL which is made according to the updated criteria of the NCI Working Group[18].

a. No known active or past hepatitis B infection

b. No history of prior hepatitis B virus vaccination (approved or investigational)

b. History of negative hepatitis B viral titers (negative HBsAg, HBsAb and HBcAb)

c. Cohort 1: Treatment naïve CLL patients

d. Cohort 2: Subjects must be receiving ibrutinib monotherapy for at least 6 months prior to administration of the first vaccine dose

e. Cohort 3: Subjects must be receiving acalabrutinib monotherapy for at least 6 months prior to administration of the first vaccine dose

f. Age ≥18 years.

g. ECOG performance status of 0-1

h. Able to comprehend the investigational nature of the protocol and provide informed consent.

### 5.2. Exclusion Criteria

a. Female patients who are currently pregnant.

b. Any uncontrolled active systemic infection

c. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk

d. History of severe allergic reaction to any component of HEPLISAV-B, including yeast

e. Receive intravenous or subcutaneous immunoglobulin (IVIG) within 3 months prior to vaccination

f. Concomitant use of immunosuppressive agents (e.g. steroids, radiotherapy, chemotherapy)

g. Hereditary or acquired immunodeficiency syndrome unrelated to CLL

h. Non-English speaking individuals will be excluded from the study

### 5.3. Patient Registration

*On-Study Procedure*: A subject deemed eligible in screening will have an eligibility checklist signed, dated, and filed in the subject's research record. The appropriate informed consent will be obtained by an authorized associate investigator. The original copy of the informed consent

will be filed electronically in the subject's Clinical Center medical record. A copy of the signed consent will be given to the subject.

# 6. TREATMENT PLAN

## 6.1. Dosing Regimen

HEPLISAV-B (Hepatitis B Vaccine [Recombinant], adjuvanted) vaccine - A series of 2 doses (0.5 ml each) will be given on a 0- and 3- month (+/- 15-day window) schedule via intramuscular injection.

## 6.2. Holding of Vaccine Administration

If medically necessary reasons to hold HEPLISAV-B occur during treatment (i.e. active systemic infection, impending workups for diagnostic and/or therapeutic purposes), HEPLISAV-B can be held based on the study team's discretion and given when it is deemed safe. Longer than recommended intervals between doses do not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered. Thus, an interruption in the vaccination schedule does not require restarting the entire series of vaccination or adding extra doses. If the vaccination series is interrupted after the first dose, the second dose should be administered as soon as possible. Subjects who receive the second HEPLISAV-B vaccine (scheduled 3 month following the first vaccine) outside the +/- 15-days window period can receive the second vaccine dose but will be excluded from the final efficacy analysis.

## 6.3. Permanent Discontinuation of Vaccine Administration

The study will be monitored to ensure that the occurrence of a specified set of vaccine related serious adverse events (VRSAEs) that occur during the treatment period does not substantially exceed an anticipated rate. VRSAEs may not exceed the reported rates in the HEPLISAV-B vaccine package insert.

Subjects who are unable to receive the second HEPLISAV-B vaccine will be followed for safety. All adverse reactions that started within 7 days after study vaccine administration will be followed until resolution.

# 7. CLINICAL MONITORING

Samples will be ordered and tracked through the CRIS screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record.

Results from other NIH protocols may be used as a part of the study evaluation.

Please refer to Appendix A – Schedule of Events for a timeline of events.

### 7.1. Screening Assessment

a. Patients currently enrolled in other protocols within the lymphoid malignancies section at NIH will not require an in-person screening visit. A chart review will be performed in order to determine whether patients are eligible based on inclusion and exclusion criteria (see section 5). Only women of childbearing potential require a negative pregnancy test that must be drawn no more than 15 days prior to receiving the first vaccine.

b. Self-referral of patients is permitted. Patients not currently enrolled in a protocol at the NIH will require an in-person screening visit performed under the Hematology Branch Screening protocol 97-H-0041 or any other available NIH screening protocol and must have an already established diagnosis of CLL. Patients can receive screening and baseline assessment at the same visit if they decide to enroll in this clinical trial.

### 7.2. Baseline Assessment

a. History and physical examination

b. Review of medications

c. The following laboratory tests will be sent prior to administration of the first vaccine. Tests must be drawn no more than 15 days prior to the first vaccine dose. Tests performed at the NIH on a different protocol will be accepted.

- CBC with differential
- Total B-cell, NK-cell and T-cell counts
- Immunoglobulin levels
- Acute Care Panel (includes Na, K, Cl, CO2, Creatinine, Glucose, Urea Nitrogen)
- Hepatic Panel (includes Alkaline Phosphatase, ALT, AST, Total Bilirubin, Direct Bilirubin)
- C-reactive protein
- Hepatitis B Viral titers (HBsAg, HBsAb, HBcAb)
- HIV screening test (only if there is no result available within 365 days prior to the first vaccine dose)
- Research blood (up to 80 mL) (Refer to Appendix C for a list of possible research tests)

### 7.3. On study Evaluations

a. Subjects will be evaluated at 3 (+/- 15-days window) and 6 months (-15-days, +180 days window) while on the study. All adverse reactions that started within 7 days after study vaccine administration will be followed until resolution.

b. The following laboratory tests will be completed. Tests performed at the NIH on a different protocol will be accepted

- CBC with differential
- Total B-cell, NK-cell and T-cell counts
- Immunoglobulin levels
- Acute Care Panel (includes Na, K, Cl, CO2, Creatinine, Glucose, Urea Nitrogen)
- Hepatic Panel (includes Alkaline Phosphatase, ALT, AST, Total Bilirubin, Direct Bilirubin)
- C-reactive protein
- Pregnancy test (for women of childbearing potential and during the 3 month assessment only)
- Hepatitis B Viral titers (HBsAg, HBsAb, HBcAb)
- Research blood (up to 80 mL) (Refer to Appendix C for a list of possible research tests)

### 7.4. Response Assessment

The primary endpoint for response assessment will be 6 months following the first vaccine administration (-15-days, +180 days window). Laboratory tests drawn during on-study evaluations (Section 7.3) will be used for the efficacy analysis. No additional tests are required.

### 7.5. Vaccine specific manifestations

Signs and/or symptoms that are possibly vaccine related may be evaluated by additional tests, procedures and specialist consultations in accordance with standard of care.

### 7.6. Exclusion of subjects with Hepatitis-B seropositivity at baseline assessment from efficacy analysis

It is possible that a very small subset of patients may have seropositive titers for either HBsAg, HBsAb or HBcAb at baseline assessment. This could indicate that patients may have received prior hepatitis vaccination or may have had hepatitis B exposure without knowing or remembering. These patients will be followed for safety monitoring, and if clinically indicated,

be seen by a hepatology specialist. Patients with hepatitis B seropositive titers at baseline will not receive the second vaccine dose and will not be included in the efficacy analysis of this trial.

An additional subject will be recruited to the study for each subject that is found to be hepatitis B seropositive.

### 7.7. Exclusion of subjects with HIV seropositivity at baseline assessment from efficacy analysis

It is possible that a very small subset of patients may have HIV seropositivity at baseline assessment. This could indicate that patients may had HIV exposure without knowing or remembering. These patients will be followed for safety monitoring, and if clinically indicated, be seen by an infectious disease specialist. Patients with HIV seropositive titers and Hepatitis seronegative titers at baseline will be provided the option to receive the second vaccine dose (patient choice) since patients with HIV are recommended to receive hepatitis B vaccinations. Patients who are both HIV and hepatitis B seropositive at baseline will not receive the second vaccine dose. Patients with HIV seropositive titers at baseline will not be included in the efficacy analysis of this trial.

An additional subject will be recruited to the study for each subject that is found to be HIV seropositive.

### 7.8. Exclusion of subjects who need to start or change treatment for CLL

The following subjects may receive the second vaccine dose (if not already received and considered medically safe and appropriate) but will not be included in the efficacy analysis of this trial:

- Subjects receiving BTK-Is: Any situation necessitating discontinuation of BTK-I therapy for >4 weeks during the study period (0-6 months following administration of the first vaccine series). An additional subject will be recruited to the study for each subject that is required to discontinue BTK-I therapy for >4 weeks.
- Subjects that are treatment naïve: Any situation necessitating starting treatment for CLL (0-6 months following administration of the first vaccine series). An additional subject will be recruited to the study for each subject that is required to start treatment for CLL.

### 7.9. Exclusion of subjects who start (Intravenous Immunoglobulin) IVIG Therapy

The following subjects may receive the second vaccine dose (if not already received and considered medically safe and appropriate) but will not be included in the efficacy analysis of this trial:

- Any subject who starts IVIG during the study period (after the first vaccine administration until the response assessment at 6 months).

## 8. CRITERIA FOR RESPONSE

The response criteria for achieving seroprotective titers following the hepatitis B vaccine are based on the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) and the HEPLISAV-B package insert.[2,17] Serologic titers to assess response to the hepatitis B vaccine will be drawn 6 months (-15-days, +180 days window) after the first vaccine dose. The primary endpoint for response assessment will be the rate of hepatitis B seroprotective titer achievement following completion of the HEPLISAV-B 2-dose vaccine series (6 months after the first vaccine administration). Seroprotective titers are defined as the following:

a. Seroprotective titer for Hepatitis B: anti-HBs $\geq$10 mIU/mL

## 9. ANCILLARY LABORATORY RESEARCH STUDIES

### 9.1. Collection of Samples

**Research Blood Samples**: A volume not to exceed 80 mL at each visit will be drawn for research blood samples.

### 9.2. Intended Use

The primary use of the samples is described in section 2 and section 8 of this protocol. Research blood specimens will also be stored for potential future assessment of future descriptive or exploratory ancillary research studies.

### 9.3. Procedures for stored specimens

All samples will be stored under the direction of the PI of the study. Research samples will be stored using BSI in accordance with NHLBI DIR Biospecimen policy. All laboratory personnel with access to subject information will complete the NIH online course in Protection of Human Subjects. Laboratory personnel are assessed for competency prior to being permitted to work with research subject samples. Efforts to ensure protection of subject information include:

The laboratory is located in a controlled access building and laboratory doors are kept locked at all times. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Hard copy records or electronic copies of documents containing research subject information are kept in the locked laboratory or other controlled access locations.

An electronic database is used to store information related to research subject samples processed by the laboratory.

Upon specimen receipt each sample is assigned a unique number.

Vials holding research subject samples are labeled with the sequential laboratory accession ID number that does not contain any personal identifier information.

### 9.4. Tracking

Samples will be ordered and tracked through the CRIS Research Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside NIH without IRB notification and an executed MTA or CTA.

### 9.5. End of study procedures

Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

At the closure of this study, remaining samples from research subjects will be transferred to an NHLBI approved biorepository.

### 9.6. Loss or destruction of samples

Should we become aware that a major breech in our plan for tracking of samples has occurred, the IRB and the NHLBI Clinical Director will be notified. The PI will report destroyed samples if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container). Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher.

## 10. BIOSTATISTICAL CONSIDERATIONS

### 10.1. Primary Endpoint:

The primary efficacy endpoint will be the rate of hepatitis B seroprotective titer achievement (anti-HBs ≥10mIU/mL) following completion of the HEPLISAV-B 2-dose vaccine series (6 months after the first vaccine administration). Response to the HEPLISAV-B vaccine is defined as an anti-HBs titer ≥ 10mIU/mL.

### 10.2. Secondary Endpoint:

The safety endpoint will be safety and tolerability of the HEPLISAV-B vaccine among subjects with CLL who are treatment naïve or taking BTK-Is (ibrutinib or acalabrutinib).

### 10.3. Sample size

This study consists of three separate groups of patients with CLL receiving (1) treatment naïve, (2) BTK-I treatment with ibrutinib and (3) BTK-I treatment with acalabrutinib. The primary analysis will examine the three groups of patients separately. Statistical tests will not be adjusted for multiplicity.

In the first group (treatment naïve CLL), we hypothesize that the study subjects who are treatment naïve will have HEPLISAV-B vaccine response rates more than 30%. Let p be the response rate, we will test the null hypothesis $H_0$: p=30% versus the alternative $H_1$: p ≠30% with a two-sided type I error of 0.05. A sample size 54 of evaluable subjects will have 83% power to detect a 20% difference based on a two-sided one-sample Z-test for proportion. We estimate the response proportion to be approximately 50% for this group, thus this group of 54 subjects will yield a two-sided 95% confidence interval of the response rate with the confidence limits within +/- 14%.

In each of the second (CLL treated with ibrutinib) and third (CLL treated with acalabrutinib) groups, the sample size is determined by testing the null hypothesis that the study subjects treated with BTK-Is will not be able to mount a response to the Heplisav-B vaccine series. Let p be the response rate, we will test the null hypothesis $H_0$: p≤10% versus the alternative $H_1$: p >10% with a type I error of 0.05. When the true response rate is 30%, a sample size of 27 evaluable subjects will have 86% power to detect a 20% difference based on a one-sided binominal test. The null hypothesis is rejected if 6 or more vaccine responses are observed in 27 subjects. We estimate the response proportion to be approximately 30% for each group, thus a sample size of 27 subjects will yield a two-sided 95% confidence interval of the response rate with the confidence limits within +/- 18%.

Therefore, we plan to enroll 27 evaluable subjects in each of the BTK-I treatment cohorts and 54 evaluable subjects in the treatment naïve cohort. As an important exploratory objective, we

will compare the vaccine response rates between subjects in cohort 1 and subjects in the combined cohort 2 and cohort 3. The study will have over 88% power to detect a 30% difference if the response rate in the treatment naïve cohort is greater than 40% based on a two-sided two-sample Z-test for comparing two proportions.

Up to 15 additional subjects may be enrolled to account for early discontinuation before completing response assessment (6 months after the first vaccine administration) due to non-treatment related reasons. Subjects who discontinue study treatment early due to non-treatment related reasons are not included in the evaluation of the primary endpoint.

### 10.4. Statistical Methods

The planned analyses will include descriptive statistics on the proportions of response probability to the HEPLISAV-B vaccine. The response probabilities will be estimated using the sample proportions and their inferences including confidence intervals and hypotheses testing will be evaluated. Time to responses and longitudinal patterns of the vaccine responses will be analyzed using appropriate parametric and nonparametric methods. Regression analysis will be used to assess the factors that may influence the response to the HEPLISAV-B vaccine.

### 10.5. Off Study Criteria

a. Per research subject choice: Research subjects may withdraw from study at any time.

b. Completion of Study

c. Death

d. Per principal investigator decision: Should any of the following events occur, the subject will be followed until resolution of the event and then taken off study:

- Subject becomes significantly noncompliant with study drug administration, study procedures, or study requirements, which might increase risk or substantially compromise the interpretation of study results.
- Subject develops a medical condition preventing the safe administration of the second vaccine dose (e.g. severe hypersensitivity reaction to the first vaccine dose).
- The principal investigator may take any research subject off study if it is determined that this would be in the best interest of the subject.

e. Lost to follow-up

f. CLL Disease Progression or Transformation (refer to section 7.8)

g. Need to Start IVIG (refer to section 7.9)

h. Need to omit or delay administration of 2nd Vaccine Dose (Refer to section 6.3 and 6.4)

i. Detection of HIV on baseline evaluation (refer to section 7.6)

j. Detection of Hepatitis B on baseline evaluation (refer to section 7.7)

### 10.6. Off-Study Procedure

A subject who goes off study will have an off-study note placed in the medical record.

## 11. DATA AND SAFETY MONITORING

### 11.1. Safety Monitoring

a. **Principal Investigator:** Accrual, efficacy and safety data will be monitored by the principal investigator (PI). The PI will also provide appropriate delegation of responsibilities to other members of the research staff. All data will be collected in a timely manner and reviewed by the PI and/or their designee for toxicity.

b. **NIH IRB:** Accrual and safety data will be monitored and reviewed annually by the Institutional Review Board (IRB). Prior to implementation of this study, the protocol and the proposed subject consent will be reviewed and approved by the properly constituted Institutional Review Board (IRB) operating according to the 45 Code of Federal Regulations Part 46. This committee will also approve all amendments to the protocol or informed consent, and conduct continuing annual review so long as the protocol is open to accrual of subjects.

c. ***NHLBI Hematology DSMB*:** The NHLBI Hematology Data Safety and Monitoring Board will review the protocol at 6 to 12 month intervals and the interval will be determined by DSMB. A progress report will be forwarded to the DSMB at these times and their recommendations will be expeditiously implemented. The DSMB may recommend early termination of the study for considerations of safety and efficacy.

### 11.2. Assessment of Safety

**Definitions**

**a. Adverse Event (AE):** Any untoward medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test vaccine and about the patient's outcome.

**b. Serious Adverse Event (SAE):** Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in in-patient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

**c. Serious event:** An event is serious if it meets the definition of a serious adverse event (above) or if it requires immediate corrective action by a PI and/or IRB to protect the safety, welfare or rights of subjects.

**d. Unexpected adverse reaction:** An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the package insert or if it occurs at a higher frequency or severity that is reported in the package insert.

**e. Unanticipated Problem (UP):** Any incident, experience, or outcome that meets all of the following criteria:

- **unexpected** in terms of nature, severity, or frequency in relation to the research risks that are described in the IRB-approved research protocol and informed consent

document; package insert; and the characteristics of the subject population being studied; and

- **related or possibly related** to participation in the research; and
- places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

**f. Unanticipated Problem that is not an Adverse Event**: An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involves risk to the subject, affect others in the research study, or significantly impact the integrity of research data. For example, report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for vaccine.

**g. Protocol Deviation (PD):** Any change, divergence, or departure from the IRB approved research protocol.

**h. Non-compliance:** The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research. Noncompliance may be further characterized as:

1. **Serious non-compliance: Non-compliance that:**
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity
    d. Invalidates the study data
2. **Continuing non-compliance:** Non-compliance that is recurring. An example may be a pattern of non-compliance that suggests a likelihood that, absent an intervention, non-compliance will continue. Continuing noncompliance could also include a failure to respond to IRB requests to resolve previous allegations of non-compliance.
3. **Minor (non-serious) non-compliance: Non-compliance that, is neither serious nor continuing.**

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, and other

laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the vaccine.

**Severity**

Definitions found in the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) will be used for grading the **severity** (intensity) of AEs:

| | | |
|---|---|---|
| **1** | **Mild** | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| **2** | **Moderate** | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL* |
| **3** | **Severe** | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |
| **4** | **Life-threatening** | Life-threatening consequences; urgent intervention indicated. |
| **5** | **Death** | Death related to AE |

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Attribution of Adverse Events

| **Relationship** | **Attribution** | **Description** |
|---|---|---|
| Unrelated to intervention | Unrelated | The AE is clearly **NOT** related to the intervention |
| | Unlikely | The AE is **doubtfully related** to the intervention |
| Related to intervention | Possibly | The AE **may be related** to the intervention |
| | Probably | The AE **is likely related** to the intervention |

| | | |
|---|---|---|
| | Definitely | The AE **is clearly related** to the intervention |

**Pregnancy**

Before study enrollment, females of childbearing potential must agree to use contraception to avoid pregnancy for the first 3 months of the study (while vaccines are being administered). However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator or anyone on the study team if she becomes pregnant from the time of consent to 90 days after the last dose of vaccine. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 90 days after the last dose of vaccine must be reported. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

In addition, the HEPLISAV-B package insert refers to a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to HEPLISAV-B during pregnancy. Patients will be encouraged to contact and enlist in this registry as recommended in the HEPLISAV-B package insert.

### 11.3. Documenting and Reporting of Adverse and Serious Adverse Events

Investigators will assess the occurrence of AEs and SAEs that start within 7 days after the first and second vaccine dose at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the subject's medical record.

Additionally, research subjects will receive an adverse event diary. Subjects will be asked to document any local (injection site) or systemic adverse effects that start within 7 days after receiving the first and second vaccine dose. Subjects will also be given contact information of

at least one study team member, in order to address any potential questions or concerns about the vaccine and/or adverse effects. (See appendix B for adverse event diary).

All adverse reactions that started within 7 days after study vaccine administration will be followed until resolution, or until the Investigator assesses the subject as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

### 11.4. NIH IRB and CD reporting

**Expedited Reporting**

Events requiring expedited reporting will be submitted to the IRB per Policy 801 “Reporting Research Events”.

**Reports to the IRB at the time of Continuing Review:**

The PI or designee will refer to HRPP Policy 801 “Reporting Research Events” to determine IRB reporting requirements.

**Reports to the CD:**

The PI or designee will refer to NHLBI DIR Policy to determine CD reporting requirements and timelines.

**Data Collections**

In view of the underlying illness of CLL, many patients will enter the study with abnormal blood counts that would meet criteria as grade 3 toxicity, and thus AEs regarding hematologic lab values including thrombocytopenia, anemia or leukocytosis will not be evaluable. However, we will collect hematologic laboratory values in the subject’s source documents.

In addition, the following non-hematologic AEs will be captured in the source documents and recorded in the database.

Because ibrutinib, acalabrutinib and SHINGRIX are FDA approved drugs with known toxicity profiles, any observed or volunteered adverse events that are listed on the package insert will be collected regardless of whether (1) the adverse event is more severe or occurs at a higher frequency than on the package insert; or (2) meets the criteria for a serious adverse event.

## 12. BIOSPECIMEN AND DATA MANAGEMENT PLAN

### 12.1. Data Management

The principal investigator will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts to ensure that data is verifiable and evaluable. Data will be abstracted from Clinical Center progress notes as well as from progress notes forwarded from the subjects' home physician. Laboratory data from NIH will be imported electronically from CRIS into an in-house clinical trial database. Laboratory values from referring home physicians will be entered into the system.

We will maintain the confidentiality of identifiable private information collected in this Clinical Trial and protect the privacy of the individual human subjects. Primary data containing individually identifiable information obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH information security standards. Neither individual personal identifiers nor the key linking coded data to individuals will be released to third parties without prior IRB approval and an executed CDA or MTA. Identifiable data will not be sent outside NIH without prior IRB approval or appropriate conditions for disclosure outlined in the executed CDA or MTA.

### 12.2. End of study procedures

Data will be stored in locked cabinets and/or in a password protected database until it is no longer of scientific value.

### 12.3. Loss or destruction of data

Should the research team become aware that a major breech in the plan to protect patient confidentiality and trial data has occurred, the IRB will be notified.

### 12.4. Publication Policy

Given the research mandate of the NIH, patient data including the results of testing and responses to treatment will be entered into an NIH-authorized and controlled research database. Any future research use will occur only after appropriate human subject protection institutional approval such as prospective NIH IRB review and approval or an exemption from the NIH Office of Human Subjects Research (OHSR).

### 12.5. Data Sharing and Future Use of Data

Research data may be shared with qualified non-collaborator recipients following publication of the primary research results after removal of PII and IRB approval. Future research use of data not defined in the research protocol may occur only after IRB review and approval or an exemption from the NIH OHSRP. Refusal of a research subject participant to permit future use of data--other than required in the protocol --will be honored. Limitations in data sharing and future use of data due to contractual obligations (e.g., CRADAs) or intellectual property proceedings (such as patent filings) will be honored.

### 12.6. Future Use of Biospecimens

Following analyses of biospecimens for primary research purposes, remaining samples suitable for future research will be stored in manner that conforms with DIR policy (such as BSI) or in a publicly accessible research biospecimen repository following IRB or OHSRP approval, as applicable. Biospecimens may be destroyed only when permitted by the clinical director and the IRB.

Any future research use of biospecimens not defined in the protocol in which NHLBI investigators are engaged in research (e.g., they are undertaking research activities and hold the key that identifies research subjects) requires IRB review and approval. Coded biospecimens (NHLBI investigators hold the key that identifies research subjects) to be shared outside of NIH for future research use requires IRB review and approval (for research collaborations) or submission of a determination to OHSRP (for non-collaborative research), and an executed transfer agreement. Unlinked biospecimens (no key to identify research subjects exists) to be shared outside of NIH for future research use requires submission of a determination to OHSRP and an executed transfer agreement. There are a few types of biospecimens that do not require IRB or OHSRP approval for future research use outside of NIH, such as specimens from deceased individuals (refer to OHSRP SOP5, Appendix A for complete list); an executed transfer agreement is required in these special cases. Refusal of a research subject participant to allow for future use of identifiable biospecimens--other than required in the protocol or for appropriate regulatory purposes--will be honored.

## 13. HUMAN SUBJECTS PROTECTION

The investigator(s) accept their responsibilities for protecting the rights and welfare of human research subjects and will permit, with reasonable advance notice and at reasonable times, the designated research monitors to monitor the conduct of the research, as well as to audit source

documents to the extent necessary to verify compliance with FDA Good Clinical Practice and the approved protocol.

## 13.1. Rationale for Subject Selection

Subjects from any gender and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. CLL are rare neoplasms that comprise a substantial proportion of all leukemia in middle-aged persons and most commonly occur among elderly persons in western populations.

In order to avoid issues with language barriers and the potential inaccuracies in the study team's understanding completion of the AE diary, the investigators have decided not to enroll non-English speaking subjects.

## 13.2. Special Patient Populations

### Justification for exclusion of patients with immunodeficiency syndromes

Vaccine efficacy is known to be decreased in patients with immunodeficiency. The purpose of this study is to determine whether patients with CLL (itself known to cause immunodeficiency) can mount an immune response to vaccines. Including patients with additional immunodeficiency states would be a potential confounding factor.

### Justification for exclusion of pregnant women

There are no clinical studies that were done on pregnant women taking HEPLISAV-B. In addition, it is highly unlikely that a woman of pre-menopausal age will present with CLL at the Clinical Center. CLL is a malignancy of B cells that predominantly affects the elderly population. Diagnosis is typically made in adults over the age of 50 and more than half of the people with CLL are over the age of 70.

### Justification for exclusion of children

Patients under the age of 18 are excluded because inclusion of an occasional younger patient will not provide generalizable information that would justify their inclusion on this study. In addition, pediatric patients with CLL are extremely rare and it is indeed doubtful that these exceptional cases are part of the same disease spectrum.

### Justification for exclusion of cognitively impaired subjects

Cognitively impaired and institutionalized persons will not participate in this study. Cognitively impaired persons may have difficulties accurately self-reporting adverse events which could

compromise the safety of the subject and the validity of study findings. Subjects must be able to provide informed consent and understand and comply with the treatment plan and follow-up

**Justification for inclusion of NIH Staff**

Per Standard Operating Procedure 14F, *Research Involving NIH Staff as Subjects*, the following guidelines apply to NIH staff who participate in intramural research studies:

- NIH staff(employees, NIH contractors, special volunteers, guest researchers, and trainees) may voluntarily participate in this protocol.
- Recruitment, enrollment and compensation of NIH staff will be consistent with the Guidelines for the Inclusion of Staff in NIH Intramural Research Studies (April 2016) (SOP 14F) and NIH Policy Manual Chapter 2300-630-3,:"Leave Policy for NIH Employees Participating in NIH Medical Research Studies" (HRPP SOP 14F).

### 13.3. Recruitment plan

The study will be listed on the following websites: clinicaltrials.gov, NIH Clinical Center (CC) Search the Studies, the CC Recruitment Website (with dedicated study webpage using IRB approved language, and Craigslist, the Leukemia and Lymphoma Foundation, Physician's Desk Query, and the National Heart, Lung and Blood Institute patient recruitment webpages. A recruitment plan will be developed by the NHLBI Patient Recruitment Office (PRO) that will include IRB-approved recruitment materials and tools, developed in partnership with OPR, to include recruitment flyers, iStock photos for marketing the study, and Public Service Announcement (PSA) including recruitment language for use with social media (Facebook and Twitter), OPR and NIH Listservs, ResearchMatch.org, Craigslist postings, NIH Record and Clinical Center News internal publications and other potential official NIH external publications as available. An informational letter to physicians will be available for electronic (and hard copy as appropriate) distribution to local and national clinical contacts. All options mentioned in PSA (i.e. ResearchMatch, Craigslist, publications, etc.) may be used for recruitment: Social media language may be posted on any and all official NIH accounts and those of CLL advocacy groups, such as the CLL Society and Leukemia and Lymphoma Foundation.

### 13.4. Payment and Reimbursement for participation

a. **General**

- Subjects will not be compensated for their participation in this study. There is no payment for the blood samples obtained for research.

b. **Travel, food, and lodging** will be consistent with NIH guidelines.

## 13.5. Risks and Discomfort

### Risks related to HEPLISAV-B

Most solicited local adverse reactions and systemic adverse events seen with HEPLISAV-B were considered by the subjects as mild and self-limiting, lasting < 7 days.

A summary of safety data from the HEPLISAV-B (Hepatitis B Vaccine [Recombinant], adjuvanted) vaccine is provided in section 3.3.

### Contraindications to Vaccine Administration

Severe allergic reaction after a previous dose of any hepatitis B- containing vaccine or to any component of HEPLISAV-B, including yeast.

### Risks related to blood draws

No major risks are involved with blood draws. Minor complications including bleeding, pain, and hematoma formation at the site of blood draws or rarely an infection may occur.

### Risks related to pregnancy and nursing mothers

There are no clinical studies of HEPLISAV-B in pregnant women. Available human data on HEPLISAV-B administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. It is also not known whether HEPLISAV-B is excreted in human milk. Data are not available to assess the effects of HEPLISAV-B on the breastfed infant or on milk production/excretion.

Developmental toxicity studies were conducted in female rats. Animals were administered 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg CpG 1018 adjuvant twice prior to mating, and on gestation days 6 and 18 (a single human dose of HEPLISAV-B contains 20 mcg HBsAg and 3000 mcg CpG 1018 adjuvant). No adverse effects on pre-natal and post-natal development up to the time.

This study will exclude patients who are pregnant. If research subjects should become pregnant while enrolled in the study, they will no longer receive further vaccine doses.

## 13.6. Risks in Relation to Benefits

**Risk to Adult Subjects**

The benefits to the subject could be a reduction in the risk of acquiring hepatitis B infection. This could potentially avoid complications arising from acute and/or chronic hepatitis (e.g. liver failure, cirrhosis, hepatocellular cancer and potentially death).

Overall there is greater than minimal risk with prospect of direct benefit to individual subjects for achieving immunity against the hepatitis-B virus.

**Risk to NIH Staff**

The study involves greater than minimal risk with the prospect of direct benefit to individual subjects.

### 13.7. Informed Consent Processes and Procedures

Informed consent shall be documented using the current IRB-approved consent form, which should be downloaded from the NIH Clinical Center active consent website. Each participant will receive an oral and written explanation of the goals, procedures, and risks of this study. When consent is obtained, the consent document(s) must be signed and dated by the subject, and the person obtaining consent. For research conducted at the NIH Clinical Center a witness is also required to sign the document. Any adult other than the person obtaining or providing consent may serve as a witness. The witness attests only to the validity of the signature or mark (i.e., that the research subject signed the consent document), not to the validity or quality of the consent. The original, signed informed consent document will be placed in the medical record, and the subject will receive a signed copy of the informed consent document. Documentation of informed consent and the signed consent form will be maintained in CRIS.

The investigational nature and research objectives of this trial, the procedure and its attendant risks and discomforts will be carefully explained to the subject and a signed informed consent document will be obtained prior to entry onto this study.

At any time during participation in the protocol, should new information become available relating to risks, adverse events, or toxicities, this information will be provided orally or in writing to all enrolled or prospective patient participants. Documentation will be provided to the IRB and if necessary the informed consent amended to reflect relevant information.

If there is an unexpected enrollment of a research participant for which there is no translated extant IRB approved consent document, the principal investigator and or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS

Policy M77-2, 45 CFR 46.117 (b) (2), and 21 CFR50.27 (b) (a)0. The summary that will be used is the English version of the extant IRB approved consent document.

We request prospective IRB approval of the use of the short form for up to a maximum of **5** research subjects in a given language and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form. Should we reach the threshold of 5, we will notify the IRB of the need for an additional use of the Short Form and that we will have that consent document translated into the given inherent language.

**Consent process for NIH Staff**

Per Standard Operating Procedure 14F, *Research Involving NIH Staff as Subjects*, the following guidelines apply to NIH staff who participate in intramural research studies:

- Neither participation nor refusal to participate as a subject in this protocol will have an effect, either beneficial or adverse, on the participant's employment or position at NIH.
- Employee subjects' privacy and confidentiality will be respected by protocol and consenting staff the same as for all subjects participating in research protocols. However, all subjects will be made aware that there are limits to these protections.
- The PI, through the consenting staff member, will make the "NIH Information Sheet on Staff Research Participation" available to staff members who are considering enrolling in research. (SOP 14F, Appendix D of this protocol).
- If the individual requesting to participate in the protocol is a co-worker, the consent from the NIH staff member (co-worker) will not be obtained by the staff member's direct supervisor but by another research staff member who is approved for obtaining informed consent and who is not a co-worker.

### 13.8. CONFLICT OF INTEREST

The Principal Investigator assures that each associate investigator listed on the protocol title page received a copy of the NIH's Guide to preventing conflict of interest. No members of the research team reported a potential conflict of interest.

### 13.9. TECHNICAL TRANSFER AGREEMENTS

This protocol has no associated CRADAs.

## 14. PHARMACEUTICALS

### 14.1. HEPLISAV-B

**Product description**

HEPLISAV-B is commercially available. Note for more detailed and comprehensive background information please refer to the HEPLISAV-B package insert.[17]

HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] is a sterile solution for intramuscular injection. The HBsAg is expressed in a recombinant strain of *Hansenula polymorpha* yeast. The fermentation process involves growth of the recombinant *H. polymorpha* on chemically-defined fermentation media containing vitamins and mineral salts.

The HBsAg is expressed intra-cellularly in the yeast cells. It is released from the yeast cells by cell disruption and purified by a series of physicochemical steps. Each dose may contain residual amounts of yeast protein (≤5.0% of total protein), yeast DNA (<20 picogram), and deoxycholate (<0.9 ppm) from the HBsAg manufacturing process.

HEPLISAV-B is prepared by combining the purified HBsAg together with the CpG 1018 adjuvant, a 22-mer phosphorothioate linked oligodeoxynucleotide in a phosphate buffered saline (sodium chloride, 9.0 mg/mL; sodium phosphate, dibasic dodecahydrate, 1.75 mg/mL; sodium phosphate, monobasic dihydrate, 0.48 mg/mL; and polysorbate 80, 0.1 mg/mL). Each 0.5-mL dose is formulated to contain 20 mcg of HBsAg and 3000 mcg of CpG 1018 adjuvant.

The vial stoppers are not made with natural rubber latex. HEPLISAV-B is formulated without preservatives.

**Packaging, and Storage**

Store in a refrigerator at 2°C to 8°C (35°F to 46°F). Do not freeze; discard if the vaccine has been frozen. Do not use the vaccine after the expiration date shown on the vial label.

**Dosage and Administration**

HEPLISAV-B is a clear to slightly opalescent, colorless to slightly yellow solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered. Administer HEPLISAV-B by intramuscular injection in the deltoid region using a sterile needle and syringe.

## 14.2. FDA Regulatory Considerations

**Off-Label Administration Timing of Vaccine Administration**

The HEPLISAV-B package insert recommends providing the HEPLISAV-B vaccine at 0 and 1 months. In this study we will be providing the HEPLISAV-B vaccine at 0 and 3 months. We are providing the vaccine series in a modified schedule for patient convenience. Both in the real world and within ongoing treatment trials within the NHLBI lymphoid malignancies branch patients are seen less frequently; typically every 3 months. Asking patients to return to clinic after 1 month could prove burdensome for a predominantly elderly CLL patient population.

The CDC and WHO best practice guidelines on timing of vaccine administration state that longer than recommended intervals between doses do not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered[19-21]. It is therefore expected that a modified dosing schedule for the HEPLISAV-B vaccine (given at 0 and 3 months) will increase compliance with vaccination without compromising vaccine efficacy.

An IND application with the FDA is not required for this project. The proposed research with the SHINGRIX vaccine meets the exemption requirements noted in 21 CRF 312.2, specifically:

1. The drug product is lawfully marketed in the United States.

2. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.

3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

5. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

6. The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

**Co-Administration of Other Vaccines**

Subjects may receive a different vaccine on the same day as HEPLISAV-B. If subjects receive two vaccines on the same day each vaccine must be administered in separate extremity. Local adverse reactions will be attributed to the vaccine that was given at the involved local site.

Systemic reactions that are expected as per the package insert(s) will be attributed to both vaccines.

**Overdose**

Any dose of vaccine in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of HEPLISAV-B overdose in patients. Subjects who received more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

**Drug Interactions**

There are no data to assess the concomitant use of HEPLISAV-B with immune globulin. When concomitant administration of HEPLISAV-B and immune globulin is required, they should be given with different syringes at different injection sites.

**Interference with Laboratory Tests**

Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of HEPLISAV-B.

**Supply**

The vaccine product HEPLISAV-B is manufactured and distributed by DYNAVAX Technologies Corporation (Berkeley, CA, 94710, USA).

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# 16. APPENDIX

## 16.1. Appendix A – Schedule of Events

| | Screening | Baseline (1st Vaccine Dose) | 3 Month Follow-Up (2nd Vaccine Dose) | 6 Month Follow-Up (Response Assessment) |
|---|---|---|---|---|
| Day of Study | N/A | D0 | D90 | D180 |
| Days (Plus/Minus) | N/A | -15 | ±15 | -15, +180 |
| NIH visit | | X | X | X |
| **Medications** | | | | |
| HEPLISAV-B Vaccine Dose | | X | X | |
| **Clinical** | | | | |
| Consent | | X | | |
| History, ECOG PS | C | X | X | O |
| Physical Exam | C | X | X | O |
| Medication Review | C | X | X | O |
| AE Diary Review | | | X | X |
| **Specific Labs/Other Tests** | | | | |
| CBC with Differential | | X | X | X |
| Acute Care Panel | | X | X | X |
| Hepatic Panel | | X | X | X |
| TBNK # | | X | X | X |
| Immunoglobulins | | X | X | X |
| C-reactive protein | | X | X | X |
| Pregnancy Test | | X* | X* | |
| HIV Screening | C | X** | | |
| Hepatitis B Viral Studies | C | X | X | X |
| Research blood | | O | O | O |

Footnotes for Schedule of Events:

[R] Optional, drawn at discretion of clinical team

C Chart Review

X Mandated

X* Mandated for women of childbearing potential only

X** Mandated only if no HIV test available within 365 prior to first vaccine administration

## 16.2. Appendix B – Adverse Event Diary for Patients

Subject Diary

### INSTRUCTIONS

1. **When to take your temperature and measure redness or swelling:**
   Take your oral temperature the **evening of your product administration** and **each morning** as soon as you get up. The best time is before eating, drinking, smoking, or brushing your teeth. Measure any redness or swelling, and/or bruising at the product administration site(s) the first evening and each morning. Also measure the site any time you have a fever, redness, or swelling that is getting worse.

2. **How to take your temperature and measure redness, swelling, and bruising:**
   Take your oral temperature with the thermometer provided. ***Do not eat, drink, or smoke for 15 minutes before taking your temperature.***
   Place thermometer under your tongue. If your temperature is less than 96°F or 36°C or greater than 100°F or 38°C, please take it again in the next 30-45 minutes.
   **Measure any redness, swelling, and/or bruising at the product administration site(s)** using the measuring device provided.
   Please complete the diary as instructed. Record the highest temperature, largest size of redness, swelling, and/or bruising and the category that reflects the WORST you felt that day, for each symptom.

3. **How to grade your symptoms:**
   Use the following guidelines to determine if your symptoms are "*NONE,*" "*MILD,*" "*MODERATE,*" or "*SEVERE.*"
   **If you are unsure how to grade your symptom(s), please contact NIH clinic staff for help.**

   - **NONE:** You have no symptoms.
   - **MILD:** Your symptoms cause no interference with work, school, or self-care activities, or almost none. You do not take medication, ***or*** you take only over-the-counter medication for relief.
   - **MODERATE:** Your symptoms noticeably interfere with work, school or self-care activities for less than 24 hours (for example, you miss a work shift or a school day). In addition, you ***might*** or ***might not*** take over-the-counter or prescription medication for relief.
   - **SEVERE:** Your symptoms keep you from performing usual work, school, or self-care activities for more than 24 hours. Medical intervention and/or hospitalization ***may*** be required.

☎ **Please *CALL* the Clinic if you have any of the following:**

- **Hives**
- **Shortness of breath or wheezing**
- **Fever (greater than 104°F or 40°C)**
- **Any symptoms that you feel are SEVERE.**

**If you are having a medical emergency, please go the nearest emergency room immediately to be evaluated.**

**Where to call:**

Monday-Friday
8:00am-4:30pm:
**301-402-0797**

All other times, or if no response within 30 minutes, please call **1-301-496-1211** and ask the hospital operator to call the **"NHLBI Outpatient Physician on Call."**

**Product Administration Date: ____/____/_____.** **SHINGRIX [ ] HEPLISAV-B [ ]**

**Patient Name: _____**

| ***Day 0*** ___ / ___ / _____ | | | | |
|---|---|---|---|---|
| **Temp: _____°F** | | **Time taken: _____** | | |
| **General Symptoms:** | **None** | **Mild** | **Moderate** | **Severe** |
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | ❑ |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | ❑ |
| Headache | ❑ | ❑ | ❑ | ❑ |
| Chills/Shivering | ❑ | ❑ | ❑ | ❑ |
| Nausea/Indigestion | ❑ | ❑ | ❑ | ❑ |
| Fever | ❑ | ❑ | ❑ | ❑ |
| Other Symptoms: | | | | |

| ***Day 1*** ___ / ___ / _____ | | | | |
|---|---|---|---|---|
| **Temp: _____°F** | | **Time taken: _____** | | |
| **General Symptoms:** | **None** | **Mild** | **Moderate** | **Severe** |
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | ❑ |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | ❑ |
| Headache | ❑ | ❑ | ❑ | ❑ |
| Chills/Shivering | ❑ | ❑ | ❑ | ❑ |
| Nausea/Indigestion | ❑ | ❑ | ❑ | ❑ |
| Fever | ❑ | ❑ | ❑ | ❑ |
| Other Symptoms: | | | | |

| **Administration Site Symptoms:** | **None** | **Mild** | **Moderate** | **Severe** |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Swelling at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: ____ cm* *Left: ____ cm* | |
| Redness at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: ____ cm* *Left: ____ cm* | |
| Bruising at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: ____ cm* *Left: ____ cm* | |

| **Administration Site Symptoms:** | **None** | **Mild** | **Moderate** | **Severe** |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Swelling at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: ____ cm* *Left: ____ cm* | |
| Redness at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: ____ cm* *Left: ____ cm* | |
| Bruising at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: ____ cm* *Left: ____ cm* | |

**Please *CALL THE NHLBI* clinic if you have: any hives, shortness of breath, wheezing, fever greater than 40 degrees Celsius or 104 degrees Fahrenheit, or symptoms that are SEVERE.**
**If you are having a medical emergency, please go the nearest emergency room immediately to be evaluated.**

**Monday-Friday, 8:00am-4:30pm: 301-402-0797**

**All other times, or if no answer: Call 301-496-1211 and ask hospital operator to call the "NHLBI Outpatient Physician on Call"**

***Day 2*** ___ / ___ / _____

**Temp:** _____ °F **Time taken:** _____

| **General Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | ❑ |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | ❑ |
| Headache | ❑ | ❑ | ❑ | ❑ |
| Chills/Shivering | ❑ | ❑ | ❑ | ❑ |
| Nausea/Indigestion | ❑ | ❑ | ❑ | ❑ |
| Fever | ❑ | ❑ | ❑ | ❑ |
| Other Symptoms: | | | | |

| **Administration Site Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Swelling at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |
| Redness at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |
| Bruising at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |

***Day 3*** ___ / ___ / _____

**Temp:** _____ °F **Time taken:** _____

| **General Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | ❑ |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | ❑ |
| Headache | ❑ | ❑ | ❑ | ❑ |
| Chills/Shivering | ❑ | ❑ | ❑ | ❑ |
| Nausea/Indigestion | ❑ | ❑ | ❑ | ❑ |
| Fever | ❑ | ❑ | ❑ | ❑ |
| Other Symptoms: | | | | |

| **Administration Site Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Swelling at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |
| Redness at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |
| Bruising at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |

**Please *CALL THE NHLBI* clinic if you have: any hives, shortness of breath, wheezing, fever greater than 40 degrees Celsius or 104 degrees Fahrenheit, or symptoms that are SEVERE.**
**If you are having a medical emergency, please go the nearest emergency room immediately to be evaluated.**

**Monday-Friday, 8:00am-4:30pm: 301-402-0797**

**All other times, or if no answer: Call 301-496-1211 and ask hospital operator to call the "NHLBI Outpatient Physician on Call"**

***Day 4*** ___ / ___ / _____

**Temp:** _____ **°F** **Time taken:** _____

| **General Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | ❑ |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | ❑ |
| Headache | ❑ | ❑ | ❑ | ❑ |
| Chills/Shivering | ❑ | ❑ | ❑ | ❑ |
| Nausea/Indigestion | ❑ | ❑ | ❑ | ❑ |
| Fever | ❑ | ❑ | ❑ | ❑ |
| Other Symptoms: | | | | |

| **Administration Site Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Swelling at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |
| Redness at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |
| Bruising at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |

***Day 5*** ___ / ___ / _____

**Temp:** _____ **°F** **Time taken:** _____

| **General Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | ❑ |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | ❑ |
| Headache | ❑ | ❑ | ❑ | ❑ |
| Chills/Shivering | ❑ | ❑ | ❑ | ❑ |
| Nausea/Indigestion | ❑ | ❑ | ❑ | ❑ |
| Fever | ❑ | ❑ | ❑ | ❑ |
| Other Symptoms: | | | | |

| **Administration Site Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Swelling at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |
| Redness at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |
| Bruising at administration site? | No ❑ R ❑ L | Yes ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:* _____ *cm* *Left:* _____ *cm* | |

**Please *CALL THE NHLBI* clinic if you have: any hives, shortness of breath, wheezing, fever greater than 40 degrees Celsius or 104 degrees Fahrenheit, or symptoms that are SEVERE.**
**If you are having a medical emergency, please go the nearest emergency room immediately to be evaluated.**

**Monday-Friday, 8:00am-4:30pm: 301-402-0797**

**All other times, or if no answer: Call 301-496-1211 and ask hospital operator to call the "NHLBI Outpatient Physician on Call"**

| Day 6 ___ / ___ / _____<br>Temp: _____°F Time taken: _____ | | | | |
|---|---|---|---|---|
| **General Symptoms:** | None | Mild | Moderate | Severe |
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | ❑ |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | ❑ |
| Headache | ❑ | ❑ | ❑ | ❑ |
| Chills/Shivering | ❑ | ❑ | ❑ | ❑ |
| Nausea/Indigestion | ❑ | ❑ | ❑ | ❑ |
| Fever | ❑ | ❑ | ❑ | ❑ |
| Other Symptoms: | | | | |

| Day 7 ___ / ___ / _____<br>Temp: _____°F Time taken: _____ | | | | |
|---|---|---|---|---|
| **General Symptoms:** | None | Mild | Moderate | Severe |
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | ❑ |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | ❑ |
| Headache | ❑ | ❑ | ❑ | ❑ |
| Chills/Shivering | ❑ | ❑ | ❑ | ❑ |
| Nausea/Indigestion | ❑ | ❑ | ❑ | ❑ |
| Fever | ❑ | ❑ | ❑ | ❑ |
| Other Symptoms: | | | | |

| **Administration Site Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Swelling at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: cm Left: cm* | |
| Redness at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: cm Left: cm* | |
| Bruising at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: cm Left: cm* | |

| **Administration Site Symptoms:** | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L |
| Swelling at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: cm Left: cm* | |
| Redness at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: cm Left: cm* | |
| Bruising at administration site? | **No** ❑ R ❑ L | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right: cm Left: cm* | |

**Please *CALL THE NHLBI* clinic if you have: any hives, shortness of breath, wheezing, fever greater than 40 degrees Celsius or 104 degrees Fahrenheit, or symptoms that are SEVERE.**
**If you are having a medical emergency, please go the nearest emergency room immediately to be evaluated.**

**Monday-Friday, 8:00am-4:30pm: 301-402-0797**

**All other times, or if no answer: Call 301-496-1211 and ask hospital operator to call the "NHLBI Outpatient Physician on Call"**

***Ongoing Adverse Reactions after Day 7:***

**Temp:** _____ **°F** **Time taken:** _____

| **General Symptoms:** | **Mild** | **Moderate** | **Severe** | **Date Resolved (mm/dd/yy)** *Leave Blank if Ongoing* |
|---|---|---|---|---|
| Unusually tired/ feeling unwell | ❑ | ❑ | ❑ | |
| Muscle/body aches ***(not at product administration site)*** | ❑ | ❑ | ❑ | |
| Headache | ❑ | ❑ | ❑ | |
| Chills/Shivering | ❑ | ❑ | ❑ | |
| Nausea/Indigestion | ❑ | ❑ | ❑ | |
| Fever | ❑ | ❑ | ❑ | |
| Other Symptoms: | | | | |

| **Administration Site Symptoms:** | **Mild** | **Moderate** | **Severe** | **Date Resolved (mm/dd/yy)** *Leave Blank if Ongoing* |
|---|---|---|---|---|
| Pain/tenderness at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | |
| Itching at administration site? | ❑ R ❑ L | ❑ R ❑ L | ❑ R ❑ L | |
| Swelling at administration site? | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:_____ cm* *Left:_____cm* | | |
| Redness at administration site? | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:_____ cm* *Left:_____ cm* | | |
| Bruising at administration site? | **Yes** ❑ R ❑ L | ***If Yes, measure largest diameter:*** *Right:_____ cm* *Left:_____cm* | | |

Reviewed by:_____ Date:_____

**Please *CALL THE NHLBI* clinic if you have: any hives, shortness of breath, wheezing, fever greater than 40 degrees Celsius or 104 degrees Fahrenheit, or symptoms that are SEVERE.**
**If you are having a medical emergency, please go the nearest emergency room immediately to be evaluated.**

**Monday-Friday, 8:00am-4:30pm: 301-402-0797**

**All other times, or if no answer: Call 301-496-1211 and ask hospital operator to call the "NHLBI Outpatient Physician on Call"**

## 16.3. Appendix C – IRB-Approved Hematology Branch Laboratory Research Studies

| | DESCRIPTION OF LABORATORY STUDY BY BRANCH SECTION | Does this test pose a greater than minimal risk to pediatric subjects per 45 CFR 46.404? | Does this test pose a greater than minimal risk to healthy pediatric donors per 45 CFR 46.404? |
|---|---|---|---|
| | | | |
| **A** | **Stem Cell Allotransplantation Section (Dr. A. John Barrett)** | | |
| **A.1** | Measurement of lymphocyte function and immune responses directed toward allogeneic tissues, malignant cells, and infectious agents. Assay of a variety of antigens, including standard proliferation, cytotoxicity, and intracellular cytokine detection including GVHD predictive markers. Measurement of antigen-specific responses including employment of tetramers, ELISPOT technique, gene amplification-based assays, and flow cytometry. Selection of cells using immunomagnetic beads or flow cytometry. Culture, expansion, and selection of cells. Surface marker analysis of PB MC using flow cytometry. Cytokine/chemokine analysis of plasma/serum samples using ELISA and/or Luminex techniques. | No | No |
| **A.2** | Generation of cell lines for the study of immune cell interactions with other cells. Transformation of B-lymphocytes using Epstein-Barr virus. Derivation of malignant cell lines from patient leukemic or solid tumor samples. | No | No |
| **A.3** | Infection of cells and cell lines with recombinant genes to ascertain the effects of expressed molecules on immune responses and on growth and development. Transfection of cell lines with specific molecules to study antigen-specific responses. | No | No |
| **A.4** | Assays of peripheral blood and bone marrow progenitor cells including primitive and late erythroid progenitor-derived colonies, myelomonocytic colonies, and primitive multi- potential progenitor-derived colonies. | No | No |

| | | | |
|---|---|---|---|
| **A.5** | Injection of human cells into experimental animals to study the immune system and the growth of normal and malignant cells under varying conditions. | No | No |
| **A.6** | Testing of selection methods, cell isolation, and cell expansion leading to the development of new cell-based therapies requiring scale-up for clinical application. | No | No |
| **A.7** | Identification of individual T cell clones by their T cell receptor sequence. | No | No |
| **A.8** | Measurement of tumor and tissue specific antigens in cells of subjects and donors by mRNA,protein, or peptide expression in cells or fluids. | No | No |
| **A.9** | Laser capture micro dissection of cells from biopsies for GVHD to determine clonotypes. | No | No |
| **A.10** | DNA and RNA typing of genes that control immune responses in lymphocytes. | No | No |
| **A.11** | Microassay studies utilizing cellular DNA, cDNA, and RNA for neoplasia and host-tumor interactions. | No | No |
| **A.12** | Serum, blood and tissue markers of post-transplant tissue injury, particularly endothelial cell damage. Investigation of transplant survivors for metabolic derangements related to cardiac and vascular risk such as lipoprotein profiles, insulin resistance, diabetes markers, growth hormone signaling, hypertension, renal dysfunction. | No | No |
| **B** | **Molecular Hematopoiesis Section (Dr. Cynthia Dunbar)** | | |
| **B.1** | Flow cytometric analysis of cell surface and cytoplasmic proteins, including cell adhesion molecules, putative retroviral receptors, and markers of differentiation, using bone marrow and mobilized peripheral blood cells. | No | No |
| **B.2** | Hematopoietic progenitor-derived colony ascertainment in vitro (as described above), and engraftment of immunodeficient mice for detection of human stem cell number and function. | No | No |
| **B.3** | Testing ability of hematopoietic progenitor cells to be transduced with retroviral, lentiviral, and novel gene transfer vectors in vitro. | No | No |
| **B.4** | Reprogramming of adult mature cells, including skin fibroblasts and blood cells, into induced pluripotent stem cells in vitro. | No | No |
| | | | |

| | | | |
|---|---|---|---|
| **C** | **Cell Biology Section (Dr. Neal Young)** | | |
| **C.1** | Studies of blood and bone marrow hematopoietic progenitor numbers, including early and late erythroid progenitors, myelomonocytic progenitors, and multi-potential progenitor cells. In addition, bone marrow may be placed in long-term bone marrow culture to assess the function of stroma and stem cells and to assay more primitive progenitors, as well as organelle culture. Whole or selected bone marrow populations are cultured short-term for CD34 cell expansion. | No | No |
| **C.2** | Assays of apoptosis in hematopoietic cells and their progeny, using flow cytometric methods such as annexin and caspase-3 staining, propidium iodide uptake, and mitochondrial permeability tests. | No | No |
| **C.3** | Separation and functional study of cell populations characteristic of paroxysmal nocturnal hemoglobinuria, identified by absence of glycosylphosphatidylinositol anchored proteins. | No | No |
| **C.4** | Studies of mutation rates in hematopoietic cells and in buccal mucosa cells, using conventional hypoxanthine phosphoribosyltransferase activity functional assays, sequencing of mitochondrial DNA after specific gene amplification, and measurement of GPI-anchored deficient cells in blood and bone marrow. | No | No |
| **C.5** | Assays of immune function of T-cells, including intracellular cytokine staining, ELISPOT, semiquantitative gene amplification for gamma-interferon, tumor necrosis factor, interleukin-2, and other cytokines, and functional assessment in co-culture using specific neutralizing monoclonal antibodies. In addition, peripheral blood lymphocytes are subjected to spectratyping for CDR3 size distribution as well as nucleotide sequence of CDR3 peaks obtained. | No | No |
| **C.6** | Studies of engraftment of human normal and diseased bone marrow and peripheral blood in immunodeficient mice in order to determine the presence of hematopoietic repopulating stem cells as well as functional differences among selected populations. | No | No |
| **C.7** | Flow cytometric analysis of blood and bone marrow for lymphocyte phenotype, especially for evidence of activation of lymphocytes, for markers of apoptosis, and for antigens associated with primitive and mature hematopoietic cell populations. | No | No |
| **C.8** | Flow cytometric analysis of blood and bone marrow for hematopoietic stem cell progenitors and CD34 positive cells. | No | No |

| | | | |
|---|---|---|---|
| **C.9** | Studies of chromosomal instability in myelopdysplastic syndromes including BM cell and CD34 cell response to PAS crosslinking and examination of the cytotoxic effect of lymphocytes to the abnormal clone of cells. | No | No |
| **C.10** | Surface Enhanced Laser/Desorption Ionization (SELDI) time-of-flight mass spectrometry (Ciphergen) (proteomics methodology). | No | No |
| **C.11** | Mitochondrial DNA (mtDNA) sequence heterogeneity. | No | No |
| **C.12** | Measurement of EBV viral load. | No | No |
| **C.13** | Measurement of EBV LMP-1 via RT-PCR for LMP-1 RNA or flow cytometry for LMP-1. | No | No |
| **C.14** | Outgrowth assay of EBV transformed B cells. | No | No |
| **C.15** | Quantification of serumchemokines and cytokines (e.g. SDF-1, IL-10, IL-6, CXCR4, CXCL12). | No | No |
| **C.16** | Quantification of EBV cytotoxic T cells (tetramerstaining). | No | No |
| **C.17** | Telomere length measurement by Southern blot, Q-PCR, flow-fish, in situ hybridization and STELA | No | No |
| **C.18** | Telomere repair complex gene mutations by nucleotide sequencing of some or all of the following: *DKC1* ,*TERC*, *TERT*, *SBDS*, *NOp10* , *NHP2.* | No | No |
| **C.19** | Analysis of inflammatory markers and/or bacterial, viral, fungal or protozoal elements in plasma or serum using molecular, colorimetric, enzymatic, flow cytometric or other assays in subjects receiving immunosuppressive therapy, chemotherapy and/or bone marrow transplantation. | No | No |
| **C.20** | Confocal microscopic imaging of bone marrow. | No | No |
| **C.21** | Characterization of intracellular signaling proteins by cell permeabilization and flow cytometry, and quantitative immunoblots. | No | No |
| **C.22** | Assays for chromosomal aneuploidy by florescence in situ hybridization (FISH) and other molecular techniques. | No | No |

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| **C.23** | Conversion of human dermal fibroblasts into hematopoietic progenitors using Oct4 transfection. | No | No |
| **C.24** | Quantification of gene expression with RNA-seq | No | No |
| **C.25** | Characterization of chromatin and promoter/enhancer landscapes with ATAC-seq | No | No |
| **C.26** | Measurement of protein markers with SomaLogic's SOMAscan assay | No | No |
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| **D** | **Virus Discovery Section (Dr. Neal Young) THESE ASSAYS WILL NOT BE PERFORMED ON SAMPLES FROM HEALTHY PEDIATRIC DONORS** | | |
| **D.1** | Assays of serum, blood cells, and bone marrow cells for B19 parvovirus and possible B19 variants using gene amplification, cell culture, and hematopoietic colony inhibition assays. | No | N/A |
| **D.2** | Assays of blood, bone marrow, liver, and other tissues for potentially novel viruses, using a variety of techniques including RNA and DNA assays, differential display, gene amplification with conserved and random primers, cell culture assays, immunohistochemical methods, and inocculation of mice, rabbits, and monkeys, as well as antibody measurements. | No | N/A |
| **D.3** | Assays of blood, bone marrow, and liver for known viruses, including herpesviruses such as cytomegalovirus, human herpesviruses 6, 7, and 8, enteric viruses such as A-6, circiviruses, and parvoviruses, using assays as in (2). | No | N/A |
| **D.4** | Spectra-typing of blood cells to determine response to known or putative viral infections. | No | N/A |
| **D.5** | HLA typing or subtyping to determine risk factors/determinants for hepatitis-AA studies. | No | N/A |
| **D.6** | Cytotoxic lymphocyte assays with intracellular cytokine measurement for determining anti-viral response and lymphocyte cloning to obtain clones with specific antiviral activity. | No | N/A |
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| **E** | **Solid Tumor Section (Dr. Richard Childs)** | | |
| **E.1** | Cr51 cytotoxicity assay to evaluating killing of patient tumor cells by patient NK cell clones and T-cells. | No | No |
| **E.2** | ELISA for IL-12 maturity of DC's made from subjects monocytes. | No | No |
| **E.3** | ELISA for IFN ã to evaluate specificity of CTL clones. | No | No |
| **E.4** | H thymidine uptake to evaluate proliferation potential of antigen specific T-cells. | No | No |
| **E.5** | PCR of STR to assess chimerism status of cellular subsets grown in-vitro or retrieved from subjects post-transplant. | No | No |
| **E.6** | Flow sorting of PBL and/or tissue samples to evaluate chimerism of different subsets. | No | No |
| **E.7** | Surface marker analysis of peripheral blood mononuclear cells using flow cytometry. | No | No |
| **E.8** | cDNA expression arrays to evaluate T-cells expression/gene patterns in subjects with GVHD and a GVT effect. | No | No |
| **E.9** | Geno typing of tumor or tissue samples by high density cDNA arrays. | No | No |
| **E.10** | VHL mutation analysis on kidney cancer tissue. | No | No |
| **E.11** | Transduction of dendritic and tissue cells with tumor antigens using plasmids, viral vectors and hybrid fusions. | No | No |
| **E.12** | Lasar capture microdisection of cells from tumor biopsies and tissue samples to determine origin (donor vs patient). | No | No |
| **E.13** | Quantification of polyoma virus BK exposure by serology and PCR in stem cell transplant donors and recipients from blood and urine samples. | No | No |
| **E.14** | Quantification of polyoma virus BK specific T cells in stem cell transplant donors and recipients from peripheral blood samples. | No | No |
| **E.15** | Determination of origin of neovasculature endothelial cells in tumor and tissue samples obtained from subjects post transplant. | No | No |
| **E.16** | Quantification of lymphocyte subsets CD34 progenitors and endovasculator progenitors in G-CSF mobilized peripheral cell allografts. | No | No |
| **E.17** | Testing for polyoma virus BK latency in CD34 progenitors, B cells and T cells in the G-CSF mobilized peripheral cell allografts. | No | No |

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| **E.18** | Determination of etiology of membraneous nephropathy using serum from subjects. | No | No |
| **E.19** | Serum Proteomic patterns analysis to diagnose complications related to allogeneic transplantation. | No | No |
| **E.20** | Determine cell origin (donor vs patient) of tissue samples using IHC, IF, sorting, and FISH. | No | No |
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| **F** | **Lymphoid Malignancies Section (Dr. Adrian Wiestner)** | | |
| **F.1** | Culture of cells from research subjects to investigate molecular disease mechanisms, model host tumor interactions, and to test effect of drugs on cell survival and cellular functions. | No | No |
| **F.2** | Generation of stable cell lines for the study of hematologic malignancies. | No | No |
| **F.3** | Modifications of cells using standard expression systems or biologic molecules, e.g. interfering RNA, to investigate the effects of candidate genes on cellular functions. | | |
| **F.4** | Identification and monitoring of B or T cell populations as identified by flow cytometry and by their B cell or T cell receptor expression. | No | No |
| **F.5** | Measurement of gene expression in cells or tissues. Techniques frequently used include gene expression profiling on microarrays, quantitative RT-PCR, Western blotting, flow cytometry and ELISA assays. | No | No |
| **F.6** | Analysis of chromosomal abnormalities or mutations in malignant cells and non-malignant cells including FISH technology and DNA sequencing. | No | No |
| **F.7** | Assays of immune function of B-cells and T-cells, including intracellular cytokine staining, ELISPOT, quantitative RT-PCR for cytokines or other immune regulatory genes. | No | No |
| **F.8** | Analysis of antibody specificities in serum and antigen specificity of the B-cell receptor on cells. Techniques may include expression of antibodies in phage display systems, generation of antibodies in cell culture systems and use of such antibodies to screen for cognate antigens. | No | No |
| **F.9** | Transplantation of human cells into mice (xenograft model) to study disease biology and to investigate the effect of experimental therapy. | No | No |

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| **F.10** | Measurements of drug concentrations, biologic molecules and disease markers in blood, serum, and plasma. | No | No |

## 16.4. Appendix D

**NIH INFORMATION SHEET ON STAFF RESEARCH PARTICIPATION (APRIL 2016)**

As an NIH employee, contractor, Special Volunteer, Guest Researcher, or trainee, you may participate in intramural research studies unless it is prohibited by your Institute or Center (IC), or if you are excluded by the criteria of the protocol in which you want to enroll. The inclusion of NIH staff in a particular protocol must also be approved by the IRB. You may be motivated by altruism, a commitment to research in your own or related fields, or want access to clinical trials of potential direct therapeutic benefit. When deciding, you should make an informed decision about participation. This information sheet offers some points to consider for NIH staff who are considering research participation at NIH.

First, similar to any individual who is considering research participation, you should seek adequate information about the study purpose, what is required of you in terms of procedures, interventions and time, and the potential risks and benefits of participation. For more information, see the NIH Clinical Center's public website "Are Clinical Studies for You?" at http://www.cc.nih.gov/participate/studies.shtml.

When you are thinking about participation in a research study that is being conducted by your supervisor, or others with whom you work closely in your laboratory, branch, or unit, you should consider some additional factors:

A. **Possible bias**: Are you confident that you can be unbiased about reporting answers, side effects, or other information that could influence the study outcome or risk to you?
B. **Confidentiality**: Has the principal investigator (PI) spoken about what information will be collected from you as part of the study? Has the PI discussed what information will be available to those within, and outside, the study team? If applicable, are you comfortable sharing your medical history (including, for example, mental health history or STDs) and your social history (e.g. substance use) with study investigators who may be your coworkers, or with the possibility of them discovering something about your health during the study (e.g. pregnancy status or a new diagnosis)? Although every effort will be made to protect your information and keep it private and confidential, your information may, depending on the nature of the protocol, become available in medical records or to authorized users outside of the study team. Discuss any concerns with the PI.

C. **Pressure**: Do you perceive any pressure or expectations from your supervisor or colleagues regarding participation? Could that pressure influence your decision or make it difficult for you to choose whether or not to participate? Remember that it is your choice whether or not to participate and that your decision to participate or not should not have an effect, either beneficial or adverse, on your position at NIH.

D. **Time and Compensation**: Can you take time off from work to complete the study requirements or participate solely during non-duty hours? Can you receive compensation for your participation in this study? Will your supervisor give you permission to participate during work hours? See the NIH Policy Manual 2300630-3 *Leave Policy for NIH Employees Participating in NIH Medical Research Studies*.

E. **Consent Process:** Is the person obtaining your consent for the study your supervisor, a subordinate, or co-worker? If so, is there an independent person monitoring the consent process? If the study PI is a supervisor and intends to obtain consent from you, an independent person (e.g., through Bioethics or the NIMH Human Subjects Protections Unit [HSPU], or others as approved by the IRB) must monitor the consent process. If the person obtaining consent from you is a co-worker then an independent person (e.g., through Bioethics or the NIMH HSPU, or others as approved by the IRB) may be required to monitor the consent process, as determined by the IRB for the specific study.

If you are thinking of enrolling as a subject at the NIH Clinical Center and you have any questions or concerns, please contact the Office of Human Subjects Research Protections (OHSRP) at 301-402-3444 and/ or the Patient Representative if you are thinking of enrolling as a subject at the NIH Clinical Center on 301-496-2626. If you are at a NIH site outside the Clinical Center then please contact local site leadership.