

**Date:** April 20, 2020

**Title:** Response to the SHINGRIX Varicella Zoster Virus (VZV) Vaccine in Chronic Lymphocytic Leukemia (CLL) Patients that are Treatment Naïve or Receiving Bruton's-tyrosine Kinase Inhibitor (BTK-I) Therapy

Other identifying words: SHINGRIX, VZV, CLL, BTK-inhibitor, Ibrutinib, Acalabrutinib

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Subjects of Study: Number	Sex	Age range	
Subjects:	108 (+15 ceiling to account for early dropout)		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 efficacy of the SHINGRIX varicella zoster virus (VZV) vaccine in chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) patients that are treatment naïve or receiving Bruton's-tyrosine kinase inhibitor (BTK-I). (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 or SLL
- b. Cohort 1: Treatment naïve CLL or SLL patients
- c. Cohort 2: Subjects must be receiving ibrutinib for at least 6 months prior to administration of the first vaccine dose
- d. Cohort 3: Subjects must be receiving acalabrutinib for at least 6 months prior to administration of the first vaccine dose
- e. Age  $\geq 18$  years
- f. ECOG performance status of 0-1

### Design:

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

### Study Objectives:

#### Primary Objective:

- a) Determine the serologic response against VZV after completing the SHINGRIX (RZV) 2-dose vaccine series in the following populations:
  - a. CLL patients that are treatment naïve (n=54)
  - b. CLL patients receiving treatment with ibrutinib (n=27)
  - c. CLL patients receiving treatment with acalabrutinib (n=27)

#### Secondary Objective:

- a) Determine the safety and tolerability of the SHINGRIX 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 serologic response against VZV after completing the SHINGRIX (RZV) 2-dose vaccine series in the following populations:
  - a. Chronic lymphocytic leukemia (CLL) patients that are treatment naïve (n=54)
  - b. CLL patients receiving treatment with ibrutinib (n=27)
  - c. CLL patients receiving treatment with acalabrutinib (n=27)

### **Secondary Objective:**

- a) Determine the safety and tolerability of the SHINGRIX 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 SHINGRIX vaccine response rates in patients on BTK-I treatment (ibrutinib and acalabrutinib) to response rates in treatment naïve CLL patients.
- b) Compare SHINGRIX vaccine response rates between patients on ibrutinib and patients on acalabrutinib.
- c) Assess changes in VZV specific T cell mediated immunity in CLL patients following SHINGRIX vaccination
- d) Assess kinetics of humoral and cell mediated immunity in CLL patients following SHINGRIX vaccination

## **3. BACKGROUND**

### **3.1. Clinical Background**

This study aims to determine the efficacy of the SHINGRIX VZV vaccine in CLL 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. Infections remain a major cause of death in patients with CLL.<sup>1</sup> The implementation of vaccination strategies provides the opportunity to deliver high-value, cost-effective care interventions.

To date, there is little evidence available to guide vaccination in immunocompromised individuals with cancer. Until recently, VZV vaccine prophylaxis was contraindicated in CLL patients, as there was only a live-vaccine variant available. A new recombinant, adjuvanted VZV vaccine (SHINGRIX) has the potential to reduce VZV infection/reactivation in this vulnerable population. It is currently unknown how effective the SHINGRIX vaccine is in protecting immunocompromised patients with CLL against VZV infection/reactivation. One study demonstrated that up to 80% of patients with hematologic malignancies (subjects with CLL were excluded) are able to mount an immune response to the SHINGRIX vaccine.<sup>2</sup> Looking at other vaccines, previous studies of the influenza vaccine in CLL patients have reported response rates ranging from 15 to 63%.<sup>3,4</sup> In addition, it is unclear to what extent CLL patients treated with BTK inhibitors respond to vaccines. To date, only two published studies with less than 20 patients each have assessed influenza vaccine responses in CLL patients treated with BTK-Is, citing response rates between 7% and 26%.<sup>5,6</sup>

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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>8</sup> Seroconversion and subsequent host immunity after vaccine administration is reliant on an effective B-cell response and it is currently unclear how BTK-Is influence immune responses to vaccines. Surprisingly, 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.<sup>9</sup> The change in IgA appears to be clinically relevant, as in a phase 2 study, patients with greater improvements in IgA developed fewer infections.<sup>10</sup> 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.<sup>11</sup> Taken together, these effects may not only decrease infection risk, but may also enhance the efficacy of vaccines and immunotherapies to treat CLL.<sup>12-14</sup>

This study will determine the SHINGRIX 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 guide clinical practice of the SHINGRIX vaccine administration to CLL patients.

### **3.2. Indications for SHINGRIX Vaccination**

The most recent guidelines from the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP)<sup>15</sup> recommend the use of the SHINGRIX recombinant, adjuvanted vaccine over the ZOSTAVAX live-attenuated herpes zoster vaccine. Specifically, the recommendations include vaccinating all immunocompetent adults  $\geq 50$  years of age, including patients who previously received the live-attenuated herpes zoster vaccine, as well as patients with a history of herpes zoster.

SHINGRIX is licensed for all persons aged  $\geq 50$  years of age, however the efficacy of the vaccine remains to be determined in immunocompromised individuals. The ACIP recommends the use of SHINGRIX in persons taking low-dose immunosuppressive therapy (e.g.  $< 20$  mg/day of prednisone or equivalent) and in persons anticipating immunosuppression or who have recovered from an immunocompromising illness.<sup>15</sup> Immunocompromised individuals were excluded from the original SHINGRIX efficacy studies, however one follow-up study demonstrated that up to 80% of patients with hematologic malignancies (subjects with CLL were excluded) are able to mount an immune response to the SHINGRIX vaccine.<sup>2,16,17</sup>

### **3.3. Summary of Clinical Safety**

A brief summary of safety data from the SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted) is provided in the table below. A large Phase III, multicenter, trial has already established safety of SHINGRIX in healthy and elderly adults.<sup>16</sup> Most solicited local adverse reactions and systemic adverse events seen with SHINGRIX were considered by the subjects as mild and self-limiting and did not last more than 7 days with a median duration of 2-3 days. The incidence of solicited local and general symptoms was lower in subjects aged 70 years and older compared with those aged 50-59 years. There were no differences in the proportions of subjects reporting any grade 3 solicited local reactions between dose 1 and dose 2. Grade 3 solicited general adverse events (headache, shivering, myalgia, and fatigue) were reported more frequently by subjects after dose 2 (2.3%, 3.1%, 3.6%, and 3.5%, respectively) compared with dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).

The following table lists the most frequently reported vaccine related adverse events (VRAEs) in subjects receiving SHINGRIX<sup>18</sup>:

<b>Rates of Local and Systemic Adverse Reactions within 7 days of receiving SHINGRIX</b>			
<b>Local</b>	<b>Aged 50-59 Years (n=1315) (%)</b>	<b>Ages 60-69 Years (n=1311) (%)</b>	<b>Ages ≥70 Years (n=2258) (%)</b>
Pain	88.4	82.8	69.2
Pain, Grade 3	10.3	6.9	4.0
Redness	38.7	38.4	37.7
Redness >100 mm	2.8	2.6	3.1
Swelling	30.5	26.5	23.0
Swelling >100 mm	1.1	0.5	1.3
<b>Systemic</b>	<b>Aged 50-59 Years (n=1315) (%)</b>	<b>Ages 60-69 Years (n=1311) (%)</b>	<b>Ages ≥70 Years (n=2258) (%)</b>
Myalgia	56.9	49.0	35.1
Myalgia, Grade 3	8.9	5.3	2.8
Fatigue	57.0	45.7	36.6
Fatigue, Grade 3	8.5	5.0	3.5
Headache	50.6	39.6	29.0
Headache, Grade 3	6.0	3.7	1.5
Shivering	35.8	30.3	19.5
Shivering, Grade 3	6.8	4.5	2.2
Fever	27.8	23.9	14.3
Fever, Grade 3	0.4	0.5	0.1
GI-Upset	24.3	16.7	13.5
GI-Upset, Grade 3	2.1	0.9	1.2

### **Serious Adverse Events (SAEs)**

In the 2 studies, SAEs were reported at similar rates in subjects who received SHINGRIX (2.3%) and placebo (2.2%) from the first administered dose up to 30 days post last vaccination<sup>16,17</sup>. SAEs were reported for 10.1% of subjects who received SHINGRIX and for 10.4% of subjects who received placebo from the first administered dose up to 1 year post last vaccination.

Vaccine related serious adverse events (VRSAs) were very rare, occurring overall in 0.2% of all patients receiving SHINGRIX (see table below for details)<sup>16</sup>:

<b>Proportions of vaccination related serious adverse events (VRS AE)</b>		
	<b>SHINGRIX Recipients (n=6950)</b>	
<b>Disorder</b>	<b>n</b>	<b>%</b>
At least on VRS AE	12	0.2
Total number of VRS AEs	16	0.2
Lymphadenitis	1	0.0
Acute Myocardial Infarction	1	0.0
Ulcerative Colitis	1	0.0
Acute Pancreatitis	1	0.0
Administration Site Erythema	1	0.0
Administration Site Pain	1	0.0
Chills	1	0.0
Pyrexia	1	0.0
Allergic Granulomatous Angiitis	1	0.0
Bacterial Arthritis	1	0.0
Erysipelas	1	0.0
Herpes Zoster Oticus	1	0.0
Neutropenic Sepsis	1	0.0
Acute Myeloid Leukemia	1	0.0
Guillain-Barre Syndrome	1	0.0
Eczema	1	0.0

Optic ischemic neuropathy was reported in 3 subjects (0.02%) who received SHINGRIX (all within 50 days after vaccination) and 0 subjects who received placebo; available information is insufficient to determine a causal relationship with SHINGRIX.

### **3.4. Clinical and Scientific Justification**

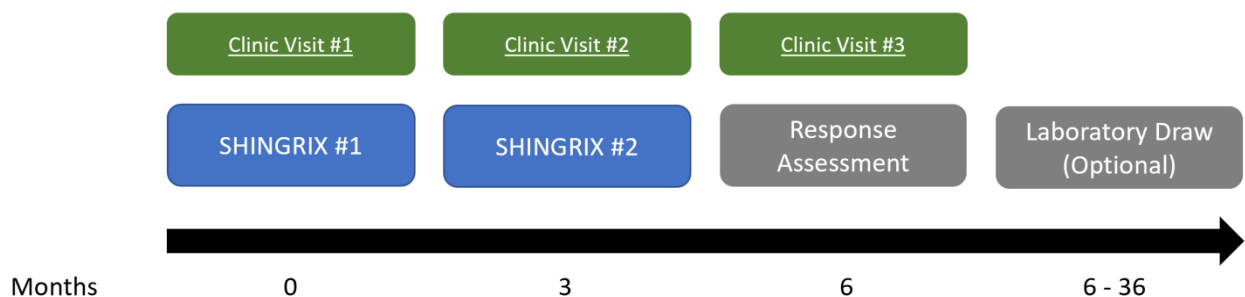
This study aims to provide critical information to clinicians and patients about the utility and feasibility of the SHINGRIX vaccine series administration in CLL patients who are treatment naïve or receiving BTK-I therapy.



SHINGRIX is licensed for all persons aged  $\geq 50$  years of age. In addition, the CDC Advisory Committee on Immunization Practices (ACIP) recommends the use of SHINGRIX in persons anticipating immunosuppression or who have recovered from an immunocompromising illness.<sup>15</sup> The SHINGRIX vaccine is highly effective and provides  $>90\%$  protection rates even in the elderly ( $\geq 70$  years of age) population.<sup>16</sup> The SHINGRIX vaccine efficacy in CLL patients is currently unknown. Previous studies investigating the response to the influenza vaccine in CLL patients have demonstrated that these patients are able to mount an immune response to vaccines, albeit at a lower rate compared to healthy individuals.<sup>4,5</sup> Herpes zoster is of particular concern in CLL, as these patients have an increased risk of VZV reactivation and ensuing complications.<sup>19,20</sup> In summary, vaccination of CLL patients against SHINGRIX can be considered as part of supportive care to reduce their risk of herpes zoster and post-herpetic neuralgia.

#### 4. STUDY DESIGN

Patients with CLL will enroll on the study for the purpose of determining the SHINGRIX vaccine efficacy in patients who are treatment naïve or receiving BTK-I therapy. A series of 2 doses of SHINGRIX will be given at 0- and 3- months (+/- 15-day window) schedule by intramuscular injection. Subjects will be followed for 6 months and receive assessment of serologic response 6 months (- 15-day, +180-day window) following the first vaccine administration. After subjects complete response assessment, they may receive optional laboratory testing to document long-term immunologic responses to the vaccine.



#### 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<sup>21</sup>

- b. Cohort 1: Treatment naïve CLL/SLL patients
- c. Cohort 2: Subjects must be receiving ibrutinib for at least 6 months prior to administration of the first vaccine dose
- d. Cohort 3: Subjects must be receiving acalabrutinib for at least 6 months prior to administration of the first vaccine dose
- e. No active, symptomatic VZV or herpes zoster infection within 12 months prior to vaccination
- f. No exposure to the live VZV vaccine (ZOSTAVAX) within 12 months prior to vaccination
- g. No prior exposure to the SHINGRIX vaccine
- h. Age  $\geq 18$  years
- i. ECOG performance status of 0-1
- j. Able to comprehend the investigational nature of the protocol and provide informed consent

## **5.2. Exclusion Criteria**

- a. Female patients who are currently in pregnancy
- 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. Severe allergic reaction to any component of SHINGRIX
- 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 chronic lymphocytic leukemia
- h. Non-English speaking individuals will be excluded from the study

## **5.3. Patient Registration**

*On-Study Procedure:* 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**

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted) - A series of 2 doses (0.5 ml each) will be given on a 0- and 3- months (+/- 15-day window) schedule via intramuscular injection.

### **6.2. Holding of Vaccine Administration**

If medically necessary reasons to hold SHINGRIX occur during treatment (i.e. active systemic infection, impending workups for diagnostic and/or therapeutic purposes), SHINGRIX 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 SHINGRIX vaccine outside the +/- 15-day 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 (VRSAs) that occur during the treatment period does not substantially exceed an anticipated rate. VRSAs may not exceed the reported rates in the Shingrix vaccine package insert.

Subjects who are unable to receive the second SHINGRIX 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 signing consent.
- 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 30 days prior to the first vaccine dose. Tests performed at the NIH on a different protocol will be accepted.
  - CBC with differential
  - Acute Care Panel (includes Na, K, Cl, CO<sub>2</sub>, Creatinine, Glucose, Urea Nitrogen)
  - Hepatic Panel (includes Alkaline Phosphatase, ALT, AST, Total Bilirubin, Direct Bilirubin)
  - Total B-cell, NK-cell and T-cell counts
  - Immunoglobulin levels
  - HLA-typing (A,B,C,DR,DQ) [if not yet already performed at NIH on other protocols]
  - C-reactive protein
  - HIV screening test (only if there is no result available within 365 days prior to the first vaccine dose)
  - Research blood (up to 80ml) (Refer to Appendix C for a list of possible research tests)

The following laboratory tests are optional and can be completed at any time between the 3- and 6-month assessment after the second vaccine dose is administered. Tests performed at the NIH on a different protocol will be accepted:

- CBC with differential
- Acute Care Panel (includes Na, K, Cl, CO<sub>2</sub>, Creatinine, Glucose, Urea Nitrogen)
- Hepatic Panel (includes Alkaline Phosphatase, ALT, AST, Total Bilirubin, Direct Bilirubin)
- Total B-cell, NK-cell and T-cell counts
- Immunoglobulin levels
- C-reactive protein
- Research blood (up to 80ml) (Refer to Appendix C for a list of possible research tests)

### **7.3. On study Evaluations**

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

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

- CBC with differential
- Acute Care Panel (includes Na, K, Cl, CO<sub>2</sub>, Creatinine, Glucose, Urea Nitrogen)
- Hepatic Panel (includes Alkaline Phosphatase, ALT, AST, Total Bilirubin, Direct Bilirubin)
- Total B-cell, NK-cell and T-cell counts
- Immunoglobulin levels
- C-reactive protein
- Pregnancy test (for women of childbearing potential and during the 3 month assessment only)
- Research blood (up to 80ml) (Refer to Appendix C for a list of possible research tests)

### **7.4. Response Assessment**

Response assessment will be performed 6 months (- 15-day, +180-day window) after receiving the first SHINGRIX vaccine dose. Laboratory tests drawn during on-study evaluations (Section 7.3) will be used for the efficacy analysis. No additional tests are required.

#### **7.5. After Response Assessment (Optional)**

After subjects complete response assessment, they may receive optional laboratory testing to document long-term immunologic responses to the vaccine. Additional laboratory testing is optional and will only be performed if the patient agrees.

The following laboratory tests may be performed between 6 and 36 months after response assessment. Tests performed at the NIH on a different protocol will be accepted.

- CBC with differential
- Acute Care Panel (includes Na, K, Cl, CO<sub>2</sub>, Creatinine, Glucose, Urea Nitrogen)
- Hepatic Panel (includes Alkaline Phosphatase, ALT, AST, Total Bilirubin, Direct Bilirubin)
- Total B-cell, NK-cell and T-cell counts
- Immunoglobulin levels
- Research blood (up to 80ml) (Refer to Appendix C for a list of possible research tests)

#### **7.6. 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.

#### **7.7. 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
- Subjects that are treatment naïve: Any situation necessitating starting treatment for CLL during the study period

#### **7.8. 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 that starts IVIG during the study period (after the first vaccine administration until the response assessment at 6 months).

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

It is possible that a very small subset of patients may have seropositive titers for HIV at baseline assessment. This could indicate that patients may have had HIV exposure without knowing. These patients will be followed for safety monitoring, and if clinically indicated, be seen by an infectious disease specialist. Patients with seropositive titers at baseline will be offered to receive the second vaccine dose (patient choice) 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 HIV seropositive.

### **8. CRITERIA FOR RESPONSE**

The response criteria for achieving serologic response against VZV following the SHINGRIX vaccine are based on a validated luciferase immunoprecipitation assay detecting VZV anti-glycoprotein E antibody.<sup>22</sup> Serologic titers to assess response to the SHINGRIX vaccine will be drawn 6 months (- 15-day, +180-day window) after the first SHINGRIX vaccine administration. The primary endpoint is serologic response defined as  $\geq$  four-fold rises in VZV anti-gE blood IgG titer achievement after completing the SHINGRIX (RZV) 2-dose vaccine series.

### **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 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 breach 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 serologic response against VZV following completion of the SHINGRIX 2-dose vaccine series. Refer to section 8 for definitions of response.

### **10.2. Secondary Endpoint**

The safety endpoint will be safety and tolerability of the SHINGRIX vaccine among subjects 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 SHINGRIX 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  $H_1: p \neq 30\%$  with a two-sided type I error of 0.05. A sample size of 54 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  $\pm 14\%$ .

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 SHINGRIX vaccine series. Let  $p$  be the response rate, we will test the null hypothesis  $H_0: p \leq 10\%$  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 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 SHINGRIX vaccine. The response probabilities will be estimated using the sample proportions and their inferences including confidence intervals and hypotheses testing will be evaluated. Regression analysis will be used to assess the factors that may influence the response to the SHINGRIX vaccine.

#### **10.5. Off Study Criteria**

- a. *Per research subject choice*: Research subjects may withdraw from study at any time.
- b. *Death*
- c. *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.
- d. Lost to follow-up
- e. CLL Disease Progression or Transformation (refer to section 7.6)
- f. Need to Start IVIG (refer to section 7.7)
- g. Need to omit or delay administration of 2<sup>nd</sup> Vaccine Dose (Refer to section 6.3 and 6.4)
- h. Detection of HIV on baseline evaluation (refer to section 7.8)

#### **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**

**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.

**NIH Intramural 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.

**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**

Definitions are per Policy 801 "Reporting Research Events".

## 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:

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

<b>Relationship</b>	<b>Attribution</b>	<b>Description</b>
Unrelated to intervention	Unrelated	The AE is clearly <b>NOT</b> related to the intervention
	Unlikely	The AE is <b>doubtfully related</b> to the intervention
Related to intervention	Possibly	The AE <b>may be related</b> to the intervention
	Probably	The AE <b>is likely related</b> to the intervention
	Definitely	The AE <b>is clearly related</b> to the intervention

## Pregnancy

Before study enrollment, females of childbearing potential must agree to use contraception 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 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.

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

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.

#### **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.

## **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 breach 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 hereditary or acquired 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 SHINGRIX. Additionally, 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.

#### **Inclusion of NIH Staff**

- 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 SHINGRIX**

Most solicited local adverse reactions and systemic adverse events seen with SHINGRIX were considered by the subjects as mild and self-limiting, with the median duration of 2-3 days.

A summary of safety data from the SHINGRIX vaccine is described in section 3.3.

##### **Contraindications to Vaccine Administration**

History of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX.

##### **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 available human data to establish whether there is vaccine-associated risk with SHINGRIX in pregnant women.

A reproductive and developmental toxicity study was performed in female rats administered SHINGRIX or the AS01B adjuvant alone prior to mating, during gestation, and during lactation. The total dose was 0.2 mL on each occasion (a single human dose of SHINGRIX is

0.5 mL). This study revealed no adverse effects on fetal or pre-weaning development due to SHINGRIX.

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 herpes zoster and post-herpetic neuralgia.

Overall there is greater than minimal risk with prospect of benefit for achieving immunity against herpes zoster VZV infection.

#### **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. Effective January 21, 2019 a witness to the long form consent is no longer required.. 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**

A CRADA is being executed between NHLBI and Dr. David Koelle, University of Washington, Seattle, WA to assess changes in VZV specific T cell mediated immunity in CLL patients following SHINGRIX vaccination. NHLBI will provide de-identified peripheral blood samples for analysis.

## **14. PHARMACEUTICALS**

### **14.1. SHINGRIX**

#### **Product description**

SHINGRIX is commercially available and FDA approved. Note for more detailed and comprehensive background information please refer to the SHINGRIX package insert.<sup>18</sup>

The study team with refer to the most recent package insert for prescribing information. Storage, preparation, dosage and administration will be performed per the CCND policy for Medication Preparation and the SOP for Medication Administration.

#### **Co-Administration of Other Vaccines**

Subjects may receive a different vaccine on the same day as SHINGRIX. If subjects receive two vaccines on the same day each vaccine must be administered in a 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.

### **14.2. FDA regulatory considerations**

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 CFR 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).

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## 16. APPENDIX

### 16.1. Appendix A – Schedule of Events

	Screening	Baseline	3 Month Follow-Up	Lab Draw after 2nd Vaccine Dose	6 Month Follow-Up (Response Assessment)	After Response Assessment (Optional)
Day of Study	N/A	D0	D90	D75-195	D180	After D180
Days (Plus/Minus)	N/A	N/A	±15	N/A	-15, +180	N/A
NIH visit		X	X		X	
<b>Medications</b>						
SHINGRIX Vaccine Dose		X	X			
<b>Clinical</b>						
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	
<b>Specific Labs/Other Tests</b>						
CBC with Differential		X	X	[R]	X	[R]
Acute Care Panel		X	X	[R]	X	[R]
Hepatic Panel		X	X	[R]	X	[R]
TBNK#		X	X	[R]	X	[R]
Imunoglobulins		X	X	[R]	X	[R]
HLA-typing		Y				
C-reactive protein		X	X	[R]	X	
Pregnancy Test		X*	X*		[R]	
HIV Screening		X**				
Research blood		X	X	[R]	X	[R]

#### Footnotes for Schedule of Events:

[R] Optional, drawn at discretion of clinical team

X Mandated

Y Mandated, unless HLA-Typing has already been performed as part of a prior protocol at NIH

X\* Mandated for women of childbearing potential only

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

C Chart Review

## 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: _____		
<b>General Symptoms:</b>				
	None	Mild	Moderate	Severe
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Symptoms:				

Day 1 ____/____/____				
Temp: _____ °F		Time taken: _____		
<b>General Symptoms:</b>				
	None	Mild	Moderate	Severe
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Symptoms:				

Administration Site Symptoms:				
	None	Mild	Moderate	Severe
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Swelling at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Redness at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Bruising at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	

Administration Site Symptoms:				
	None	Mild	Moderate	Severe
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Swelling at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Redness at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Bruising at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> 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 to 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: ____		
<b>General Symptoms:</b>				
	None	Mild	Moderate	Severe
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Symptoms:				

Day 3 ____ / ____ / ____				
Temp: ____ °F		Time taken: ____		
<b>General Symptoms:</b>				
	None	Mild	Moderate	Severe
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Symptoms:				

<b>Administration Site Symptoms:</b>				
	None	Mild	Moderate	Severe
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Swelling at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Redness at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Bruising at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	

<b>Administration Site Symptoms:</b>				
	None	Mild	Moderate	Severe
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Swelling at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Redness at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Bruising at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> 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: _____		
<b>General Symptoms:</b>				
	None	Mild	Moderate	Severe
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Symptoms:				

<b>Administration Site Symptoms:</b>				
	None	Mild	Moderate	Severe
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Swelling at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Redness at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Bruising at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	

Day 5 ____ / ____ / ____				
Temp: _____ °F		Time taken: _____		
<b>General Symptoms:</b>				
	None	Mild	Moderate	Severe
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Symptoms:				

<b>Administration Site Symptoms:</b>				
	None	Mild	Moderate	Severe
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Swelling at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Redness at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Bruising at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> 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 ____ / ____ / ____				
Temp: _____°F		Time taken: _____		
<b>General Symptoms:</b>				
	None	Mild	Moderate	Severe
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Symptoms:				



Day 7 ____ / ____ / ____				
Temp: _____°F		Time taken: _____		
<b>General Symptoms:</b>				
	None	Mild	Moderate	Severe
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Symptoms:				

<b>Administration Site Symptoms:</b>				
	None	Mild	Moderate	Severe
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Swelling at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Redness at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Bruising at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	

<b>Administration Site Symptoms:</b>				
	None	Mild	Moderate	Severe
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L
Swelling at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Redness at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm	
Bruising at administration site?	No <input type="checkbox"/> R <input type="checkbox"/> L	Yes <input type="checkbox"/> R <input type="checkbox"/> 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"**

<b>Ongoing Adverse Reactions after Day 7:</b>				
Temp: _____ °F		Time taken: _____		
<b>General Symptoms:</b>	Mild	Moderate	Severe	Date Resolved (mm/dd/yy) <i>Leave Blank if Ongoing</i>
Unusually tired/ feeling unwell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Muscle/body aches ( <i>not at product administration site</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Chills/Shivering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Nausea/Indigestion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Symptoms:				

<b>Administration Site Symptoms:</b>	Mild	Moderate	Severe	Date Resolved (mm/dd/yy) <i>Leave Blank if Ongoing</i>
Pain/tenderness at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	
Itching at administration site?	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	<input type="checkbox"/> R <input type="checkbox"/> L	
Swelling at administration site?	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm		
Redness at administration site?	Yes <input type="checkbox"/> R <input type="checkbox"/> L	If Yes, measure largest diameter: Right: _____ cm Left: _____ cm		
Bruising at administration site?	Yes <input type="checkbox"/> R <input type="checkbox"/> 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**

	<b>DESCRIPTION OF LABORATORY STUDY BY BRANCH SECTION</b>
<b>A</b>	<b>Stem Cell Allograft Transplantation Section (Dr. A. John Barrett)</b>
<b>A.1</b>	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.
<b>A.2</b>	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.
<b>A.3</b>	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.
<b>A.4</b>	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.
<b>A.5</b>	Injection of human cells into experimental animals to study the immune system and the growth of normal and malignant cells under varying conditions.
<b>A.6</b>	Testing of selection methods, cell isolation, and cell expansion leading to the development of new cell-based therapies requiring scale-up for clinical application.
<b>A.7</b>	Identification of individual T cell clones by their T cell receptor sequence.
<b>A.8</b>	Measurement of tumor and tissue specific antigens in cells of subjects and donors by mRNA, protein, or peptide expression in cells or fluids.



<b>A.9</b>	Laser capture micro dissection of cells from biopsies for GVHD to determine clonotypes.
<b>A.10</b>	DNA and RNA typing of genes that control immune responses in lymphocytes.
<b>A.11</b>	Microassay studies utilizing cellular DNA, cDNA, and RNA for neoplasia and host-tumor interactions.
<b>A.12</b>	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.
<b>B</b>	<b>Molecular Hematopoiesis Section (Dr. Cynthia Dunbar)</b>
<b>B.1</b>	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.
<b>B.2</b>	Hematopoietic progenitor-derived colony ascertainment in vitro (as described above), and engraftment of immunodeficient mice for detection of human stem cell number and function.
<b>B.3</b>	Testing ability of hematopoietic progenitor cells to be transduced with retroviral, lentiviral, and novel gene transfer vectors in vitro.
<b>B.4</b>	Reprogramming of adult mature cells, including skin fibroblasts and blood cells, into induced pluripotent stem cells in vitro.
<b>C</b>	<b>Cell Biology Section (Dr. Neal Young)</b>
<b>C.1</b>	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.

<b>C.2</b>	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.
<b>C.3</b>	Separation and functional study of cell populations characteristic of paroxysmal nocturnal hemoglobinuria, identified by absence of glycosylphosphatidylinositol anchored proteins.
<b>C.4</b>	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.
<b>C.5</b>	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.
<b>C.6</b>	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.
<b>C.7</b>	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.
<b>C.8</b>	Flow cytometric analysis of blood and bone marrow for hematopoietic stem cell progenitors and CD34 positive cells.
<b>C.9</b>	Studies of chromosomal instability in myelodysplastic 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.
<b>C.10</b>	Surface Enhanced Laser/Desorption Ionization (SELDI) time-of-flight mass spectrometry (Ciphergen) (proteomics methodology).
<b>C.11</b>	Mitochondrial DNA (mtDNA) sequence heterogeneity.
<b>C.12</b>	Measurement of EBV viral load.

<b>C.13</b>	Measurement of EBV LMP-1 via RT-PCR for LMP-1 RNA or flow cytometry for LMP-1.
<b>C.14</b>	Outgrowth assay of EBV transformed B cells.
<b>C.15</b>	Quantification of serum chemokines and cytokines (e.g. SDF-1, IL-10, IL-6, CXCR4, CXCL12).
<b>C.16</b>	Quantification of EBV cytotoxic T cells (tetramer staining).
<b>C.17</b>	Telomere length measurement by Southern blot, Q-PCR, flow-FISH, in situ hybridization and STELA
<b>C.18</b>	Telomere repair complex gene mutations by nucleotide sequencing of some or all of the following: <i>DKC1</i> , <i>TERC</i> , <i>TERT</i> , <i>SBDS</i> , <i>NOP10</i> , <i>NHP2</i> .
<b>C.19</b>	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.
<b>C.20</b>	Confocal microscopic imaging of bone marrow.
<b>C.21</b>	Characterization of intracellular signaling proteins by cell permeabilization and flow cytometry, and quantitative immunoblots.
<b>C.22</b>	Assays for chromosomal aneuploidy by fluorescence in situ hybridization (FISH) and other molecular techniques.
<b>C.23</b>	Conversion of human dermal fibroblasts into hematopoietic progenitors using Oct4 transfection.
<b>C.24</b>	Quantification of gene expression with RNA-seq
<b>C.25</b>	Characterization of chromatin and promoter/enhancer landscapes with ATAC-seq
<b>C.26</b>	Measurement of protein markers with SomaLogic's SOMAscan assay
<b>D.1</b>	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.

<b>D.2</b>	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 inoculation of mice, rabbits, and monkeys, as well as antibody measurements.
<b>D.3</b>	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, circoviruses, and parvoviruses, using assays as in (2).
<b>D.4</b>	Spectra-typing of blood cells to determine response to known or putative viral infections.
<b>D.5</b>	HLA typing or subtyping to determine risk factors/determinants for hepatitis-AA studies.
<b>D.6</b>	Cytotoxic lymphocyte assays with intracellular cytokine measurement for determining anti-viral response and lymphocyte cloning to obtain clones with specific antiviral activity.
<b>E</b>	<b>Solid Tumor Section (Dr. Richard Childs)</b>
<b>E.1</b>	Cr51 cytotoxicity assay to evaluating killing of patient tumor cells by patient NK cell clones and T-cells.
<b>E.2</b>	ELISA for IL-12 maturity of DC's made from subjects monocytes.
<b>E.3</b>	ELISA for IFN $\alpha$ to evaluate specificity of CTL clones.
<b>E.4</b>	H thymidine uptake to evaluate proliferation potential of antigen specific T-cells.
<b>E.5</b>	PCR of STR to assess chimerism status of cellular subsets grown in-vitro or retrieved from subjects post-transplant.
<b>E.6</b>	Flow sorting of PBL and/or tissue samples to evaluate chimerism of different subsets.
<b>E.7</b>	Surface marker analysis of peripheral blood mononuclear cells using flow cytometry.
<b>E.8</b>	cDNA expression arrays to evaluate T-cells expression/gene patterns in subjects with GVHD and a GVT effect.
<b>E.9</b>	Geno typing of tumor or tissue samples by high density cDNA arrays.
<b>E.10</b>	VHL mutation analysis on kidney cancer tissue.

<b>E.11</b>	Transduction of dendritic and tissue cells with tumor antigens using plasmids, viral vectors and hybrid fusions.
<b>E.12</b>	Laser capture microdissection of cells from tumor biopsies and tissue samples to determine origin (donor vs patient).
<b>E.13</b>	Quantification of polyoma virus BK exposure by serology and PCR in stem cell transplant donors and recipients from blood and urine samples.
<b>E.14</b>	Quantification of polyoma virus BK specific T cells in stem cell transplant donors and recipients from peripheral blood samples.
<b>E.15</b>	Determination of origin of neovasculature endothelial cells in tumor and tissue samples obtained from subjects post transplant.
<b>E.16</b>	Quantification of lymphocyte subsets CD34 progenitors and endovascular progenitors in G-CSF mobilized peripheral cell allografts.
<b>E.17</b>	Testing for polyoma virus BK latency in CD34 progenitors, B cells and T cells in the G-CSF mobilized peripheral cell allografts.
<b>E.18</b>	Determination of etiology of membranous nephropathy using serum from subjects.
<b>E.19</b>	Serum Proteomic patterns analysis to diagnose complications related to allogeneic transplantation.
<b>E.20</b>	Determine cell origin (donor vs patient) of tissue samples using IHC, IF, sorting, and FISH.
<b>F</b>	<b>Lymphoid Malignancies Section (Dr. Adrian Wiestner)</b>
<b>F.1</b>	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.
<b>F.2</b>	Generation of stable cell lines for the study of hematologic malignancies.
<b>F.3</b>	Modifications of cells using standard expression systems or biologic molecules, e.g. interfering RNA, to investigate the effects of candidate genes on cellular functions.
<b>F.4</b>	Identification and monitoring of B or T cell populations as identified by flow cytometry and by their B cell or T cell receptor expression.

<b>F.5</b>	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.
<b>F.6</b>	Analysis of chromosomal abnormalities or mutations in malignant cells and non-malignant cells including FISH technology and DNA sequencing.
<b>F.7</b>	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.
<b>F.8</b>	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.
<b>F.9</b>	Transplantation of human cells into mice (xenograft model) to study disease biology and to investigate the effect of experimental therapy.
<b>F.10</b>	Measurements of drug concentrations, biologic molecules and disease markers in blood, serum, and plasma.

## 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.