

# **Phase II Trial Evaluating the Efficacy of Moderna COVID-19 Vaccine Booster Dosing in Patients with Hematologic Malignancies Who Did Not Have an Adequate Response to Prior Vaccination**

## **Short Title: KCI COV19 VAX Booster MM/AL/Heme**

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## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

## 1 PROTOCOL SUMMARY

### 1.1 SYNOPSIS

**Title:** **Phase II Trial Evaluating the Efficacy of Moderna COVID-19 Vaccine Booster Dosing in Patients with Hematologic Malignancies Who Did Not Have an Adequate Response to Prior Vaccination**

**Study Description:** Patients with multiple myeloma, AL amyloidosis, or other hematologic cancers who have not had a strong positive serologic response to prior anti-COVID-19 vaccination will be given a single booster dose of the Moderna mRNA COVID-19 vaccine, and serologic response will be measured 28 days (+/- 3 days) later.

**Objectives:** Primary Objective: To determine whether booster dosing with the Moderna COVID-19 vaccine can induce humoral immune responses in patients with hematologic malignancies who did not have an adequate response to prior first vaccination with any of the SARS-CoV2 vaccines authorized for use in the USA.

Secondary Objectives:

1. To determine whether booster dosing with the Moderna COVID-19 vaccine is safe in patients with multiple myeloma, AL amyloidosis, or other hematologic malignancies.
2. To compare the humoral immune responses between the patients who had a WEAK POSITIVE RESPONSE to prior vaccine (Cohort 3) vs. those with NO RESPONSE to prior vaccination (Cohorts 1 and 2).
3. To descriptively summarize clinical and immune characteristics which contribute to likelihood of responding to booster dosing with the Moderna COVID-19 vaccine.

**Endpoints:**

**Primary Endpoint:**

The primary endpoint is the observed rate of anti-SARS-CoV2 IgG antibody seroconversion (from negative to positive) measured 28 days (+/- 3 days) following a booster dose of the Moderna mRNA COVID-19 vaccine.

**Secondary Endpoints:**

1. AEs and SAEs observed in participants, determined according to daily phone calls or video chats for 1 week following vaccine administration, and then weekly after that until 4 weeks after vaccination (Pts will also be examined 4 weeks after vaccination).
2. The observed rate of anti-SARS-CoV2 IgG antibody seroconversion (from negative to positive) measured 28 days (+/- 3 days) following a booster dose of the Moderna mRNA COVID-19 vaccine
- 3.a. Clinical characteristics of enrolled participants, including treatment history, disease, status, or presence of immunoparesis (i.e., hypogammaglobulinemia)
- 3.b. Characterization of other aspects of patients' immune status through T-cell profiling, including analysis of T-cell receptor (TCR) reactivity against COVID-19 antigens

**Study Population:**

Three 52-person cohorts. Cohort 1: multiple myeloma and amyloidosis patients who did not develop an anti-spike antibody titer of >1 S/CO after prior COVID-19 vaccination. Cohort 2: patients with other hematologic malignancies who did not develop an anti-spike antibody titer of >1 S/CO after prior COVID-19 vaccination. Cohort 3: patients with multiple myeloma, amyloidosis, or other hematologic malignancy who had a "weak positive" response to prior COVID-19 vaccine, defined as an anti-spike antibody titer of 1-2 S/CO. Patients with a history of severe prior adverse vaccine reaction are excluded. Patients must be 18 yo or older.

**Phase:**

Phase 2

**Description of**

**Sites/Facilities Enrolling Participants:** The Karmanos Cancer Institute (Dresner and Weisberg Facilities)

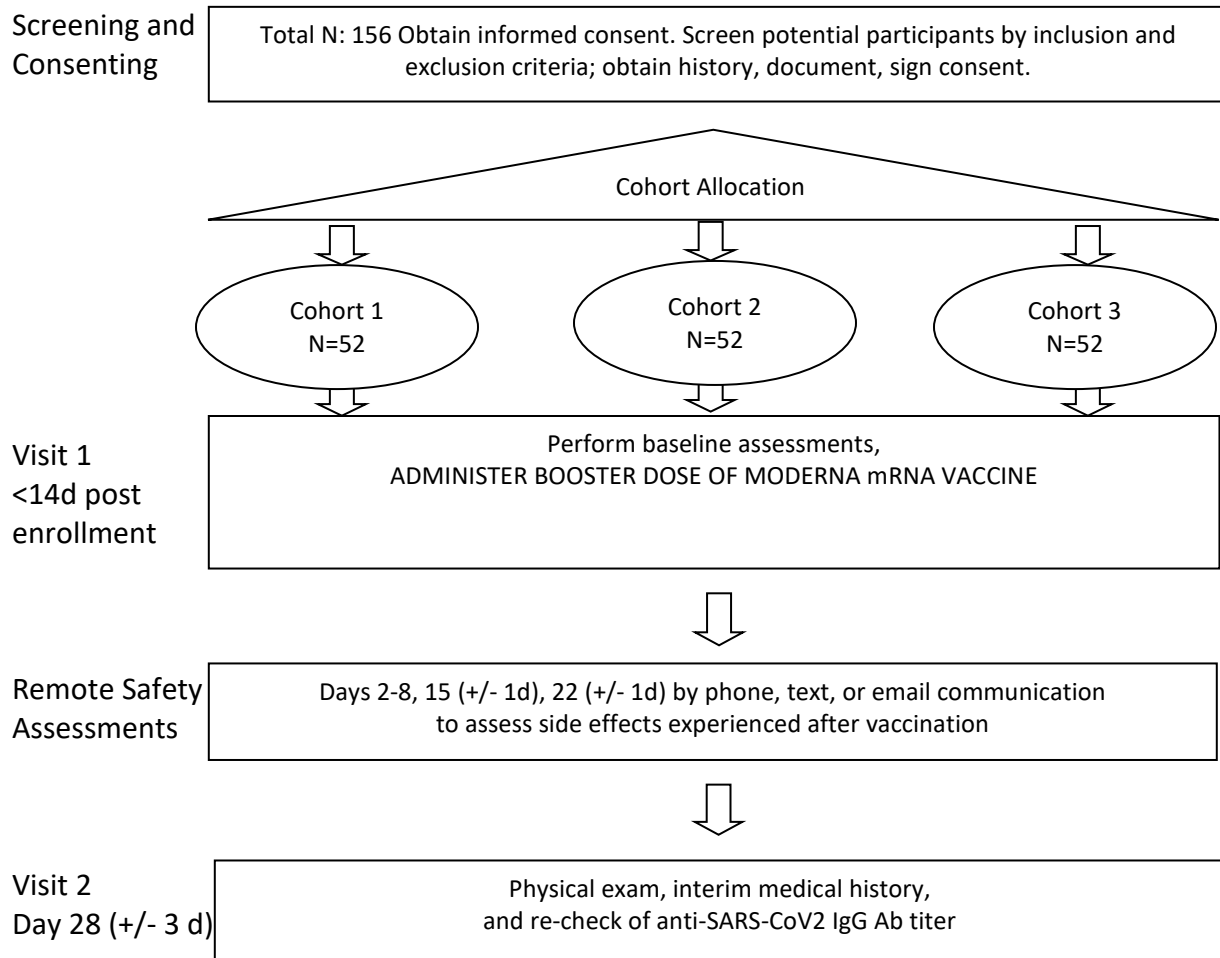
**Description of Study Intervention:** A single “booster” dose of the Moderna mRNA COVID-19 vaccine will be administered intramuscularly

**Study Duration:** All participants will be dosed within 3 months of the trial opening, and the primary endpoint will be assessed in all participants by 28 days (+/- 3 days) of the last participant being dosed. Thus, the expected study duration is ~10 months (factoring in ~2-month accrual duration and also ~4-months each for IRB approval and data analysis)

**Participation Duration:** 6-8 weeks

## 1.2 SCHEMA

### Flow diagram





## 1.3 SCHEDULE OF ACTIVITIES (STUDY CALENDAR)

	Screening/Consenting Day -14 to -1	Enrollment/Baseline Visit 1, Day 1	Days 2-8, 15, 22 (+/- 1 day) Phone/Text/Email	Study Visit 2 Day 28 +/- 3 days
<b>Procedures</b>				
Informed consent	X			
Demographics	X			
Medical history update	X			X
Administer vaccine dose		X		
Concomitant medication review	X			X
Physical exam	X			X
Vital signs	X	X		X
Height	X			
Weight	X			X
Performance status <sup>f</sup>	X			X
Hematology <sup>a</sup>	X			X
Serum chemistry <sup>b</sup>	X			X
Cardiac Biomarkers <sup>e</sup>	X		(X) <sup>d</sup>	X
Coagulation testing <sup>c</sup>	X			
Anti-SARS-CoV2 IgG Ab titer	X			X
Patient-reported AE assessment		X	X---X	X
Correlative blood sample collection	X			X
a. CBC with diff b. standard CMP, uric acid, magnesium, phosphorus, LDH, quantitative immunoglobulins (IgG, IgA, IgM) c. PT/INR, PTT, fibrinogen d. only if patient reports chest pain, palpitations, shortness of breath, or other symptoms suggesting cardiac etiology e. hsTrop I and BNP f. See Appendix 1: ECOG Performance Status				

## 2 INTRODUCTION

### 2.1 STUDY RATIONALE

While vaccines authorized for emergency use to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection provide most recipients resistance to SARS-CoV2 infection, it has become clear that immunocompromised patients (including solid organ transplant recipients, patients on therapy for autoimmune diseases, and people with hematologic malignancies such multiple myeloma and chronic lymphocytic leukemia) may not mount an adequate humoral immune response after a standard initial vaccine course. There is no consensus on how to approach such patients. This trial will examine whether administration of booster doses of an authorized SARS-CoV2 vaccine can induce an immune response in such patients with hematologic malignancies.

### 2.2 BACKGROUND

As of June 2021, there have been over 33,000,000 SARS-CoV2 infections in the United States, with over 600,000 deaths (REF 1). Further, many survivors of the infection suffer with long-term symptoms or complications. Three different SARS-CoV2 vaccines have been authorized by the FDA for emergency use to prevent SARS-CoV2 infections: the Pfizer-BioNTech COVID-19 vaccine, the Moderna COVID-19 vaccine, and the Janssen (Johnson & Johnson) COVID-19 vaccine. The Pfizer and Moderna products are mRNA vaccines with approximately 95% efficacy in preventing SARS-CoV2 infections in patients who are not immunocompromised (REFS 2 and 3). The safety and immunogenicity of the Moderna vaccine in immunocompetent older adults appears to be similar to that observed in younger adults (REF 4). That said, it has been clearly demonstrated that individuals with compromised immune systems are less likely to mount a protective humoral immune response to any of the available SARS-CoV2 vaccines. This includes patients with hematologic malignancies. For example, in a series of 92 multiple myeloma (MM) patients who had received first vaccination with either the Pfizer or AstraZeneca COVID-19 vaccines, 30% failed to mount any measurable immune response (REF 5). Other investigators have corroborated these findings in a series of vaccinated patients with MM or myeloproliferative diseases (REF 6). In the latter report, patient age as well as treatment history were also associated with the likelihood of vaccine responsiveness. The list of potential interventions to address inadequate humoral immune response to first SARS-CoV2 vaccination includes administration of booster dose(s) with any of the available vaccines. In this trial, we will specifically evaluate the efficacy and safety of administering booster dose(s) of the Moderna mRNA vaccine to patients with MM, AL amyloidosis, or other hematologic malignancies who did not have an adequate humoral immune response after first vaccination with any of the available COVID-19 vaccines.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

The data listed herein related to risks related to the Moderna COVID-19 vaccine are derived from the available prescribing information for the product (REF 7).

In clinical studies, the adverse reactions in participants 18 years of age and older were pain at the injection site (92.0%), fatigue (70.0%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23.0%), axillary swelling/tenderness (19.8%), fever (15.5%), swelling at the injection site (14.7%), and erythema at the injection site (10.0%). Severe allergic reactions, including anaphylaxis, have been reported following administration of the Moderna COVID-19 Vaccine during mass vaccination outside of clinical trials.

Syncope (fainting) may occur in association with administration of injectable vaccines. Procedures will be in place to avoid injury from fainting.

#### Myocarditis and Pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals

have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. Some, but not all, observational analyses of postmarketing data suggest that the risk of myocarditis and pericarditis in males under 40 years of age may be higher following the second dose of the Moderna COVID-19 Vaccine relative to other authorized or approved mRNA COVID-19 vaccines. Although postmarketing data following a booster dose of mRNA vaccines are limited, available evidence suggests a lower myocarditis risk following a booster dose relative to the risk following the primary series second dose. We will follow the published CDC considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis ( <https://www.cdc.gov/vaccines/covid-19/clinicalconsiderations/myocarditis.html>).

**Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. Overall, 15,419 participants aged 18 years and older received at least one dose of Moderna COVID-19 Vaccine in three clinical trials (NCT04283461, NCT04405076, and NCT04470427). The safety of Moderna COVID-19 Vaccine was evaluated in an ongoing Phase 3 randomized, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of Moderna COVID-19 Vaccine (n=15,185) or placebo (n=15,166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older. Overall, 52.7% were male, 47.3% were female, 20.5% were Hispanic or Latino, 79.2% were White, 10.2% were African American, 4.6% were Asian, 0.8% were American Indian or Alaska Native, 0.2% were Native Hawaiian or Pacific Islander, 2.1% were other races, and 2.1% were Multiracial. Demographic characteristics were similar among participants who received Moderna COVID-19 Vaccine and those who received placebo. Solicited Adverse Reactions Data on solicited local and systemic adverse reactions and use of antipyretic medication were collected in an electronic diary for 7 days following each injection (i.e., day of vaccination and the next 6 days) among participants receiving Moderna COVID-19 Vaccine (n=15,179) and participants receiving placebo (n=15,163) with at least 1 documented dose. Solicited adverse reactions were reported more frequently among vaccine participants than placebo participants. The reported number and percentage of the solicited local and systemic adverse reactions by age group and dose are presented in Table 1 and Table 2, respectively.

**Table 1: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Within 7 Days\* After Each Dose in Participants 18-64 Years (Solicited Safety Set, Dose 1 and Dose 2)**

	Moderna COVID-19 Vaccine		Placebo <sup>a</sup>	
	Dose 1 (N=11,406) n (%)	Dose 2 (N=10,985) n (%)	Dose 1 (N=11,407) n (%)	Dose 2 (N=10,918) n (%)
<b>Local Adverse Reactions</b>				
Pain	9,908 (86.9)	9,873 (89.9)	2,177 (19.1)	2,040 (18.7)
Pain, Grade 3 <sup>b</sup>	366 (3.2)	506 (4.6)	23 (0.2)	22 (0.2)
Axillary swelling/tenderness	1,322 (11.6)	1,775 (16.2)	567 (5.0)	470 (4.3)
Axillary swelling/tenderness, Grade 3 <sup>b</sup>	37 (0.3)	46 (0.4)	13 (0.1)	11 (0.1)
Swelling (hardness) ≥25 mm	767 (6.7)	1,389 (12.6)	34 (0.3)	36 (0.3)
Swelling (hardness), Grade 3 <sup>c</sup>	62 (0.5)	182 (1.7)	3 (<0.1)	4 (<0.1)
Erythema (redness) ≥25 mm	344 (3.0)	982 (8.9)	47 (0.4)	43 (0.4)
Erythema (redness), Grade 3 <sup>c</sup>	34 (0.3)	210 (1.9)	11 (<0.1)	12 (0.1)
<b>Systemic Adverse Reactions</b>				
Fatigue	4,384 (38.4)	7,430 (67.6)	3,282 (28.8)	2,687 (24.6)
Fatigue, Grade 3 <sup>d</sup>	120 (1.1)	1,174 (10.7)	83 (0.7)	86 (0.8)
Fatigue, Grade 4 <sup>e</sup>	1 (<0.1)	0 (0)	0 (0)	0 (0)
Headache	4,030 (35.3)	6,898 (62.8)	3,304 (29.0)	2,760 (25.3)
Headache, Grade 3 <sup>f</sup>	219 (1.9)	553 (5.0)	162 (1.4)	129 (1.2)
Myalgia	2,699 (23.7)	6,769 (61.6)	1,628 (14.3)	1,411 (12.9)
Myalgia, Grade 3 <sup>d</sup>	73 (0.6)	1,113 (10.1)	38 (0.3)	42 (0.4)
Arthralgia	1,893 (16.6)	4,993 (45.5)	1,327 (11.6)	1,172 (10.7)
Arthralgia, Grade 3 <sup>d</sup>	47 (0.4)	647 (5.9)	29 (0.3)	37 (0.3)
Arthralgia, Grade 4 <sup>e</sup>	1 (<0.1)	0 (0)	0 (0)	0 (0)
Chills	1,051 (9.2)	5,341 (48.6)	730 (6.4)	658 (6.0)

	Moderna COVID-19 Vaccine		Placebo <sup>a</sup>	
	Dose 1 (N=11,406) n (%)	Dose 2 (N=10,985) n (%)	Dose 1 (N=11,407) n (%)	Dose 2 (N=10,918) n (%)
Chills, Grade 3 <sup>b</sup>	17 (0.1)	164 (1.5)	8 (<0.1)	15 (0.1)
Nausea/vomiting	1,068 (9.4)	2,348 (21.4)	908 (8.0)	801 (7.3)
Nausea/vomiting, Grade 3 <sup>b</sup>	6 (<0.1)	10 (<0.1)	8 (<0.1)	8 (<0.1)
Fever	105 (0.9)	1,908 (17.4)	37 (0.3)	39 (0.4)
Fever, Grade 3 <sup>i</sup>	10 (<0.1)	184 (1.7)	1 (<0.1)	2 (<0.1)
Fever, Grade 4 <sup>i</sup>	4 (<0.1)	12 (0.1)	4 (<0.1)	2 (<0.1)
Use of antipyretic or pain medication	2,656 (23.3)	6,292 (57.3)	1,523 (13.4)	1,248 (11.4)

**Table 2: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Within 7 Days\* After Each Dose in Participants 65 Years and Older (Solicited Safety Set, Dose 1 and Dose 2)**

	Moderna COVID-19 Vaccine		Placebo <sup>a</sup>	
	Dose 1 (N=3,762) n (%)	Dose 2 (N=3,692) n (%)	Dose 1 (N=3,748) n (%)	Dose 2 (N=3,648) n (%)
<b>Local Adverse Reactions</b>				
Pain	2,782 (74.0)	3,070 (83.2)	481 (12.8)	437 (12.0)
Pain, Grade 3 <sup>b</sup>	50 (1.3)	98 (2.7)	32 (0.9)	18 (0.5)
Axillary swelling/tenderness	231 (6.1)	315 (8.5)	155 (4.1)	97 (2.7)
Axillary swelling/tenderness, Grade 3 <sup>b</sup>	12 (0.3)	21 (0.6)	14 (0.4)	8 (0.2)

	Moderna COVID-19 Vaccine		Placebo <sup>a</sup>	
	Dose 1 (N=3,762) n (%)	Dose 2 (N=3,692) n (%)	Dose 1 (N=3,748) n (%)	Dose 2 (N=3,648) n (%)
Swelling (hardness) ≥25 mm	165 (4.4)	400 (10.8)	18 (0.5)	13 (0.4)
Swelling (hardness), Grade 3 <sup>c</sup>	20 (0.5)	72 (2.0)	3 (<0.1)	7 (0.2)
Erythema (redness) ≥25 mm	86 (2.3)	275 (7.5)	20 (0.5)	13 (0.4)
Erythema (redness), Grade 3 <sup>c</sup>	8 (0.2)	77 (2.1)	2 (<0.1)	3 (<0.1)
<b>Systemic Adverse Reactions</b>				
Fatigue	1,251 (33.3)	2,152 (58.3)	851 (22.7)	716 (19.6)
Fatigue, Grade 3 <sup>d</sup>	30 (0.8)	254 (6.9)	22 (0.6)	20 (0.5)
Headache	921 (24.5)	1,704 (46.2)	723 (19.3)	650 (17.8)
Headache, Grade 3 <sup>c</sup>	52 (1.4)	106 (2.9)	34 (0.9)	33 (0.9)
Myalgia	742 (19.7)	1,739 (47.1)	443 (11.8)	398 (10.9)
Myalgia, Grade 3 <sup>d</sup>	17 (0.5)	205 (5.6)	9 (0.2)	10 (0.3)
Arthralgia	618 (16.4)	1,291 (35.0)	456 (12.2)	397 (10.9)
Arthralgia, Grade 3 <sup>d</sup>	13 (0.3)	123 (3.3)	8 (0.2)	7 (0.2)
Chills	202 (5.4)	1,141 (30.9)	148 (4.0)	151 (4.1)
Chills, Grade 3 <sup>f</sup>	7 (0.2)	27 (0.7)	6 (0.2)	2 (<0.1)
Nausea/vomiting	194 (5.2)	437 (11.8)	166 (4.4)	133 (3.6)
Nausea/vomiting, Grade 3 <sup>g</sup>	4 (0.1)	10 (0.3)	4 (0.1)	3 (<0.1)
Nausea/vomiting, Grade 4 <sup>h</sup>	0 (0)	1 (<0.1)	0 (0)	0 (0)
Fever	10 (0.3)	370 (10.0)	7 (0.2)	4 (0.1)
Fever, Grade 3 <sup>i</sup>	1 (<0.1)	18 (0.5)	1 (<0.1)	0 (0)
Fever, Grade 4 <sup>j</sup>	0 (0)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Use of antipyretic or pain medication	673 (17.9)	1,546 (41.9)	477 (12.7)	329 (9.0)

Solicited local and systemic adverse reactions reported following administration of Moderna COVID-19 Vaccine had a median duration of 1 to 3 days. Grade 3 solicited local adverse reactions were more

frequently reported after Dose 2 than after Dose 1. Solicited systemic adverse reactions were more frequently reported by vaccine recipients after Dose 2 than after Dose 1. As of November 25, 2020, among participants who had received at least 1 dose of vaccine or placebo (vaccine=15,185, placebo=15,166), unsolicited adverse events that occurred within 28 days following each vaccination were reported by 23.9% of participants (n=3,632) who received Moderna COVID-19 Vaccine and 21.6% of participants (n=3,277) who received placebo. In these analyses, 87.9% of study participants had at least 28 days of follow-up after Dose 2.

Lymphadenopathy-related events that were not necessarily captured in the 7-day e-diary were reported by 1.1% of vaccine recipients and 0.6% of placebo recipients. These events included lymphadenopathy, lymphadenitis, lymph node pain, vaccination-site lymphadenopathy, injection-site lymphadenopathy, and axillary mass, which were plausibly related to vaccination. This imbalance is consistent with the imbalance observed for solicited axillary swelling/tenderness in the injected arm.

Hypersensitivity adverse events were reported in 1.5% of vaccine recipients and 1.1% of placebo recipients. Hypersensitivity events in the vaccine group included injection site rash and injection site urticaria, which are likely related to vaccination. Delayed injection site reactions that began >7 days after vaccination were reported in 1.2% of vaccine recipients and 0.4% of placebo recipients. Delayed injection site reactions included pain, erythema, and swelling and are likely related to vaccination.

Throughout the same period, there were three reports of Bell's palsy in the Moderna COVID-19 Vaccine group (one of which was a serious adverse event), which occurred 22, 28, and 32 days after vaccination, and one in the placebo group which occurred 17 days after vaccination. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine.

There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Moderna COVID-19 Vaccine.

**Serious Adverse Events:** As of November 25, 2020, serious adverse events were reported by 1.0% (n=147) of participants who received Moderna COVID-19 Vaccine and 1.0% (n=153) of participants who received placebo, one of which was the case of Bell's palsy which occurred 32 days following receipt of vaccine. In these analyses, 87.9% of study participants had at least 28 days of follow-up after Dose 2, and the median follow-up time for all participants was 9 weeks after Dose 2. There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination and was likely related to vaccination. There was one serious adverse event of intractable nausea and vomiting in a participant with prior history of severe headache and nausea requiring hospitalization. This event occurred 1 day after vaccination and was likely related to vaccination. There were no other notable patterns or imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Moderna COVID-19 Vaccine.

From an independent study (NCT04885907), in 60 participants who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years) who received a third vaccine dose (0.5 mL), the adverse event profile was similar to that after the second dose and no Grade 3 or Grade 4 events were reported. There is an ongoing Phase 2, randomized, observer-blind, placebo-controlled, dose confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series. In an open label-phase, 171 of those participants received a single booster dose (0.25 mL) at least 6 months (range of 5.8 to 8.5 months) after receiving the second dose of the primary series. Safety monitoring after the booster dose was the same as that described for Study 1 participants who received the primary series.

Among the 171 booster dose recipients, the median age was 55 years (range 18-87), 39.2% were male and 60.8% were female, 95.9% were White, 5.8% were Hispanic or Latino, 2.9% were Black or African American, 0.6% were Asian, and 0.6% were American Indian or Alaska Native. Following the booster dose, the median follow-up time was 5.7 months (range of 3.1 to 6.4 months)

**Table 3: Number and Percentage of Study 2 Participants 18-64 Years of Age With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days\* After the Booster Dose or After the Second Dose of Primary Series (Solicited Safety Set)**

	<b>Study 2 Second Dose of Primary Series (N=155) n (%)</b>	<b>Study 2 Booster Dose (N=129) n (%)</b>
<b>Local Adverse Reactions</b>		
<b>Pain</b>	<b>137 (88.4)</b>	<b>111 (86.0)</b>
<b>Pain Grade 3</b>	<b>1 (0.6)</b>	<b>4 (3.1)</b>
	<b>18 (11.6)</b>	<b>32 (24.8)</b>
<b>Axillary swelling/tenderness, Grade 3</b>	<b>0 (0)</b>	<b>1 (0.8)</b>
<b>Swelling (hardness) ≥25 mm</b>	<b>16 (10.3)</b>	<b>8 (6.2)</b>
<b>Erythema (redness) ≥25 mm</b>	<b>12 (7.7)</b>	<b>7 (5.4)</b>
<b>Erythema (redness), Grade 3</b>	<b>2 (1.3)</b>	<b>1 (0.8)</b>
<b>Systemic Adverse Reactions</b>		
<b>Fatigue</b>	<b>105 (67.7)</b>	<b>80 (62.0)</b>
<b>Fatigue Grade 3</b>	<b>16 (10.3)</b>	<b>4 (3.1)</b>
<b>Headache</b>	<b>87 (56.1)</b>	<b>76 (58.9)</b>



Headache Grade 3	8 (5.2)	1 (0.8)
Myalgia	89 (57.4)	64 (49.6)
Myalgia Grade 3	15 (9.7)	4 (3.1)
Arthralgia	66 (42.6)	64 (49.6)
Arthralgia Grade 3	8 (5.2)	4 (3.1)
Chills	71 (45.8)	52 (40.3)
Chills, Grade 3	1 (0.6)	0 (0)
Nausea/vomiting	36 (23.2)	16 (12.4)
Fever	24 (15.5)	9 (7.0)
Fever, Grade 3	3 (1.9)	2 (1.6)
Rash	5 (3.2)	3 (2.3)
Use of antipyretic or pain medication	86 (55.5)	64 (49.6)

**Table 4: Number and Percentage of Study 2 Participants ≥65 Years of Age With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days\* After the Booster Dose or After the Second Dose of Primary Series (Solicited Safety Set)**

	Study 2 Second Dose of Primary Series (N=43) n (%)	Study 2 Booster Dose (N38) n (%)
Local Adverse Reactions		
Pain	32 (74.4)	29 (76.3)
Pain Grade 3	0 (0.0)	2 (5.3)
	2 (4.7)	2 (5.3)
Axillary swelling/tenderness, Grade 3	5 (11.6)	1 (2.6)
Swelling (hardness) ≥25 mm	1 (2.3)	1 (2.6)
Erythema (redness) ≥25 mm	3 (7.0)	1 (2.6)
Erythema (redness), Grade 3	3 (7.0)	0 (0)
Systemic Adverse Reactions		
Fatigue	23 (53.5)	18 (47.4)
Fatigue Grade 3	2 (4.7)	3 (7.9)
Myalgia	15 (34.9)	18 (47.4)
Myalgia Grade 3	0 (0)	1 (2.6)
Headache	17 (39.5)	16 (42.1)
Headached Grade 3	1 (2.3)	1 (2.6)
Arthralgia	11 (25.6)	15 (39.5)
Arthralgia Grade 3	0 (0)	1 (2.6)
Chills	7 (16.3)	7 (18.4)
Nausea/vomiting	5 (11.7)	3 (7.9)

<b>Fever</b>	<b>2 (4.7)</b>	<b>2 (5.4)</b>
<b>Fever, Grade 3</b>	<b>1 (2.3)</b>	<b>0 (0)</b>
<b>Rash</b>	<b>1 (2.3)</b>	<b>0 (0)</b>
<b>Use of antipyretic or pain medication</b>	<b>11 (25.6)</b>	<b>11 (28.9)</b>

#### Serious Adverse Events

Of the 171 participants who received a booster dose of Moderna COVID-19 Vaccine, there were no serious adverse events reported from the booster dose through 28 days after the booster dose. Through the cut-off date of August 16, 2021, there were no serious adverse events following the booster dose considered causally related to the Moderna COVID-19 Vaccine.

#### Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

The safety of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from the safety of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series (homologous booster dose) and from data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine (0.5 mL), Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following the Moderna COVID-19 Vaccine heterologous booster dose (0.5 mL) did not identify any new safety concerns, as compared with adverse reactions reported following Moderna COVID-19 Vaccine primary series doses or homologous booster dose (0.25 mL).

#### Post Authorization Experience:

The following adverse reactions have been identified during post-authorization use of the Moderna COVID-19 Vaccine. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to

vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis

Immune System Disorders: anaphylaxis

Nervous System Disorders: syncope

**.Other:** There are no anticipated social, legal, or economic risks associated with participation in this trial, other than those which could theoretically stem from sustaining any of the listed physical AEs/SAEs listed above.

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### 2.3.2 KNOWN POTENTIAL BENEFITS

There are no large-scale prospective data available regarding the systematic administration of booster dosing of the Moderna COVID-19 vaccine. However, if patients respond to booster dosing, they would likely have the benefit of protection against SARS-CoV2 infection including a reduced risk of severe infection, similar to that observed amongst individuals responsive to first vaccination. These benefits, summarized below in Tables 3 and 4, are derived from the Full Prescribing Information for the Moderna COVID-19 vaccine.

**Table 3: Primary Efficacy Analysis: COVID-19\* in Participants 18 Years of Age and Older Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set**

Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI)†
Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)

\* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom. Cases starting 14 days after Dose 2.

† VE and 95% CI from the stratified Cox proportional hazard model.

The subgroup analyses of vaccine efficacy are presented in Table 4.

**Table 4: Subgroup Analyses of Vaccine Efficacy: COVID-19\* Cases Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per- Protocol Set**

Age Subgroup (Years)	Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI)*
	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)

\* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom. Cases starting 14 days after Dose 2.

† VE and 95% CI from the stratified Cox proportional hazard model.

In the organ transplant recipient series by Werbel et al referenced above, twelve out of 30 participants demonstrated a high-titer antibody response, and another two participants demonstrated a low-titer antibody response, providing evidence that there may be utility to booster dosing immunocompromised patients to induce an adequate anti-COVID-19 immune response.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Taken together, the potential benefits of participation in this trial outweigh the risks. The safety profile of the Moderna COVID-19 vaccine has been studied in >11,000 patients, and has been shown to have an acceptable safety profile. In the previously conducted randomized trial noted above, the risk of AEs was higher after dose #2 of the vaccine compared to dose #1, but there is little reason to believe the risk would be any higher after a booster dose compared to after dose #2 of the standard first vaccination schedule, particularly in patients who have humoral immunodeficiency. Any participant who has an immune response from booster dosing would enjoy the benefit of protection against SARS-CoV2

infection, and if there are many such responding patients observed on this trial, it would suggest that systematic use of booster dosing could have immense future societal and public health benefit.

Specific measures are being taken to minimize risk to participants in this trial. First, patients who report any severe (Grade 3) reaction to prior COVID-19 vaccination will be excluded, Second, participants will be contacted on a daily basis for one week after Moderna COVID-19 vaccine dosing, and then weekly for another 4 weeks after that. This should permit investigators to detect any unexpected AEs/SAEs related specifically to booster dosing which were not observed in prior trials. Third, to minimize the risk of recurrent failure to respond to vaccine, all patients who are on anti-neoplastic therapy with the potential to suppress the immune system (including steroids, chemotherapy, or antibody therapy) will have such therapy held for a minimum of two weeks prior to and two weeks following booster dosing.

### 3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
<b>Primary</b>		
To determine whether booster dosing with the Moderna COVID-19 vaccine can induce humoral immune responses in patients with hematologic malignancies who did not have an adequate response to prior first vaccination with any of the SARS-CoV2 vaccines authorized for use in the USA.	The primary endpoint is the observed rate of anti-SARS-CoV2 IgG antibody seroconversion (from negative to positive) measured 28 days (+/- 3 days) following a booster dose of the Moderna COVID-19 vaccine.	The described assay measures antibodies against the SARS-CoV2 spike protein, which is what the Moderna vaccine is designed to induce. This is a commercially available assay which is already in use at the Karmanos Cancer Center and Detroit Medical Center.
<b>Secondary</b>		
<p>1. To determine whether booster dosing with the Moderna COVID-19 vaccine is safe in patients with multiple myeloma, AL amyloidosis, or other hematologic malignancies.</p> <p>2. To compare the humoral immune responses between the patients who had a WEAK POSITIVE RESPONSE to prior vaccine (Cohort 3) vs. those with NO RESPONSE to prior vaccination (Cohorts 1 and 2).</p> <p>3. To descriptively summarize clinical and immune characteristics which contribute to likelihood of</p>	<p>1. AEs and SAEs observed in participants, determined according to daily phone calls or video chats for 1 week following vaccine administration, and then weekly after that until 4 weeks after vaccination (Pts will also be examined 4 weeks after vaccination).</p> <p>2. Humoral immune responses measured 28 days (+/- 3 days) following a booster dose of the Moderna COVID-19 vaccine.</p> <p>3.a. Clinical characteristics of enrolled participants, including treatment history, disease, status, or presence</p>	<p>This is an early experience with booster dosing using the Moderna COVID-19 vaccine. Though new AEs/SAEs are not expected, it is important to document the safety of this intervention.</p> <p>Clinical factors related to disease or immune status may be associated with likelihood of responding to booster</p>

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
responding to booster dosing with the Moderna COVID-19 vaccine.	<p>of immunoparesis (i.e., hypogammaglobulinemia)</p> <p>3.b. Characterization of other aspects of patients' immune status through T-cell profiling, including analysis of T-cell receptor (TCR) reactivity against COVID-19 antigens</p>	dosing (or failing to respond), so detailed documentation of these factors is important.

## 4 STUDY DESIGN

### 4.1 OVERALL DESIGN

The specific hypothesis being tested is that it may be possible to induce a protective humoral immune response with a booster dose of the Moderna COVID-19 vaccine in patients with hematologic malignancies who did not have an adequate response to first vaccination with any of the available COVID-19 vaccines. To test this hypothesis, the Karmanos Cancer Institute will conduct a Phase II single-stage trial in which patients with a negative or weak positive anti-SARS-CoV2 IgG antibody test (defined as <1.00 S/CO and 1.00-1.99 S/CO, respectively) will receive a single standard dose of the Moderna COVID-19 vaccine intramuscularly, and then have anti-SARS-CoV2 IgG antibody levels checked 28 days (+/-3 days) later. This will be a single institution trial which will be open to enrollment at the Detroit (Dresner) and Farmington Hills (Weisberg) treatment facilities. As this is an open label Phase 2 trial, there is no randomization or stratification involved. There will be three cohorts enrolled: a cohort of MM and AL amyloidosis patients with an anti-SARS-CoV2-IgG Ab level of <1.0 S/CO, a cohort of patients with other hematologic malignancies (HM) with an anti-SARS-CoV2-IgG Ab level of <1.0 S/CO and a mixed MM/AL/HM cohort in which patients have an anti-SARS-CoV2-IgG Ab level of 1.0-1.99 S/CO ("low-positive cohort"). Each cohort will be of sufficient size to evaluate the efficacy of the intervention separately, and all secondary endpoints will be analyzed on the entire combined patient set.

### 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A Phase II trial design using the surrogate endpoint of humoral seroconversion to assess vaccine response is more appropriate than using SARS-CoV2 infection rate because of the unpredictable timing and frequency of the latter. Immune response should be evident in the first few weeks after vaccination in any individual who is ultimately destined to respond. The size of the trial was selected so as to be sufficient to determine whether the vaccine booster can induce humoral immune response.

### 4.3 JUSTIFICATION FOR DOSE

The dose of the Moderna COVID-19 vaccine used is the standard dose: 0.5 mL, administered intramuscularly.

#### 4.4 END OF STUDY DEFINITION

The trial will be concluded after the last patient is enrolled and has completed the 28-day post-vaccination follow-up visit.

### 5 STUDY POPULATION

#### 5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 years of age or older
4. Previously diagnosed with MM/AL amyloidosis (Cohorts 1 or 3) or other hematologic malignancy (Cohorts 2 or 3).
5. Previously received any one of the available COVID-19 vaccines (between 4 and 36 weeks prior to enrollment)
6. Anti-SARS-CoV2 IgG antibody titer of results less than 1.0 units (Cohorts 1 and 2), or 1.0-1.99 units (Cohort 3). Antibody titers will be measured within 14 days of enrollment.
7. If currently receiving potentially immunosuppressive anti-neoplastic therapy for their underlying hematologic condition, a two-week interruption in therapy before and after the booster dose of vaccine is ENCOURAGED BUT NOT REQUIRED (physician discretion).

#### 5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Daily corticosteroids at a dose equivalent to Prednisone 20 mg/day or greater during the period two weeks before enrollment to the trial. *Intermittent* steroid dosing at or above this level is permitted (i.e., weekly dexamethasone dosing as part of myeloma therapy)
2. History of previous severe reaction to any available COVID-19 vaccine (defined as any Grade 3 or higher reaction)
3. Febrile illness within 3 days of booster dosing.
4. Documented SARS-CoV2 infection within 2 weeks of enrollment.
5. Less than 3 months post-autologous or allogeneic stem cell transplant (NOTE: transplant between initial standard vaccine administration and enrollment is NOT otherwise grounds for exclusion from participation).

### 5.3 LIFESTYLE CONSIDERATIONS

Patients who are diagnosed with an acute SARS-CoV2 infection in the post-vaccine follow-up period (i.e., between the vaccine and the serologic testing for response to vaccine) will be considered non-evaluable for the primary endpoint of the trial.

### 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently confirmed to be eligible to receive the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a febrile illness or other factor which has resolved may be rescreened at the discretion of the enrolling investigator. Rescreened participants should be assigned the same participant number as for the initial screening.]

### 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential participants will be identified from amongst the hematologic malignancy patients seen at the Karmanos Cancer Institute. Post-vaccination anti-SARS-CoV2 IgG Ab testing is being conducted as part of routine clinic practice at the cancer center, so many patients meeting eligibility criteria are already identified. We anticipate the majority of participants will be enrolled within a month of the trial opening. We also anticipate that patients may be referred for participation from within the McLaren Network or from other hospital networks, or they may self-refer. We also plan to inform myeloma, amyloidosis, and hematologic malignancy patient support groups across the state of Michigan using IRB-approved communications. African American patients who have previously received any of the available COVID-19 vaccines are having anti-SARS-CoV2 IgG Ab titers checked at the same frequency as other patient populations, and thus will have equal opportunity to participate in this trial. There is no compensation provided for participating in this trial.

## 6 STUDY INTERVENTION

### 6.1 STUDY INTERVENTION(S) ADMINISTRATION

#### 6.1.1 STUDY INTERVENTION DESCRIPTION

All participants in each of the cohorts will receive a single dose of the Moderna mRNA COVID-19 vaccine. This is an open label, non-randomized trial.

#### 6.1.2 DOSING AND ADMINISTRATION



The dose of Moderna mRNA vaccine to be administered is the same for all patients in all enrollment cohorts: 0.5 mL administered intramuscularly as a single dose, according to the manufacturer's package insert.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

The Moderna mRNA COVID-19 vaccine product to be used in this trial will be obtained from the McLaren Network Pharmacy Department. The product will be transferred to the Karmanos Cancer Institute's Investigational Pharmacy for dispensation to trial participants. As the vaccine is supplied in multi-dose vials, there will be sustained effort to schedule trial participants in such fashion as to minimize wastage of any doses. Unused product will be discarded according to standard pharmacy operating procedure.

### 6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Moderna COVID-19 Vaccine is provided as a white to off-white suspension for intramuscular injection. Each 0.5 mL dose of Moderna COVID-19 Vaccine contains 100 mcg of nucleoside- modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus.

Each dose of the Moderna COVID-19 Vaccine contains the following ingredients: a total lipid content of 1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.20 mg sodium acetate trihydrate, and 43.5 mg sucrose.

Moderna COVID-19 Vaccine does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

### 6.2.3 PRODUCT STORAGE AND STABILITY

During storage, minimize exposure to room light.

The Moderna COVID-19 Vaccine multiple-dose vials are stored frozen between -50° to -15°C (-58° to 5°F). Store in the original carton to protect from light.

Do not store on dry ice or below -50°C (-58°F). Use of dry ice may subject vials to temperatures colder than -50°C (-58°F).

Vials may be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use.

Vials may be stored between 8° to 25°C (46° to 77°F) for a total of 24 hours.

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Vials should be discarded 12 hours after the first puncture.

Thawed vials can be handled in room light conditions.

Do not refreeze once thawed.

#### Transportation of Thawed Vials at 2° to 8°C (35° to 46°F)

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials for up to 12 hours at 2° to 8°C (35° to 46°F) when shipped using shipping containers which have been qualified to maintain 2° to 8°C (35° to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Once thawed and transported at 2° to 8°C (35° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (35° to 46°F) until use.

### 6.2.4 PREPARATION

#### Dose Preparation

The Moderna COVID-19 Vaccine multiple-dose vials contain a frozen suspension that does not contain a preservative and must be thawed prior to administration.

Vial	Thaw in Refrigerator	Thaw at Room Temperature
<b>Maximum 11-Dose Vial (range: 10-11 doses)</b>	Thaw in refrigerated conditions between 2° to 8°C for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C for 1 hour.
<b>Maximum 15-Dose Vial (range: 13-15 doses)</b>	Thaw in refrigerated conditions between 2° to 8°C for 3 hours. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C for 1 hour and 30 minutes.

Remove the required number of vial(s) from storage and thaw each vial before use following the instructions below.

After thawing, do not refreeze.

Swirl vial gently after thawing and between each withdrawal. **Do not shake.**

Do not dilute the vaccine.

The Moderna COVID-19 Vaccine is a white to off-white suspension. It may contain white or translucent product-related particulates. Visually inspect the Moderna COVID- 19 Vaccine vials for other particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

The Moderna COVID-19 Vaccine is supplied in two multiple-dose vial presentations:

- A multi-dose vial containing a maximum of 11 doses: range 10-11 doses (0.5 mL each)
- A multi-dose vial containing a maximum of 15 doses: range 13-15 doses (0.5 mL each)

Depending on the syringes and needles used for each dose, there may not be sufficient volume to extract more than 10 doses from the maximum of 11 doses vial or more than 13 doses from the maximum of 15 doses vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.5 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.5 mL, discard the vial and contents. Do not pool excess vaccine from multiple vials.
- Pierce the stopper at a different site each time.

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Record the date and time of first use on the Moderna COVID-19 Vaccine vial label. Discard vial after 12 hours. Do not refreeze.

### 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable (non-blinded, non-randomized trial)

### 6.4 STUDY INTERVENTION COMPLIANCE

Administration of the Moderna mRNA COVID-19 booster dose as part of this protocol will be documented in the medical record and there will also be a study-specific dose administration documentation form. Copies of post-administration safety assessments reflecting patient-reported symptoms/side effects on days 2-8, 15, 22, and 28 will be filed in each participant's shadow chart in CTO.

### 6.5 CONCOMITANT THERAPY

For this protocol, the only prohibited medication is daily corticosteroids at a dose equivalent to or greater than Prednisone 20 mg/day. *Intermittent* steroid dosing, including higher doses such as the weekly dexamethasone dosing used as part of typical myeloma or AL amyloidosis regimens, is permitted. In such cases, as well as for patients currently receiving potentially immunosuppressive anti-neoplastic therapy for their underlying hematologic condition, a two-week interruption in therapy before and after the booster dose of vaccine is ENCOURAGED BUT NOT REQUIRED (physician discretion).

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#### 6.5.1 RESCUE MEDICINE

Standard medications used for the management of a hypersensitivity reaction (in the unlikely event such a reaction occurs) are permitted, to be administered according to the discretion of the treating physician.

## 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1 DISCONTINUATION OF STUDY INTERVENTION

If a clinically significant finding is identified after participants are enrolled and treated on study, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

### 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Documented SARS-CoV2 infection
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to return for post vaccination assessment at 28 days (+/- 3 days) after vaccination. NOTE: patients who miss this window but are able to return to complete required assessments may be able to remain on trial (treating physician must discuss with the PI).

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are enrolled but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

### 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the day 28 visit and is unable to be contacted by the study site staff. A participant will be considered "at-risk" to be lost to follow-up if he or she is unable to be contacted by the study site staff during the safety assessment period between the date of vaccine dose administration and the day 28 follow up visit.

The following actions must be taken if a participant fails to return to the clinic for a required study visit or cannot be reached for protocol-specified remote safety assessments:

- The site will attempt to contact the participant and reschedule the missed calls/visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 EFFICACY ASSESSMENTS

**Please refer to the Study Calendar (Section 1.3) for a complete list of protocol-related assessments.**

A blood specimen collection will be performed on day 28 (+/- 3 days) after the administration of the booster dose of the Moderna mRNA COVID-19 vaccine. An anti-SARS-CoV2 IgG Ab titer will be measured using this sample. This is the primary efficacy assessment being performed as part of this trial.

### 8.2 SAFETY AND OTHER ASSESSMENTS

Safety Assessments: participants will have a medical history, vitals, and physical exam and bloodwork for laboratory testing including cardiac biomarkers performed during screening and on day 28 (+/- 3 days). Participants will also be contacted by phone/text/email/video platform on days 2-8, 15, and 22 to document any AEs experienced. Any patients reporting chest pain, palpitations, shortness of breath, or other symptoms which in the opinion of the treating physician suggest cardiac etiology will be asked to have additional bloodwork done to measure cardiac biomarkers (hsTrop I, BNP).

Baseline Patient characteristics: The patient's chart in the EMR will be accessed to document general demographics, their hematologic diagnosis and the status of that disease, current and past treatment history for the underlying hematologic condition, other past medical history, medications, and baseline laboratory parameters (including but not limited to neutrophil count, lymphocyte count, immunoglobulin levels). These and other variables (TBD) will be entered into a CRF to be used for eventual univariate and multivariate analyses. Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements will be followed, as applicable.

Blood sample collection for future correlative testing (e.g., immune cell profiling, assessment of immune exhaustion, etc). The following samples will be collected and stored in Asfar Azmi's laboratory: **one 15 mL EDTA tube of peripheral blood** obtained prior to administration of the booster dose, and **a second 15 mL EDTA tube of peripheral blood obtained at the day 28 visit**. The first correlative testing we are planning to perform is a detailed anti-viral protein antibody evaluation using the Bio-Plex Pro SARS-CoV-2 Serology assay. This assay is a sensitive and specific method to monitor the antibody immune response profile against viral proteins. There are three isotype-specific 4-plex panels that measure antibodies against SARS-CoV-2 Nucleocapsid, Receptor Binding Domain, Spike 1, and Spike 2 viral proteins. The isotype-specific antibodies detected are IgA, IgG, and IgM. The viral-protein-coated beads can be used to assay antibodies in multiple species and only need to be paired with a species-specific biotinylated

antibody for detection. The results will elucidate the spectrum of humoral response over time before and after COVID-19 vaccine booster administration or natural exposure to SARS-CoV-2 compared to those obtained using the CLIA-certified assay currently in clinical use. Further, it will provide useful information regarding any additional humoral response to vaccination amongst patients who have not only been previously vaccinated but also had a prior COVID-19 infection. Additional correlative testing may be performed with internal and/or external partners such as Adaptive Biosciences with the intention of characterizing other aspects of patients' immune status through T-Cell profiling, including analysis of T-cell receptor (TCR) reactivity against COVID-19 antigens. Any such research will always involve de-identified samples and patient's privacy will be protected.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization 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 participant 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, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

AEs will be graded according to CTCAE v4 criteria.

For adverse events (AEs) not included in the CTCAE grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

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### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **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 study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
- **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 study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Potentially 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 study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) 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 intervention 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.

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### 8.3.3.3 EXPECTEDNESS

The Principal Investigator or treating Co-Investigator will be responsible for determining whether an adverse event (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 for the study intervention.

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### 8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (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.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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.

All reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation will be recorded in the participant's study chart. 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.

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### 8.3.5 ADVERSE EVENT REPORTING

AE reporting to the IRB and/or Karmanos Data Safety and Monitoring Committee will be carried out according to the Karmanos Cancer Institute SOP.

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### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless the event is unexpected and there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the DSMC and IRB.

SAEs and any vaccine administration errors for protocol 2021-036 will be reviewed at the Myeloma and Amyloidosis biweekly research team meeting and any reportable events will be reported to the Vaccine Adverse Event Reporting System (VAERS) and Moderna TX, Inc.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event requested by the IRB or DSMC should be provided as soon as possible.



The study sponsor will be responsible for notifying the Food and Drug Administration (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.

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#### 8.3.7 REPORTING EVENTS TO PARTICIPANTS

All participants will be informed of AEs or SAEs occurring during the conduct of this trial which in the opinion of the PI change the risk/benefit profile of the intervention and/or which may impact participants' willingness to continue on the protocol. Such information will be conveyed to participants by phone, email, and/or certified letter to ensure their awareness.

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#### 8.3.8 EVENTS OF SPECIAL INTEREST

None (Not applicable)

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#### 8.3.9 REPORTING OF PREGNANCY

The CDC recommends that pregnant or breastfeeding women be vaccinated against COVID-19. Neither pregnancy nor breastfeeding is an exclusion to participating in this trial. Any participant who is pregnant at the time of enrollment or becomes pregnant during the course of participation in the trial will be asked to inform her treating physician of the pregnancy so that information regarding CDC and FDA monitoring programs related to this can be provided.

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### 8.4 UNANTICIPATED PROBLEMS

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#### 8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of 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 Institutional Review Board (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.

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#### 8.4.2 UNANTICIPATED PROBLEM REPORTING

[The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). 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.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 72 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials and the Office for Human Research Protections (OHRP) according to KCI/WSU institutional requirements.

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#### 8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

All participants will be informed of UPs occurring during the conduct of this trial which in the opinion of the PI change the risk/benefit profile of the intervention and/or which may impact participants' willingness to continue on the protocol. Such information will be conveyed to participants by phone, email, and/or certified letter to ensure their awareness.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 OBJECTIVES

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#### 9.1.1 PRIMARY OBJECTIVE

To determine whether booster dosing with the Moderna COVID-19 vaccine can induce humoral immune responses in patients with hematologic malignancies who did not have an adequate response to prior first vaccination with any of the SARS-CoV2 vaccines authorized for use in the USA.

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#### 9.1.2 SECONDARY OBJECTIVES

1. To determine whether booster dosing with the Moderna COVID-19 vaccine is safe in patients with multiple myeloma, AL amyloidosis, or other hematologic malignancies.
2. To compare the humoral immune responses between the patients who had a WEAK POSITIVE RESPONSE to prior vaccine (Cohort 3) vs. those with NO RESPONSE to prior vaccination (Cohorts 1 and 2).

3. To descriptively summarize clinical and immune characteristics which contribute to likelihood of responding to booster dosing with the Moderna COVID-19 vaccine.

## 9.2 END POINTS

The primary and second secondary endpoints are the observed response rate of anti-SARS-CoV2 IgG antibody seroconversion (positive vs. negative) measured 28 days (+/- 3 days) following a booster dose of the Moderna mRNA COVID-19 vaccine.

The first secondary endpoints are AEs and SAEs observed in participants, determined according to daily phone calls or video chats. The third secondary endpoints are (a) clinical characteristics of enrolled participants, including treatment history, disease, status, or presence of immunoparesis (i.e., hypogammaglobulinemia) and (b) characterization of patients' immune status through lymphocyte subset profiling, cytokine level analysis, and assessment of immune exhaustion markers.

## 9.3 SAMPLE SIZE DETERMINATION

The specific hypothesis being tested is that it may be possible to induce a protective humoral immune response with a booster dose of the Moderna COVID-19 vaccine in patients with hematologic malignancies who did not have an adequate response to first vaccination with any of the available COVID-19 vaccines. The null hypothesis is that 5% or less of patients who have an anti-SARS-CoV2-IgG Ab titer of less than 2.0 S/CO will spontaneously develop a higher titer. We hypothesize that at least 15% of patients in each cohort will develop a titer of 2.0 S/CO or greater in response to the vaccine, without toxicity in excess of that previously described amongst COVID-19 vaccine recipients.

Thus, the sample size for each cohort of this trial was determined using the Phase 2 single-arm single-stage design based on the following statistical assumptions:  $p_0=5\%$ ,  $p_1=15\%$ , 1-sided  $\alpha = 5\%$ , and power = 80%. In this case, 52 patients would be enrolled to each of the three cohorts. In each cohort, at least 6 patients would need to develop an anti-SARS-CoV2-IgG Ab titer of  $>2.0$  S/CO to reject the null hypothesis. Therefore, a total of 156 response-evaluable patients would be enrolled in this 3-parallel cohort, single-arm, single-stage Phase 2 trial. Given that the study intervention is a single vaccination, and the primary endpoint requires a single visit for a physical a blood sample collection, there should be relatively few non-evaluable patients. Patients who are non-evaluable for the primary endpoint will be replaced only if it becomes evident that this is needed to determine whether or not the primary endpoint is met in any/all of the cohort(s). We expect this will amount to no more than 5 additional patients in any of the three cohorts, so the maximum number of enrolled participants is 171 (= 57 x 3 cohorts).

The size of the trial will also permit a comparison of the likelihood of developing a strong positive response amongst the pooled participants from Cohorts 1 and 2 (i.e., the participants with NO RESPONSE to prior vaccination) versus the participants in Cohort 3 (i.e., the patients who had a WEAK POSITIVE RESPONSE to prior vaccine) as the second secondary objective. We hypothesize that the absolute difference in response rate between Cohort 3 vs. Cohort 1+2 is 20% or more against the response rate of 15% in Cohort 1+2 (i.e., Cohort 3: 35% vs. Cohort 1+2: 15%). The sample sizes of 156

(Cohort 3: 52 vs. Cohort 1+2: 104) will achieve 82.7% power to detect a difference of 20% between two groups at a 1-sided 5% level when the Fisher's exact test is used.

Each cohort in the primary object will be tested at a 1-sided 5% level and the second secondary objective will be also evaluated at a 1-sided 5% level. No correction for multiple comparison is planned between these primary and second secondary objectives

## 9.4 ANALYSIS PLAN

### 9.4.1 EFFICACY ANALYSES

Within each cohort, all participants who receive the protocol-specified booster dose of the Moderna COVID-19 vaccine and then have blood sampled within the protocol-specified time window will be included in the efficacy analysis ("efficacy analysis datasets"). There will be an efficacy dataset for each cohort individually.

For the primary and second secondary objectives, the response rate (RR), which is the primary endpoint, will be summarized with frequency, percentage and its associated 2-sided 90% confidence interval (i.e., 1-sided 95% confidence interval), separately by each cohort and by the combined cohort (Cohort 1+2).

For the second secondary objectives, the Fisher's exact test will be used to compare between Cohort 3 vs. Cohort 1+2.

For the third secondary objective, the patient demographic, clinical, and immune characteristics will be summarized by mean, median, standard deviation, range, confidence interval for continuous variables and by frequency, percentage and its associated confidence interval for categorical variables.

As an exploratory analysis, univariable logistic models will be used to explore the associations between patient characteristics and the treatment response.

### 9.4.2 SAFETY AND TOXICITY ANALYSES

All patients from any cohort who receive the planned vaccine booster dose will be included in a pooled "toxicity analysis dataset," whether or not they are also included in an "efficacy analysis dataset."

The incidence and severity of adverse events and/or toxicity will be summarized with frequency, percentage and its associated confidence interval.

### 9.4.3 PLANNED INTERIM ANALYSES

Not Applicable: there is no planned interim analysis.

## 9.5 EXPECTED DURATION

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### 9.5.1 ACCRUAL DURATION

Based on the current practice at KCI, we expect that it will take 6-8 weeks to accrue 52 patients for each of three cohorts.

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### 9.5.2 STUDY DURATION

All participants will be dosed within 3 months of the trial opening, and the primary endpoint will be assessed in all participants by 28 days (+/- 3 days) of the last participant being dosed. Thus, considering ~2-months (6-8 weeks) for patient accrual and ~4-months for IRB approval and data analysis, the expected study duration is ~10 months (= 3 months + 28 days + ~2 months + ~ 4 months).

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## 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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### 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

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#### 10.1.1 INFORMED CONSENT PROCESS

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##### 10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

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##### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or a designated surrogate will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's 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 family or 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. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. 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.

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### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, co-investigators, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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 that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

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### 10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. 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.

All research activities will be conducted at 2 of the Karmanos Cancer Institute locations (Main Campus and Farmington Hills) and all efforts will be made to secure complete privacy for patients participating in clinical trials per HIPAA regulations

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies 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 the Karmanos Cancer Institute 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 the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Karmanos Cancer Institute. 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 by the Karmanos Cancer Institute's research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Karmanos Cancer Institute.

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#### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the laboratory of Dr. Asfar Azmi. These samples could be used to research the causes of failure to respond to booster dosing with the Moderna COVID-19 vaccine, vaccine-related complications, or other conditions for which individuals with hematologic malignancies are at increased risk, and to improve treatment. Dr. Asfar's lab will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data (i.e., underlying hematologic condition and baseline anti-SARS-CoV2 IgG Ab titer) from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

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#### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

*Provide the name and contact information of the Principal Investigator and the Medical Monitor.*

<b>Principal Investigator</b>	<b>Medical Monitor</b>
Jeffrey A Zonder, MD	Jeffrey A. Zonder, MD
Karmanos Cancer Institute	Karmanos Cancer Institute
4100 John R., Detroit, MI 48201	4100 John R., Detroit, MI 48201
313-576-8673	313-576-8673
<a href="mailto:zonderj@karmanos.org">zonderj@karmanos.org</a>	zonderj@karmanos.org

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#### 10.1.6 SAFETY OVERSIGHT

Given the number of patients to be enrolled in this trial and the short enrollment time, the Principal Investigator has created a task force with the participation of key personnel in charge of different logistical areas of the trial. There will be an open daily communication with all participants of the task force to go over issues that may have come up concerning patient's care, vaccine supply, logistics, compliance, record keeping, enrollment, communications with treating physicians, follow up etc.

The task force will utilize a generic e-mail address (KCIvaccinebooster@karmanos.org) created particularly for this study to communicate with everyone in the team about any issue that may arise. Participants who wish to utilize an e-mail, will be provided with this e-mail address so their message is received on a timely manner by everyone in the team and the appropriate physician is informed.

Safety information that is collected during the study include, per study calendar: AE's/SAE's, (Symptoms that patients may have experiences post vaccination such as injection site pain, muscle aches, fever, redness, fatigue, shortness of breath, palpitations, chest paint etc). If any of the participants will report any of the above listed AEs/SAEs, the treating physician will be informed and the subject will be contacted with guidance on how to proceed.

Additionally, the PI will submit Data and Safety Monitoring Reports to the KCI DSMC committee. These reports will be submitted monthly. The reports require the following information: accrual, AE's, patient status and response, protocol deviations, and summary of IRB amendments. The reports will be reviewed and response will be sent back to the PI to determine if the study can continue without modification.

Safety oversight will be under the direction of a Data and Safety Monitoring Committee (DSMC) composed of individuals with the appropriate expertise. Members of the DSMC are independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The KCI DSMC meets monthly to assess safety and efficacy data on each arm of the study. The DSMC regularly reviews every Investigator Initiated Trial conducted at the Karmanos Cancer Institute, and provides its input regarding each study to the associated Principal Investigator.

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#### 10.1.7 CLINICAL MONITORING

Not applicable: This is a single site trial. There are no additional sites to monitor.

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#### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) is assessed and enforced by the Karmanos Cancer Institute's Quality Assurance Committee (KCI QAC). All Investigator Initiated Trials are subject to KCI QAC audits, both periodic (routine) and for-cause.

Following written Standard Operating Procedures (SOPs), the monitors from the KCI QAC will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The clinical investigation team will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the KCI QAC, and/or inspection by local and regulatory authorities.]

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#### 10.1.9 DATA HANDLING AND RECORD KEEPING

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##### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff under the supervision of the study Principal Investigator. 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.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into OnCore, a 21 CFR Part 11-compliant data capture system. 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.

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#### 10.1.9.2 STUDY RECORDS RETENTION

Study documents are retained on site at the Karmanos Cancer Institute's Clinical Trials Office (KCI CTO) for a minimum of 3 years after completion of the trial. After that, the records are stored at Iron Mountain indefinitely. No records will be destroyed without the written consent of the Principal Investigator.

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#### 10.1.10 PROTOCOL DEVIATIONS

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The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities.

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#### 10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (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.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As

such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

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#### 10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Karmanos Cancer Institute and Wayne State University have established policies and procedures for all investigators to disclose all conflicts of interest and mechanisms for the management of all reported dualities of interest.]



## 11 REFERENCES

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APPENDIX 1: ECOG PERFORMANCE STATUS

**ECOG PERFORMANCE STATUS**

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	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
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead