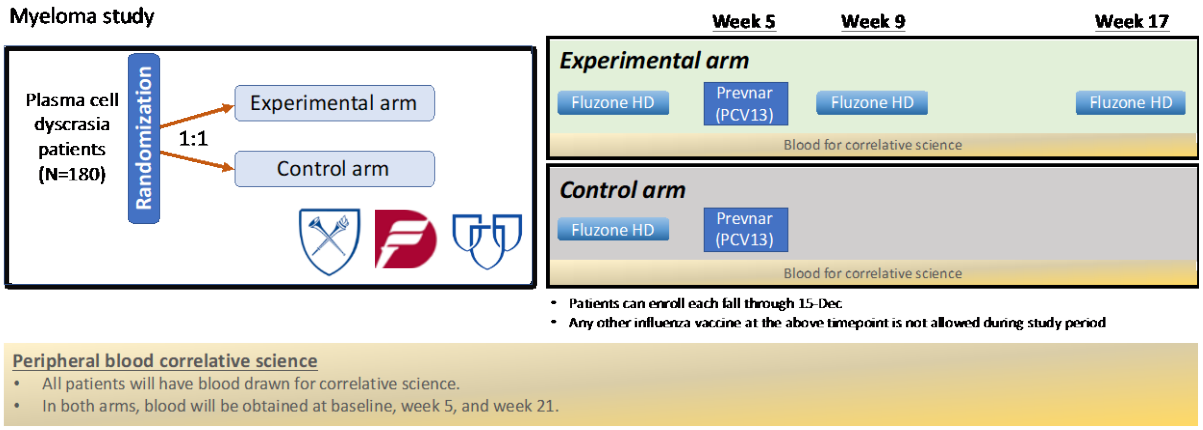
TITLE:	**INFLUENZA VACCINATION IN PLASMA CELL DYSCRASIAS**
Coordinating Center:	**Winship Cancer Institute of Emory University**
Winship PI:	Craig Hofmeister MD MPH
Laboratory investigator:	Madhav Dhodapkar MBBS
Sanofi:	Fluzone HD
Commercial Agent:	Prevnar 13 (PCV 13)
Statistician:	Yuan Liu, Ph.D Winship BBISR
Protocol / Date:	Initial / 7-May-2019 V 1.1 / 22-May-2019 V 1.2 / 13-Jul-2019 V 1.3 / 31-Oct-2019 V 1.31 / 13-Nov-2019 V 2.0 / 9-Mar-2020 V 2.1 / 7-Apr-2020 V 2.2 / 3-Jul-2020 V 2.3 / 20-Jul-2020 V 2.4 / 14-Sep-2020
CTCAE version:	5.0
Total consented patients:	175 total 50 patients (2019-2020) of which 23 were evaluable 125 patients (2020-2021)

Text color legend

Blue text Instructions and detailed for correlative science for laboratory #1

Blue text Instructions and detailed for correlative science for laboratory #2

SCHEMA



This is a phase IV randomized trial of 148 evaluable patients with a plasma cell disorder to be enrolled as early as possible in the influenza season through 15-Dec.

Fluzone HD refers to TIV formulation for 2019-2020 influenza season and QIV formulation for 2020-2021 season.

After eligibility is confirmed, patients will be randomized 1:1 to either an experimental arm where each patient receives three injections of Fluzone HD and a control arm where each patient receives one injection of Fluzone HD.

All patients receive Prevnar at week 5 if they have not received either PCV13 or PPSV23 in that calendar year.

STANDARD OF CARE AND RESEARCH INTERVENTIONS

Experimental arm

Timing	Week 1	Week 5	Week 9	Week 17	Week 21
Standard of care tests	• Blood tests • Clinic visit	Prevnar (PCV13)			Myeloma proteins
Research	• Consent • Eligibility • Research blood • Fluzone HD #1	Research blood	Fluzone HD #2	Fluzone HD #3	Research blood

Control arm

Timing	Week 1	Week 5	Week 9	Week 17	Week 21
Standard of care tests	• Blood tests • Clinic visit	Prevnar (PCV13)			Myeloma proteins
Research	• Consent • Eligibility • Research blood • Fluzone HD #1	Research blood			Research blood

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1. PRIMARY HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Clinical		
Hypothesis	**Objective**	**Endpoint**
Continuous Fluzone HD throughout the flu season will improve hemagglutination inhibition (HAI > 40) as measured at the end of the season compared to those patients that receive Fluzone HD once.	Demonstrate an absolute 25% increase in seroprotection, defined as HAI>40 against all strains, at week 21 in the experimental arm compared to the control arm.	HAI will be measured in all patients at baseline, week 5, and week 21 to calculate seroconversion at week 5 and seroprotection at week 21. Seroconversion: Pre-vaccination HAI<10 and a post-vaccination HAI>40 or a pre-vaccination HAI >10 and a ≥ 4-fold rise in post-vaccination HAI at week 5.

The above measurables will appear in the results section of www.clinicaltrials.gov at trial completion

2. EXPLORATORY SCIENTIFIC HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Measurement of B & T-cell subsets and flu-specific responses as a way of understanding immunosuppression in this patient population, correlating with influenza-like illness.

3. BACKGROUND

3.1 Influenza overview

Influenza is an acute viral respiratory illness from three main types (A, B, and C), where type A is subcategorized based on viral surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). Primary influenza pneumonia is a rare but severe, complicated by otitis media and exacerbations of chronic respiratory conditions. Other complications include otitis media, exacerbations of chronic respiratory disease, myocarditis – often the concern is for influenza infection to 'set the stage' for a subsequent lethal bacterial pneumonia. Those at high-risk for complications include those with cardiopulmonary diseases, chronic care facility residents, and those over 65 years old.

Influenza vaccines contain antigens of the circulating influenza viruses and are intended to trigger antibody-mediated protection. Influenza A viruses undergo continual changes in the hemagglutinin (HA) and neuraminidase (NA) proteins, which necessitate annual updates. Current influenza vaccines are available as inactivated vaccine (IV), trivalent (TIV) or quadrivalent (QIV), usually A/H1N1, A/H3N2, and either one or two strains of B), and as a recombinant vaccine which may be TIV or QIV.

3.2 Influenza risk in adult cancer patients

There is no perfect sign of acquired immunosuppression in humans. Neutropenia is often the consequence of chemotherapy that is watched most closely as it is associated with lethal bacterial infections especially when the absolute neutrophil count is less than 500/uL, and not surprisingly is associated with more influenza-

related complications than in the general population[1]. In two studies of different cancer patient populations, absolute lymphocyte count of less than 200/uL was an independent predictor of progression to influenza-related pneumonia[2].

A review of vaccine immunogenicity among patients with both liquid and solid tumors demonstrated decreased seroconversion rate among cancer patients receiving chemotherapy (17% to 52%) compared to cancer patients not receiving chemotherapy (50% to 83%) and compared to healthy controls (67% to 100%)[3].

People undergoing chemotherapy or those that have acquired profound immunosuppression seen after allogeneic stem cell transplantation are at increased risk of influenza-related complications[4,5]. People at highest risk include those with impaired cell-mediated and antibody-mediated immunity, as reflected by a decrease in the number or function of T and B cells[6]. Influenza-related hospitalization rates are four times higher and mortality 10 times higher among people with cancer compared with the general population[7,8].

3.3 Influenza vaccination research in allogeneic transplant patients

An open-label randomized trial included 78 patients at least a week before a planned allogeneic stem cell transplant[9]. Odds ratio for all-cause mortality was 1.05 (95% CI 0.4 to 2.77) among those vaccinated. Influenza-related mortality was similar as well between the groups (2/40 among vaccinated versus 2/38 among non-vaccinated). Documented influenza infection rate was similar in vaccinated and unvaccinated patients (3/40 versus 4/38, respectively). GMTs at 30 days post-vaccination among the vaccinated population were significantly higher for influenza A/H1N1 and influenza A/H3N2 strains (15 versus 10, p= 0.03 and 30 versus 12.5, p< 0.001, respectively).

Another open-label randomized trial enrolled 73 adults after allogeneic HSCT, of which 35 were randomized to receive an adjuvanted influenza vaccine (Fluad) and the rest (38) randomized to a non-adjuvanted influenza vaccine (Influvac)[10]. There were five cases (14%) of laboratory-confirmed influenza among patients receiving the adjuvanted vaccine compared to three cases (8%) in the non-adjuvanted vaccine group. Vaccine immunogenicity, reported as seroconversion rate, seroprotection rate, and GMTs, was not significantly higher in the adjuvanted vaccine group. This study was underpowered for conclusions regarding seroprotection or to identify differences in influenza-like illness between the groups.

3.4 Multiple myeloma

Multiple myeloma (MM) affects approximately 83,000 US citizens and over 50% of patients die within 5 years of diagnosis; more than half of patients older than 70 years with low albumin and high β2microglobulin die within a year of diagnosis[11,12]. Of the 30,330 new cases estimated in 2016 in the U.S.[13], MM is twice as common in African Americans as Caucasians, and genetic changes accumulate as plasma cells degenerate from monoclonal gammopathy of undetermined significance, through smoldering myeloma, to MM[14]. MM is characterized by fractures, anemia, kidney failure, and hypercalcemia with a

predisposition for bacterial infections from the inherent immunoparesis and varicella reactivation often aided by proteasome inhibition[15].

Advances in high-dose chemotherapy and stem cell transplantation have improved overall survival and event-free disease periods in patients with MM, but relapses are inevitable[16,17] New therapeutic agents, such as new generation proteasome inhibitors (carfilzomib and ixazomib), immunomodulatory agents (lenalidomide and pomalidomide, the histone deacetylase inhibitor (HDACi) panobinostat, and monoclonal antibodies (elutuzumab and daratumumab) have shown promising clinical benefit in patients with relapsed or refractory disease. Current treatments include regimens using proteasome inhibitors and/or immunomodulatory agents in combination with HDACi, alkylating agents, and monoclonal antibodies.

3.5 Myeloma patients and influenza

In myeloma patients on treatment, there is a 20% likelihood of influenza-like illness[18,19] with a 10-fold higher risk of viral URIs[20] than the general population. Even patients with precancerous conditions such as monoclonal gammopathy of undetermined significance (MGUS) and Smoldering Myeloma are at increased risk of bacterial and viral infections[21]. While only 3-5% of these viral illnesses are influenza, the mortality is high in the immunosuppressed and post-influenza bacterial pneumonias have high morality. In addition myeloma and it's precursor diseases provide a novel window to studying vaccination in a full spectrum of immunosuppression from non-cancerous low-risk MGUS to end-stage lymphopenic patients with relapsed multiple myeloma.

Vaccine preventable illnesses have not been prevented in patients with myeloma due in part to lack of seroresponse with standard dosing algorithms. Based on available trial data restricted to myeloma patients, serologic protection (HAI titer ≥40) to all three influenza strains following trivalent influenza vaccine is achieved in less than 20% of myeloma patients in each trial[22-24]. There have been two trials investigating the benefit of booster vaccine in myeloma patients. In 2005 Ljungmen et al, studied 70 patients with hematologic malignancies (10 with myeloma and 4 with WM) and administered a booster dose 30 days following standard influenza vaccine booster and found no increase in serologic protection[25]. More recently, in the past 2013-2014 flu season, Hahn et al gave a standard dose influenza booster vaccine after 30 days to 25 myeloma patients and noted a doubling of serologic protection (HAI titer ≥40) from 14% to 33%[26]. This suggests that there may be a role for booster vaccines in patients with hematologic malignancies, however there is obviously much room to improve.

Prior studies by the Dhodapkar lab has evaluated serologic responses to repeat influenza vaccination in patients with plasma cell disorders. In the first SHIVERING trial, we analyzed a strategy of 2 vaccine Fluzone HD doses, which led to higher rates of seroprotection compared to historic controls[27]. This was followed by a placebo-assisted randomized controlled study (SHIVERING-2 trial) comparing single dose versus 2-dose vaccination strategy. This trial[28] provided first evidence that 2-dose strategy leads to higher rates of seroprotection compared to current standard of annual influenza vaccination in these patients. At the end of the influenza season, the rates of sero-protection were 58% in the cohort with 2 vaccines versus 33% for the cohort with standard vaccines ($P<0.05$). These results

however need to be replicated in an independent study, before considering a change in standard practice. These considerations have led to the design of the current trial, wherein we will evaluate 3 doses of the vaccine (versus standard influenza vaccination) in order to further extend the rates of seroprotection at the end of study and test the hypothesis that repeat dosing of influenza vaccines leads to superior sero-protection in patients with plasma cell disorders, compared to that achieved with current standard vaccination strategy. If this trial replicates the findings with SHIVERING-2 trial, we believe it should lead to a change in current clinical practice for influenza vaccination in patients with plasma cell disorders.

3.6 Assessment of influenza vaccination response

Influenza vaccines work by activating antigen-specific B-cells to proliferate and differentiate into plasmablasts that secrete protective antibodies and memory B cells that can rapidly proliferate and differentiate into plasmablasts upon re-encountering the immunizing antigen. Studies in healthy individuals demonstrated a transient plasmablast response after vaccination peaking at around 7 days after vaccination at which point it makes up to 16% of all B-cell, and returning to baseline levels by day 14. Memory B-cell response, on the other hand, peaks at 14-28 days after vaccination followed by a slower rate of decline[29-31]. A subset of the plasmablasts migrate to the bone marrow and become long-lived plasma cells secreting antigen-specific antibodies for protracted periods of time. Memory B-cell and plasma cells provide a remarkably stable immunological memory that can persist over 50 years after vaccination in humans. Interestingly, plasma cells are not intrinsically long-lived and only a finite number of plasma cells survive after an immune response irrespective of the number of plasma cells generated, suggesting that plasma cells require a specialized niche for survival[32]. It remains unclear what factors direct the differentiation of activated, antigen-specific B-cells into either memory B-cells or plasmablasts and plasma cells. Studies in mice suggested that the B-cell repertoire in the memory B-cell and the plasma cells compartments differ in terms of antigen-binding affinity and breadth[33].

Generation of immunological memory is the hallmark of adaptive immune responses. Clinically, this can be measured by determining seroprotection, defined as the percentage of subjects with a post-vaccination hemagglutination antibody inhibtion (HAI) titer > 1:40; and seroconversion, the percentage of subjects with either a pre-vaccination HAI titer < 1:10 and a post-vaccination HAI titer > 1:40 or a pre-vaccination HAI titer > 1:10 and a minimum four-fold rise in post-vaccination HAI antibody titer by week 5.

Clearance of viral infection and vaccine responses are dependent on cell mediated immunity. The most common serologic measurement of antibody protection following influenza vaccine administration is an HAI titer of 40 or higher. However, this cutoff corresponds to an estimated 50% clinical benefit of preventing influenza infections, based on studies in young healthy adults[34,35]. It is believed that cell-mediated immunity declines with age, which may help explain why the elderly are more vulnerable to influenza infections. HAI titers have also been shown to be lower in the elderly compared to young adults. Based on studies showing increased serologic protection, Fluzone HD (TIV) was FDA approved in 2009 for adults aged 65 and older, the QIV formulation in Nov-2019.

3.7 Study rationale

The challenge of decreasing influenza infection rate and severity in patients with hematologic malignancies are manifold: first, influenza virus undergoes antigenic drift and antigenic shift allowing it to overcome pre-existing immunity; second, the fact that most vaccine-elicited neutralizing antibodies are directed against hypervariable epitopes of the HA protein, facilitating the emergence of antibody-escape viral variants; third, the apparent short half-life of vaccine-mediated antibody titers in immunocompetent individuals; forth, the underlying immune suppressive state caused by the hematologic malignancy and worsened by the treatments that these patients need to receive; and fifth, the lack of high quality data looking at the response to influenza vaccination in patients with hematologic malignancy at the different stages of their disease course. Therefore, more studies are needed to define the optimal timing of influenza vaccination in patients with hematologic malignancies and to design an influenza vaccination strategy that provides a long-lived antibody response targeting a conserved epitope in HA.

The National Comprehensive Cancer Network still recommends yearly vaccination using an inactivated influenza vaccine with the hope of achieving some protection and decrease the severity in the event of an infection. It is presumed that the higher incidence of viral infections in patients with hematologic malignancies is due to immune suppression associated with treatment and poor rates of seroconversion after vaccination. However, the exact mechanism of how this occurs is not well understood, limiting our ability to design better preventive measures against influenza infection. This study will measure immune responses to influenza vaccination in patients with plasma cell dyscrasias.

3.8 Potential risks and benefits

3.8.1 Potential risks

1. **Additional blood draws** - The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.
2. **Extra influenza vaccination** - The side effects from inactivated influenza vaccine are generally mild. They include soreness at injection site (10-64% of subjects) that lasts <2 days. When the vaccine is given, the subject may feel a slight pain and burning during the injection. Fever, malaise and myalgia can occur after vaccination with inactivated influenza vaccine. These reactions begin 6-12 hours after vaccination and can persist for 1-2 days. Patients with a history of severe allergic reaction are not eligible to participate in this study. Very rarely, occurring in about 1 in 4 million people given a vaccination, there can be a serious allergic reaction to a vaccine. These reactions can manifest as skin rash (hives), angioedema, bronchospasm, tachycardia, or hypotension. If these reactions occur, they can usually be stopped by the administration of emergency

medications by the study personnel. It is not known whether additional influenza risk will increase the risk of Guillain-Barre syndrome (GBS), estimated at 2.84 per million doses.

3. **Data security-** Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

3.8.2 Potential benefits

There is no guarantee of benefit to subjects who enroll in this protocol. However, seasonal influenza vaccine is considered beneficial to most subjects, as it generally provides protective immunity against the influenza strains within the vaccine. It is also considered standard of care for patients with hematologic malignancies. Data from this study may yield a better understanding of the current body of knowledge describing human infections with influenza viruses.

4. PATIENT SELECTION

4.1 Inclusion criteria

4.1.1 Patient must have a plasma cell dyscrasia that fits in the IMWG diagnostic criteria[15].

4.1.2 Both men and women of all races and ethnic groups are eligible for this study.

4.1.3 Age $\geq$ 18 years. Because plasma cell dyscrasias are extraordinarily rare in a pediatric population, children are excluded from this study.

4.1.4 ECOG performance status $\leq$ 3 (Karnofsky $\geq$30%, see Appendix A) is required for eligibility.

4.1.5 Patient must be eligible to receive standard of care influenza vaccination. If the patient has a history of egg allergy with symptoms more severe than urticaria, e.g. angioedema, respiratory distress, lightheadedness, or recurrent emesis, they remain eligible to receive influenza vaccination but must receive the vaccine in a facility able to recognize and manage severe allergic reactions. Persons who are able to eat lightly cooked egg

(e.g., scrambled egg) without reaction are unlikely to be allergic, although egg-allergic persons might tolerate egg in baked products

4.1.6 Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

4.2.1 Patients who have already received the seasonal influenza vaccine in the current season.

4.2.2 History of Guillain-Barré Syndrome

4.2.3 Patients with a previous severe allergic reaction to influenza vaccination or PCV13.

4.2.4 Expected survival < 9 months

4.2.5 Prisoners

5. REGISTRATION, ACCRUAL, AND EARLY TERMINATION

5.1 Accrual

5.1.1 Enrollment overall

The research team member obtaining informed consent will tell the patient that (1) participation is voluntary, (2) participation or non-participation will not affect their usual care and management, and (3) patient confidentiality will be maintained if the results of the study are published. The potential toxicities of protocol therapy and the study calendar will be explained to the potential participant. Patients will be provided with a consent form to review, and an opportunity to discuss the study and have all questions answered.

5.1.2 Registration Process

Patients will be registered after meeting all entry requirements and signing of the informed consent document.

To register a patient, the following should be completed

- Signed patient consent form
- HIPAA authorization form (if separate from consent from)

At Winship Cancer Institute [Emory], the research coordinator will verify eligibility per standard Clinical Trials Office procedures. To complete the registration process, the research coordinator will

- register the patient on the study
- assign the patient a study sequence ID

5.1.3 Strategies for recruitment and retention

This protocol follows NIH policy on inclusion of women and minorities as participants in research involving human subjects.

No incentives are provided to patients for trial participation.

5.1.4 Initial treatment arms

The total sample size of 148 patients will be split equally between the single versus 3-shot arms.

5.1.5 Method of treatment allocation

A patient number will be assigned upon registration.

5.1.6 Estimated accrual based on race, ethnicity and gender

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	3	+	4	=	15
Not Hispanic or Latino	61	+	80	=	165
Ethnic Category: Total of all subjects	64	+	84	=	148
Racial Category					
American Indian or Alaskan Native	1	+	0	=	1
Asian	1	+	2	=	3
Black or African American	10	+	18	=	28
Native Hawaiian or other Pacific Islander	1	+	0	=	1
White	51	+	64	=	115
Racial Category: Total of all subjects	64	+	84	=	148

5.2 Duration of therapy

Patient may remain on study until one of the following criteria applies:

- Intercurrent illness that prevents administration of vaccine or follow-up,
- Per physician discretion in the setting of unacceptable adverse event(s), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant. In patients who are randomized to the experimental arm only, specific adverse events include grade 3 adverse event that occurs without alternative etiology in the 7 days following the first study vaccination

- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the PI.
- Termination or suspension of the study for safety reasons

5.3 Duration of follow-up

Patients will be followed for 4 weeks after removal from study and patient records will be reviewed until death or 2 years from enrollment (whichever comes first) to assess progression and survival. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.4 Criteria for removal from study

Patients will be removed from study when any of the criteria listed in Duration of therapy applies. The reason for study removal and the date the patient was removed must be documented in the appropriate case report form.

5.5 Early stopping rules

If there are any deaths possible, probably, or definitely related to protocol therapy, the trial will be suspended and the DSMC will provide recommendations for proceeding with the study to the PI.

5.6 Premature termination or suspension of the study

This study may be suspended or prematurely terminated if there is sufficient cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency (as applicable) and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

6. STUDY PROCEDURES & SCHEDULE

6.1 Agent administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks of protocol therapy are described in the pharmaceutical section.

No investigational or commercial agents or therapies other than those described in this protocol may be administered with the intent to vaccinate the patient for influenza or S. pneumoniae.

6.1.1 Experimental arm – Intense Fluzone HD

Fluzone HD vaccine for a total of 3 doses beginning at the time of enrollment

6.1.2 Control arm – Single Fluzone HD

Fluzone HD vaccine once at the time of enrollment for a total of 1 dose.

6.2 Definition of dose-limiting toxicity

N/A

6.3 Standard of care study procedures

See Standard of care and research interventions

6.4 Research specific procedures

See Standard of care and research interventions

6.5 Schedule of events

Experimental arm

Assessment	Screening + First visit	Week 5[a]	Week 9[a]	Week 17[a]	Week 21[a]
Signed informed consent	X				
Vital signs	X				
CBC/d/p[d]	X				
CRP, Serum IG's, LDH	X				
Myeloma proteins[e]	X				X
Blood for research[f]	40 mL	40 mL			40 mL
Fluzone HD	X		X	X	
Prevnar (PCV13)		X			
Record grade ≥ 2 adverse events[g]	X		X	X	
Influenza-like illness update[b]		X	X	X	X
PFS and OS[h]					X

Control arm

Assessment	Screening + First Visit	Week 5[a]	Week 9[a]	Week 17[a]	Week 21[a]
Signed informed consent	X				
Vital signs	X				
CBC/d/p[d]	X				
CRP, Serum IG's, LDH	X				
Myeloma proteins[e]	X				X
Blood for research[f]	40 mL	40 mL			40 mL
Fluzone HD	X				
Prevnar (PCV13)		X			
Record grade ≥ 2 adverse events[g]	X				
Influenza-like illness update[b]		X	X	X	X
PFS and OS[h]					X

a. Assessments on these days can be performed within a ± 5 day window. Subsequent visits (weeks 5, 9, 17, 21) are based on the actual time of Fluzone HD vaccination, not the pneumonia vaccination.
b. Involves contact between study personnel and the patient regarding influenza-like illness and SAEs. An in-person visit is not required.
c. All patients (N=148) will have research blood drawn for correlative science. In both arms, blood will be obtained at baseline, week 5, and week 21. The first 20 patients in each group (n=40 total), split evenly between intervention arm (20 experimental, 20 control), had additional blood drawn 1 week after each Fluzone HD dose (week 2 for control arm and weeks 2, 10, and 18 in the experimental arm) – this was completed 17-Nov-2019.
d. CBC, differential, and platelets will be performed pre-vaccination.
e. If not done with results available within 30 days of initial vaccination, a modified myeloma disease assessment requested but not required to include SPEP and free light chains if either were measurable per IMWG criteria in the past. Serum IgD or IgE are requested if a monoclonal IgD or IgE were present in the past. For patients with an IgA monoclonal protein, Hevylite IgA can be used to replace serum immunoglobulins and SPEP.
f. Peripheral blood samples will be obtained and analyzed as described in correlative science section.
g. Adverse events related to vaccination will be assessed on day of vaccination, and 7 days after each Fluzone HD vaccination (in-person visit for significant adverse events). If patient is unable to be seen in-person, every effort will be made to obtain documentation of patient evaluation, treatment, and resolution of vaccine-related toxicities.
h. Survival information will be collected through chart review only. An in-person clinic visit is not required.

6.6 Dose levels for protocol-specific drugs

N/A

6.7 Dose interruptions

N/A

6.8 Dose reduction for overlapping toxicities

N/A

7. PHARMACEUTICAL INFORMATION

Complete production and toxicity information for commercial agents can be found in the appropriate FDA approved package insert. Investigator brochure for study agent describes preclinical results and clinical experience to date.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

7.1 Fluzone HD

Fluzone HD refers to QIV formulation for 2020-2021 season.

Ingredient	Quantity (per dose)
	Fluzone High-Dose Quadrivalent 0.7 mL Dose
Active Substance: Split influenza virus, inactivated strains*:	240 mcg HA total
A (H1N1)	60 mcg HA
A (H3N2)	60 mcg HA
B (Victoria Lineage)	60 mcg HA
B (Yamagata Lineage)	60 mcg HA
Other:	
Sodium phosphate-buffered isotonic sodium chloride solution	QS† to appropriate volume
Formaldehyde	≤140 mcg
Octylphenol ethoxylate	≤350 mcg
Gelatin	None
Preservative	None

*per United States Public Health Service (USPHS) requirement
†Quantity sufficient

Fluzone HD refers to TIV formulation for 2019-2020 influenza season

Ingredient	Quantity (per dose)
	Fluzone High-Dose 0.5 mL Dose
Active Substance: Split influenza virus, inactivated strains[a]:	180 mcg HA total
A (H1N1)	60 mcg HA
A (H3N2)	60 mcg HA
B	60 mcg HA
Other:	
Sodium phosphate-buffered isotonic sodium chloride solution	QS[b] to appropriate volume
Formaldehyde	≤ 100 mcg
Octylphenol ethoxylate	≤ 250 mcg
Gelatin	None
Preservative	None

7.1.1 Formulation, appearance, packaging, and labeling

Fluzone HD (TIV) [2019-2020]is supplied as a single-dose, prefilled syringe, without needle, 0.5 mL, in a package of 10.

Fluzone HD Quadrivalent (QIV) [2020-2021] is supplied as a single-dose, prefilled syringe, without needle, 0.7 mL, in a package of 10.

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1.2 Product storage and stability

Fluzone HD will be stored at 2-8ºC

The temperature of the storage unit must be recorded daily (excluding non-business days and holidays as applicable), monitored during the duration of the trial per the sites' standard operating procedures, and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). The pharmacist must alert the site principal investigator and study coordinator, if the temperature fluctuates outside of the required range. In the event the temperature fluctuates outside of the required range, including accidental deep-freezing or disruption of the cold chain, the affected study product(s) must not be administered. Based on the information collected, the manufacturer will determine whether the affected study product(s) can be used. If it cannot be used, the site will receive specific instructions on how to return the affected study product(s) to the manufacturer or destroy it on site.

7.1.3 Route of administration

Each dose of study vaccine will be administered via a single IM injection given in the deltoid muscle of the subjects' preferred arm. Aseptic technique will be used for the withdrawal and administration of each dose of study vaccine using a disposable sterile needle appropriate in length for each subject and a disposable sterile syringe.

7.1.4 Returns, reconciliation, and destruction

The investigator is responsible for keeping accurate records of the clinical supplies received from pharmaceutical supply or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Sponsor/Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the Sponsor SOPs and a copy provided to pharmaceutical supporter upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for pharmaceutical supporter to review throughout the clinical trial period as per the study agreement.

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

7.1.5 Expected adverse events / toxicities

Adult recipients of inactivated influenza virus vaccines may develop influenza-like reactions such as fever, feverishness (chills/shivering/ sweating), gastrointestinal side effects (emesis and diarrhea), fatigue (tiredness), malaise (general unwell feeling), myalgia (body aches/muscular pain), arthralgia (joint pain), headache, and/or nausea. Some subjects may develop reactions at the injection site, including pruritus (itching), ecchymosis (bruising), erythema (redness), induration (hardness)/swelling, pain, and/or tenderness. With unadjuvanted licensed,
inactivated influenza virus vaccines most of these reactions peak in intensity in the first 24 hours after vaccination and usually disappear without treatment within 1 or 2 days. Analgesics (e.g., acetaminophen, or ibuprofen or similar non-steroidal anti-inflammatory drugs (NSAIDs)) and rest may generally relieve or lessen these reactions. Bruising can sometimes occur due to the vaccination procedure.

In addition, post-marketing surveillance indicates the following adverse events of special interest (AESI) as potential risks for pandemic vaccines based on those identified for the seasonal influenza vaccines: neuritis, convulsions, severe allergic reactions, encephalitis, thrombocytopenia, vasculitis, and Guillain-Barré (GBS) syndrome. Reports of these reactions were rare; however, exact incidence rates cannot be precisely calculated.

Acute and potentially life-threatening allergic reactions are also possible. Very rarely, occurring in about 1 in 4 million people given a vaccination, there can be a serious allergic reaction to a vaccine. These reactions can manifest as skin rash (hives), swelling around the mouth, throat or eyes, difficulty breathing, a fast pulse, or loss of blood pressure. If these reactions occur, they can usually be stopped by the administration of emergency medications by the study personnel. As with any vaccine or medication, there is a very small chance of a fatal reaction (death), although researchers do not expect this to occur.

GBS: During the swine influenza (H1N1) vaccine campaign of 1976, some recipients developed a paralytic illness called Guillain-Barr. syndrome (GBS). GBS is an acute inflammatory neuropathy characterized by weakness, hyporeflexia or areflexia, and elevated protein concentrations in cerebrospinal fluid. The rate of GBS was significantly increased in individuals receiving the 1976 swine influenza (H1N1) vaccine at about 1 per 100,000 vaccine recipients. This syndrome has not been seen consistently with other influenza vaccines. Most persons who develop GBS recover completely, although the recovery period may be as little as a few weeks or as long as a few years. About 30% of those with GBS still have residual weakness after 3 years and about 3% may suffer a relapse of muscle weakness and tingling sensations many years after the initial attack. Intensive surveillance of GBS after administration of inactivated influenza vaccines since 1976 has shown a slight

increase in risk over background cases (more than one additional case of GBS per million persons) following vaccination, typically with onset within 6 weeks after vaccination[36]. Interestingly, although vaccination rates have increased in the last 10 years the numbers of reported cases of vaccine-associated GBS have declined[37]. A recent study in Canada showed that the 2009 H1N1 vaccine was associated with a small but significant risk of GBS in persons 50 years and older[38]. An active, population-based surveillance study conducted during the 2009-2010 influenza season found less than 1 excess GBS case per million doses of 2009 H1N1 vaccine administered – a rate similar to that associated with some previously administered annual influenza vaccines[39,40]. Another study using the Medicare system showed an elevated risk of GBS with 2009 monovalent H1N1 vaccination (incidence rate ratio = 2.41, 95% confidence interval: 1.14, 5.11; attributable risk = 2.84 per million doses administered, 95% confidence interval: 0.21, 5.48)[41]. An international collaboration study also supported a conclusion of an association between 2009 H1N1 vaccination and GBS[42].

8. CORRELATIVE/SPECIAL STUDIES

Assessment of biomarkers and changes relevant to influenza vaccination are paramount in this protocol.

Correlative Objective	IHC/Assay/Test	Tissue/Body Fluid Tested and Timing of Collection
Determine seroconversion and seroprotection	HAI titer	Peripheral blood at baseline, week 5, and week 21
B-cell and CD4 T-cell responses	Mass cytometry & other immunologic assays	Peripheral blood at baseline, week 5, and week 21.

8.1 Objective for lab 1 - Sanofi

8.1.1 Collection of specimens

Peripheral blood will be drawn at baseline, week 5, and week 21.

8.1.2 Specimen handling

Blood will be cryopreserved by the Dhodapkar laboratory and batch shipped to a central laboratory at Sanofi for processing.

8.1.3 Specimen analysis

HAI titer will be assessed.

8.1.4 Site performing study

Sanofi

8.2 Objective for lab 2 – Dhodapkar laboratory

8.2.1 Collection of specimens

30-40 mL of peripheral blood will be drawn, labeled and logged under the supervision of the principal investigator and in accordance with site specific SOPs.

8.2.2 Specimen handling

Specimens will be shipped to the Dhodapkar laboratory for processing – see protocol specific tissue collection worksheet.

8.2.3 Specimen analysis

- Mass cytometry: Phenotypic analysis of T and B cells, including plasmablasts and TFH cells will be performed by mass cytometry utilized a panel as described.[43]
- Pneumococcal antibody responses by Elisa
- Antigen-specific T cells (CRM-197 and HA-specific T cells; T cells specific to control viral antigens (CMV, EBV).
- B cell receptor sequencing (selected cases)
- Single cell transcriptome analysis (selected cases).

8.2.4 Site performing study

Dhodapkar laboratory

9. RESPONSE

Time to progression (TTP): Time to progression is defined as the time from last treatment until progression. Patients who have died without evidence of progression are censored in the TTP analysis at the time of death and patients who are alive without progression are censored at the last disease assessment.

Progression-Free Survival (PFS): Defined as the time from last treatment to the disease progression or death from any cause. Patients who have not progressed or died are censored at the date last known progression-free. Patients with no on-study assessment will be censored at the time of registration.

Overall survival (OS): OS is defined as the time from randomization to death. Alive patients are censored at the date last known alive.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical hypotheses

This is a randomized study to determine whether three doses of Fluzone HD, aka continuous dosing throughout the influenza season will maintain seroprotection throughout the entire study. Specifically we hypothesize that 58% of patients in the experimental arm will achieve seroprotection at week 21, e.g. HAI>40; the null hypothesis is that only 33% will demonstrate seroprotection at the end of the study.

10.2 Analysis datasets

Safety Population: The safety analysis dataset will include all eligible patients who begin treatment and receive at least one dose of protocol therapy. Patients will be analyzed in the cohort to which they were enrolled.

Efficacy Evaluable Population: All evaluable patients will be included in the analysis of efficacy endpoint. The term evaluable is defined as any eligible patient who receives at least one dose of protocol therapy and does not withdraw consent until the patient's first response assessment. Patients who fail to have a response assessment due to early progression or death will be categorized as non-responders.

10.3 Sample size determination

In the initial design, the sample sizes of 81 in each group achieved 90% power to detect a difference between the group proportions of 0.2520. The proportion in group one (the intense Fluzone HD arm) is assumed to be 0.3330 under the null hypothesis and 0.5850 under the alternative hypothesis. The proportion in group two (the control group) is 0.3330. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test (the alpha) was targeted at 0.0500, i.e. the probability of rejecting a true null hypothesis that was desired. The significance level

actually achieved by this design is 0.0513. The planned power was 0.9, i.e. the probability of rejecting a false null hypothesis. We assume 10% drop off rate in the study so that we planned to enroll 90 patients in each group.

During the first influenza season (2019-2020), we enrolled 50 patients of which only 23 were evaluable as 27 patients missed the week 21 study assessment due to COVID19.

We aim to complete the trial during the influenza season 2020-2021, and hence will need to control season as a confounder through a logistic regression model. A logistic regression of a binary response variable (e.g. HAI>40) on a binary independent variable (e.g. the treatment arms) with a sample size of 134 observations (of which the two treatment arms are evenly distributed) achieves 80% power at a 0.05 significance level to detect a change in the rate of HAI>40 from the baseline value of 0.333 to 0.585. This change corresponds to an odds ratio of 2.82. An adjustment was made since a multiple regression of the independent variable of interest on the other independent variables (e.g. the seasons) in the logistic regression obtained an R-Squared of 0.1. Hence we will need 67 patients in each randomized arm. After taking into account the expected 10% dropout rate, we plan to enroll 74 patients in each arm, producing a total sample size of 148 patients. Given we already accrued 11 evaluable patients per arm during the first season, we will plan to enroll an additional 125 patients in the second season.

10.4 Statistical methods

10.4.1 Design operating characteristics

N/A

10.4.2 Safety analyses

Adverse event data will be described and graded per the NCI CTCAE guidelines. For each adverse event, information to be collected includes event description, time of onset, clinician assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All vaccine-related AEs will be recorded with start dates occurring any time after patient receives any study drug until 7 (for non-serious AEs) or 100 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level

of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. Adverse events will be summarized and described within each cohort. They will initially be reviewed regardless of attribution, but also whether they are possibly, probably, or definitely related to treatment. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either "unrelated" or "unlikely to be related" to study treatment in the event of an actual relationship developing. The incidence of severe adverse events or toxicities will be described. We will assess the proportion of patients who experience grade 3 or higher non-hematologic toxicity. To assess tolerability, we will also capture the proportion of patients who go off treatment due to adverse events.

Temporary suspension of enrollment due to toxicity (aka stopping rules) are described elsewhere.

10.4.3 Baseline descriptive statistics

Baseline characteristics will be summarized within each cohort using descriptive statistics. For categorical variables, frequencies and percentages will be presented. For continuous variables, the median and range will be presented. Inferential tests will not be performed.

10.4.4 Planned interim analyses (if applicable)

N/A

10.4.5 Analysis of influenza response and disease status endpoints

HAI will first be measured and summarized with mean and standard deviation at different time-points, respectively. Paired t-test will be further used to test whether there is significant change in HAI at different time points from baseline, respectively. Two sample t-test will be used to compare the change in HAI from baseline between two groups, at different time-point, respectively. Chi-Square test will be used to compare the Seroconversion and Seroprotection between two groups, respectively. Logistic regression model will be used to compare adjusted difference in Seroconversion and Seroprotection between two groups after adjusting for other factors, respectively.

Spearman/Pearson correlation coefficient will be used to measure the relationship between correlation between HAI, predefined risk of influenza-like illness (low, moderate, high), respectively. Finally Mixed model will be employed to test their correlations over the whole period with and without

adjusting for other factors, respectively. Kaplan Meir method, Log-rank test, and Cox model will be used to test the relationship between peak HAI and PFS.

10.4.6 Analysis of secondary endpoints

Time to event outcomes including TTP, PFS and OS will be assessed with patients censored at time of last follow-up. TTP, PFS and OS rates of two patient groups will be estimated with the Kaplan-Meier method and compared between different groups using the log-rank test, respectively. The TTP, PFS and OS of each patient group at specific time points, such as 1 year, 3 years, and 5 years, etc. will be estimated alone with 95% CI. Cox proportional hazards models will be used in the multivariable analyses to assess adjusted effects of biomarkers on the patients' TTP, PFS and OS after adjusting for other factors. The proportional hazards assumption will be evaluated graphically and analytically with regression diagnostics.

Protocol therapy related toxicities rate will be summarized using descriptive statistics such as frequencies and proportions. Differences in the proportion of patients who experience protocol-related toxicities will not be compared between cohorts.

10.5 Measure to minimize bias

10.5.1 Randomization

The total sample size of 148 patients will be split equally between the arms.

10.5.2 Evaluation of success of blinding (N/A)

10.5.3 Breaking the study blind / participant code (N/A)

11. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

11.1 Identification of AEs and follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

The only adverse events to be captured in this protocol must relate to vaccination or influenza-like illness, and these will be captured on the appropriate CRF. Changes in the severity of these AE's only will be documented to allow an assessment of the duration of the event at each level of severity to be performed. These AEs will be followed to adequate resolution.

Information to be collected includes event description, time of onset, clinician assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Unanticipated problems will be recorded in the data collection system throughout the study.

The site PI will record all reportable events with start dates occurring any time after patient receives the any study drug until 7 (for non-serious AEs) or 14 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2 Expectedness

Expected adverse reactions are AEs that are common and known to occur for the study agent being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Describe the method of determining the expectedness of an AE. Expectedness refers to the awareness of AEs previously observed, not based on what might be anticipated from the properties of the study agent.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the current Investigator's Brochure (IB), consent, or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the drug under investigation.

The PI, working together with treating physician, will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the IB for the study agent.

11.3 Adverse event characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical

judgment. The degree of certainty about causality will be graded using the categories below:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal. Re-challenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

The determination of causality will include some of the following characteristics:

Exposure	Is there evidence that the subject was exposed to the product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
Time course	Did the AE follow in a reasonable temporal sequence from administration of the product? Is the time of onset of the AE compatible with a drug-induced effect?
Likely cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug/vaccine, or other host or environmental factors
Dechallenge	Was the product discontinued or exposure reduced? If yes, did the AE resolve or improve?

Rechallenge	Was the subject re-exposed to the product in this study? If yes, did the AE recur or worsen?
Consistency with trial treatment profile	Is the clinical presentation of the AE consistent with previous knowledge regarding the product or drug class?

11.4 Definition of serious adverse event (SAE)

The only adverse events to be captured in this protocol must relate to vaccination or influenza-like illness. Within this definition, an AE is considered "**serious**" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- Is life-threatening
- Inpatient hospitalization (>24hrs) or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home thought to be related to an influenza-like illness or influenza vaccination.

Events not considered to be serious adverse events (SAEs) are hospitalizations for

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures of a condition unrelated to the studied condition or its treatment
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care

Distinction between seriousness and severity of an AE. Severity is a measure of intensity of an event (mild, moderate, severe). However, the event itself may be of relatively minor medical significance; thus, a severe reaction may not necessarily be classified as a serious reaction. This differs from seriousness, which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event

does not necessarily need to be considered serious. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Any vaccine- or influenza-like illness related-AE considered serious must be submitted on an SAE form to the Data and Safety Monitoring Committee (DSMC) if one exists for the study. The DSMC may request to receive real-time notification of all SAEs or only SAEs thought to be related to study agent.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

11.5 Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

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

The PI will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to

the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

11.6 Expedited adverse event reporting

All serious adverse events that occur after the date of informed consent signature, during treatment, or within 14 days of the last dose of study drug must be reported on a MEDWATCH FDA Form 3500A to the principal investigator. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form.

11.6.1 Reporting to Sanofi

SAE reports and reports of adverse events of special interest will be submitted to Sanofi Pharmacovigilance within 1 business day.

11.6.2 Non-serious adverse event reporting

Non-serious adverse events will be reported on the adverse event case report form(s).

11.6.3 Reporting to the institutional review board (IRB)

Clinical trials office (CTO) staff will report all serious adverse events directly to the IRB according to IRB reporting requirements.

11.6.4 Coordinating center reporting to the food and drug administration (FDA)

The Principal Investigator will be responsible for all applicable communication with the FDA.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but no later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information. Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800- FDA-0178) using MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

An annual safety report containing all SAEs, expected and unexpected, will be sent to applicable regulatory authorities.

11.7 Monitoring of adverse events and period of observation

The only adverse events to be captured in this protocol must relate to vaccination or influenza-like illness. These adverse events, both serious and non-serious, and deaths that are encountered from the date of informed consent signature, throughout the study, and within 14 days of the last study drug treatment administration should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up.

The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

After this period, only SAEs considered reasonably study-related by the investigator must be reported to the sponsor (for example, a delayed SAE) without limitation.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study.

11.8 Second and secondary malignancy

n/a

12. DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Source documents and access to source data

Each participating site will maintain appropriate medical and research records for this trial, in compliance with relevant federal and institutional requirements pertaining to ICH E6 for the protection of confidentiality of participants.

If applicable, as part of participating in a NIH IC-sponsored or NIH IC -affiliated study, each site will permit authorized representatives of the NIH IC and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. CRFs can be source documents as well as the medical record.

12.2 Quality assurance

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.3 Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant official electronic study record.

At the coordinating center, clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into OnCore, a data capture system available at each center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.4 Study records retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.5 Winship Data and Safety Monitoring (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions

independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

12.6 Protocol deviations

A protocol deviation in this protocol relates only to the administration of vaccine – specifically incorrect dose, incorrect timing, incorrect administration procedure (including injection). Within this definition, a deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 60 working days of identification of the protocol deviation, or within 180 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

12.7 Publication and data sharing policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

12.8 Audit and inspection

In accordance with GCP, the investigators agree to comply with the requirements of the sponsor and the Regulatory Authorities about an audit or inspection of the trial.

The audit may be performed at any of the stages of the study, from development of the protocol to publication of the results.

Regulatory authorities or the sponsor may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be granted by the investigator, who must provide support always for these activities.

13. ETHICS AND PROTECTION OF HUMAN SUBJECTS

13.1 Ethical standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, as well as the federal regulations pertaining to ICH E6.

13.2 Institutional review board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed consent

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

Informed consent is a process that is initiated prior to the individual consent to participate in the study and continues throughout the individual's participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 Participant and data confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to

cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

13.5 Research use of stored samples, specimens, or data

13.5.1 Current use

Samples and data collected under this protocol may be used to study multiple myeloma. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.5.2 Future use

N/A

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APPENDIX A – PERFORMANCE STATUS

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	%	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.