Review Memorandum

Date:	**October 20, 2021**
To:	**The File**
From:	**David Cho, PhD (CBER/OD)**
Through:	**Peter Marks, MD, PhD (CBER/OD)**
Applicant name:	**Moderna**
Application Number:	**EUA 27073**
Product:	**Moderna COVID-19 Vaccine**
Subject:	**EUA amendment to support use of a Moderna COVID-19 Vaccine heterologous booster dose following primary vaccination with other authorized COVID-19 vaccines.**

This memorandum provides a summary, review, and recommendation on the request by the National National Institute for Allergy and Infectious Diseases of the National Institutes of Health (further referred to as NIH) that FDA amend the existing Emergency Use Authorization (EUA) for the Moderna COVID-19 Vaccine to include its use as a single heterologous booster dose following completion of primary vaccination with other currently authorized COVID-19 vaccines. The requested authorization is as follows:

A single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

Executive Summary

NIH has proposed amending EUA 27073 to allow a single dose of the Moderna COVID-19 Vaccine to be used as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. To support this request, NIH has provided information from a 3 x 3 matrixed booster study that evaluated the three currently authorized or approved COVID-19 vaccines and documented that booster administration of each of the vaccines resulted in a booster response, regardless of the primary vaccination. These data were presented at the FDA's Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting on October 15th, 2021, and the advisors endorsed implementing an allowance for heterologous boosting of the currently authorized and approved COVID-19 vaccines.

Review

The NIH data submitted data that is available as a preprint on line:

Atmar RL, Lyke, RE, Deming, ME, et al. Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report. 2021; medRxiv preprint doi: https://doi.org/10.1101/2021.10.10.21264827.

This is a Phase 1/2 open-label clinical trial being conducted at 10 sites in the United States. 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, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. The dose volume and antigen content used for the booster dose of each of the vaccines was the same as that authorized for the primary vaccination. Adverse events were assessed through 28 days after the booster dose. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose (and on Day 29 after the Moderna booster dose, with Day 29 data pending for the other vaccines).

The following table from the preprint summarizes patient enrollment into the trial:

Table 1. Characteristics of the Participants at Enrollment

Group	1	2	3	4	5	6	7	8	9
Primary EUA Immunization Vaccine	Janssen Ad26.COV2-S $5x10^{10}$ vp	Moderna mRNA-1273 100-mcg	Pfizer/BioNTech BNT162b2 30-mcg	Janssen Ad26.COV2-S $5x10^{10}$ vp	Moderna mRNA-1273 100-mcg	Pfizer/BioNTech BNT162b2 30-mcg	Janssen Ad26.COV2-S $5x10^{10}$ vp	Moderna mRNA-1273 100-mcg	Pfizer/BioNTech BNT162b2 30-mcg
Booster	Moderna mRNA-1273 100-mcg			Janssen Ad26.COV2-S $5x10^{10}$ vp			Pfizer/BioNTech BNT162b2 30-mcg		
Total Number	53	51	50	50	49	51	53	51	50
Sex – no. (%)									
Female	26 (49.1)	32 (62.7)	29 (58.0)	27 (46.0)	16 (32.7)	23 (45.1)	29 (54.7)	26 (51.0)	23 (46.0)
Male	27 (50.9)	19 (37.3)	21 (42.0)	23 (54.0)	33 (67.3)	28 (54.9)	24 (45.3)	25 (49.0)	27 (54.0)
Age – years									
Mean (s.d.)	56.8 (14.5)	53.1 (16.2)	54.8 (17.4)	50.1 (13.9)	49.9 (16.8)	50.3 (15.4)	47.7 (14.5)	54.3 (16.8)	50.4 (17.9)
Range	24-81	24-76	22-85	24-77	20-75	20-76	22-74	23-75	19-80
Race – no. (%)									
Asian	4 (7.5)	5 (9.8)	4 (8.0)	3 (6.0)	5 (10.2)	6 (11.8)	1 (1.9)	2 (3.9)	1 (2.0)
Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Black/African American	1 (1.9)	2 (3.9)	3 (6.0)	0 (0.0)	0 (0.0)	2(3.9)	0 (0.0)	2 (3.9)	1 (2.0)
White	46 (86.8)	41 (80.4)	43 (86.0)	44 (88.0)	43 (87.8)	40 (78.4)	50(94.3)	47 (92.2)	43 (86.0)
Multi-racial	1 (1.9)	3 (5.9)	0 (0.0)	3 (6.0)	1 (2.0)	2 (3.9)	1 (1.9)	0 (0.0)	4 (8.0)
Other	1 (1.9%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0%)	0 (0.0)	0 (0.0)	1 (2.0%)
Ethnicity – no (%)									
Non-Hispanic	49 (92.5)	46 (90.2)	47 (94.0)	47 (94.0)	49 (100.0)	48 (94.1)	51 (96.2)	49 (96.1)	45 (90.0)
Hispanic/Latino	4 (7.5)	4 (7.8)	3 (6.0)	2 (4.0)	0 (0.0)	3 (5.9)	2 (3.8)	2 (3.9)	5 (10.0)
Unknown/Not reported	0 (0.0)	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Boost Interval weeks									
Mean (s.d.)	13.7 (1.0)	16.4 (1.9)	16.8 (2.2)	17.7 (2.0)	19.3 (4.2)	20.6 (5.8)	19.9 (2.5)	22.9 (4.6)	24.1 (5.2)
Range	12.0-15.9	12.4-20.0	12.0-20.9	13.9-21.0	12.6-26.0	12.3-41.3	10.9-23.0	12.6-28.7	14.3-31.9

An overall review of adverse reactions reported following the Moderna COVID-19 Vaccine heterologous booster dose 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. The following figure summarizes the reactogenicity reported in the study:

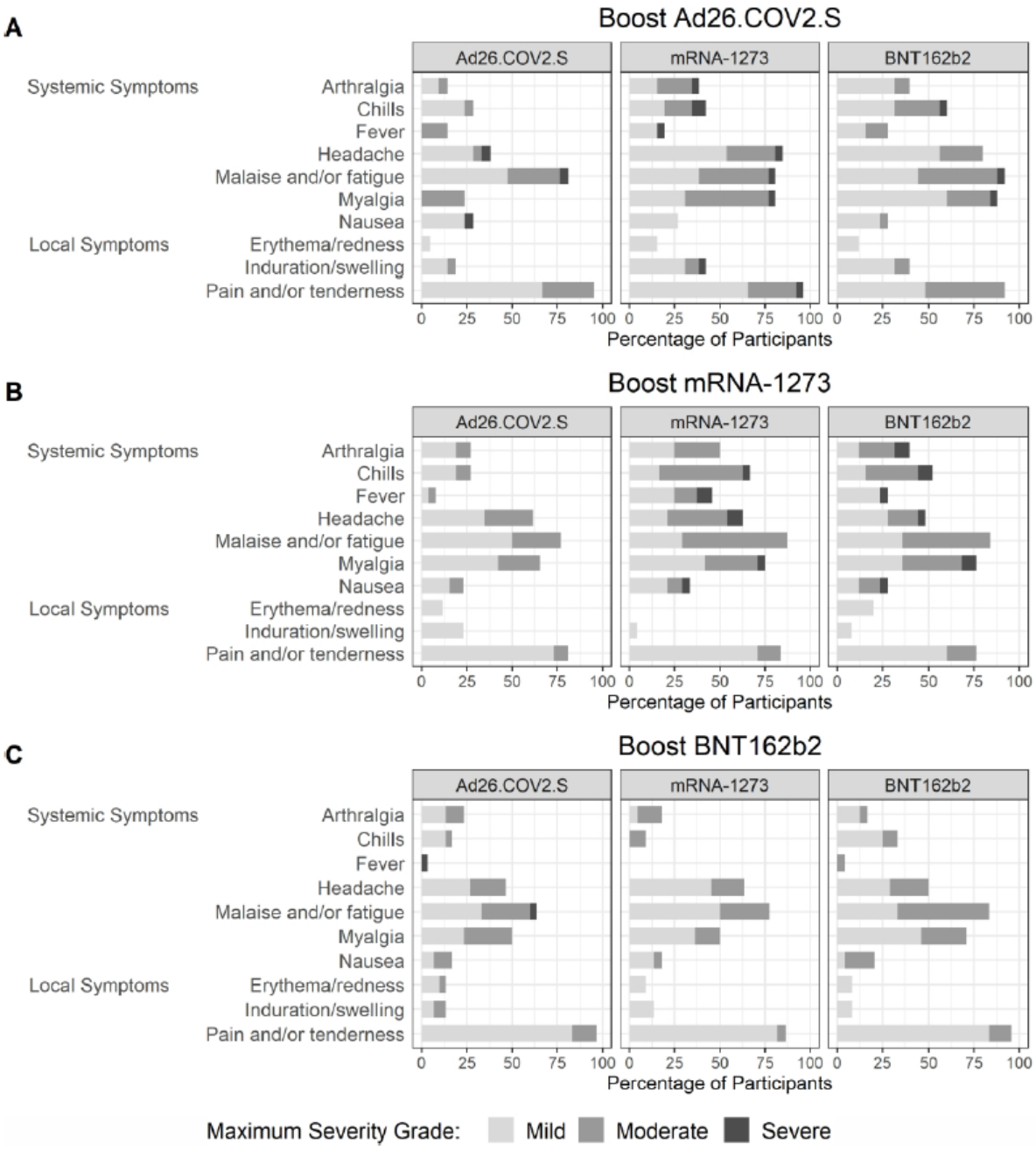

Figure 1 | Reactogenicity

Two serious adverse events were reported in this trial (rhabdomyoslysis following a fall and acute cholecystitis). Neither was judged to be related to booster vaccine administration.

The following table summarizes the neutralizing antibody responses to homologous and heterologous boosting in this study. Geometric mean neutralizing antibody titers to SARS-CoV-2 D614G increased

between 4.2 and 75.9 fold from pre-booster baseline to 15 days post-booster. The data support that the Moderna COVID-19 Vaccine booster dose elicited a booster response regardless of the vaccine received for primary vaccination.

Table 2. SARS-CoV-2 IgG Binding and Neutralizing Antibody Assays

Group	1	2	3	4	5	6	7	8	9
Primary EUA Immunization	Janssen	Moderna	Pfizer/BioNTech	Janssen	Moderna	Pfizer/BioNTech	Janssen	Moderna	Pfizer/BioNTech
Vaccine	Ad26.COV2-S	mRNA-1273	BNT162b2	Ad26.COV2-S	mRNA-1273	BNT162b2	Ad26.COV2-S	mRNA-1273	BNT162b2
	$5x10^{10}$ vp	100-mcg	30-mcg	$5x10^{10}$ vp	100-mcg	30-mcg	$5x10^{10}$ vp	100-mcg	30-mcg
Booster	Moderna mRNA-1273 100-mcg			Janssen Ad26.COV2-S $5x10^{10}$ vp			Pfizer/BioNTech BNT162b2 30-mcg		
Neutralizing Antibody Titer (International Unit (IU)/mL)									
D614G ‡									
Day 1 GMT (95% CI)	8.9 (6.2-12.8)	88.7 (67.7-115.9)	24.8 (18.0-34.2)	7.6 (4.9-11.8)	61.7 (45.0-84.6)	18.6 (13.4-25.7)	9.4 (6.4-13.6)	57.6 (45.0-73.7)	21.4 (15.3-30.0)
Day 15 GMT (95% CI)	676.1 (517.5-883.3)	901.8 (727.5-1117.8)	785.8 (596.4-1035.2)	31.42 (22.3-44.3)	382.1 (290.5-502.5)	216.4 (157.8-296.9)	341.3 (239.6-486.3)	677.9 (559.4-821.3)	446.7 (340.3-586.3)
Day 29 GMT (95% CI)	431.7 (322.6-577.6)	700.0 (568.6-861.8)	495.7 (370.4-663.4)	In process	In process	In process	In process	In process	In process
Percentage with four-fold rise at Day 15 (95% CI)	100.0% (93.2%-100.0%)	86.0% (73.3%-94.2%)	100.0% (92.9%-100.0%)	50.0% (35.5-64.5%)	61.2% (46.2-74.8%)	82.0% (68.6-91.4%)	98.0% (89.0-99.9%)	93.8% (82.8-98.7%)	97.9% (88.9-99.9%)
Day 15 geometric mean fold rise (95% CI)	75.9 (55.0-104.8)	10.2 (8.0-12.8)	31.7 (23.8-42.2)	4.2 (3.0-5.8)	6.2 (4.5-8.5)	12.5 (8.7-17.9)	35.1 (23.9-51.6)	11.5 (9.0-14.8)	20.0 (14.6-27.4)

* GMT- Geometric mean titers

Following presentation of the data from the heterologous booster dose study to the VRBPAC on October 15, 2021, the committee discussed the nature of the study and its implications. Although the relatively small sizes of the populations were noted, and no formal vote was taken, the consensus of the committee was that the presented analyses would support use of the authorized or approved COVID-19 vaccines as heterologous booster doses.

Recommendation

The data from the NIH Heterologous SARS-CoV-2 Booster Vaccination study indicate that each of the three currently authorized or approved COVID-19 vaccines (Moderna, Janssen, Pfizer) are capable of generating a booster response when administered to indiviuals who completed primary vaccination with another authorized or approved COVID-19 vaccine. Geometric mean neutralizing antibody titers to SARS-CoV-2 D614G increased between 4.2 and 75.9 fold from pre-booster baseline to 15 days post-booster. While some differences in reactogenicity following the booster dose were apparent, depending on the primary vaccination and/or the booster vaccination, no new safety concerns were identified as compared with the characterized safety profiles of the vaccines when used for primary vaccination or for homologous boosting. A limitation of the study is its relatively small size, with a total of 458 individuals (approximately 50 individuals each in 9 arms). Although boosting of neutralizing antibody titers was documented for each of the nine combinations of primary vaccination and booster dose, because of the limited sample size and

short duration of follow-up, it is not possible at this time to determine if there is a preferred strategy for use of heterologous COVID-19 vaccine booster doses.

Data obtained using the Moderna COVID-19 Vaccine booster dose (100 mcg) in the NIH study indicate that the booster response in individuals who previously received the Janssen COVID-19 Vaccine or Pfizer-BioNTech COVID-19 Vaccine resulted in geometric mean fold increases in neutralizing antibody titers of 75.9-fold and 31.7-fold, respectively. These increases are substantially higher than the corresponding increases for the Janssen COVID-19 Vaccine and Pfizer COVID-19 Vaccine homologous booster responses (4.2-fold and 20.0-fold, respectively). Additionally, neutralizing antibody titers are available from a Phase 2 study (mRNA-1273-P201) conducted by the vaccine manufacturer in which vaccine naïve and SARS-CoV-2 naïve participants received the first dose of the Moderna COVID-19 Vaccine primary series at either 50 mcg or 100 mcg mRNA content. The neutralizing antibody GMT at Day 29 after the 50 mcg dose was 76% of that elicited by the 100 mcg dose, indicating that use of a 50 mcg heterologous Moderna COVID-19 Vaccine booster dose is likely to achieve geometric mean fold increases in neutralizing antibody titers of a similar magnitude as a 100 mcg heterologous booster dose. Furthermore, available immunogenicity data support the effectiveness of a homologous Moderna COVID-19 Vaccine 50 mcg booster dose. The use of a Moderna COVID-19 Vaccine 50 mcg booster dose for both the homologous and heterologous settings is, therefore, preferable to avoid potential logistic challenges and medication errors that could otherwise occur were two different doses to be recommended in these settings.

In considering the appropriate populations that would be eligible for a heterologous booster dose and the appropriate interval between primary vaccination and a heterologous booster dose, the need for a booster dose is determined by immunity elicited by the primary vaccination. Thus, the eligible population(s) and dosing interval for a Moderna COVID-19 Vaccine heterologous booster dose that would be supported by available data would be the same as those authorized for a homologous booster dose of the vaccine used for primary vaccination.[1]

Based on the totality of the data submitted by NIH, the Moderna COVID-19 vaccine, when administered as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine may be effective in improving protection against serious outcomes of COVID-19 among individuals in whom immunity elicited by primary vaccination has waned. Additionally, the known and potential benefits outweigh the known and potential risks for use of a booster dose of the Moderna COVID-19 Vaccine when given following completion of primary vaccination with another authorized or approved COVID-19 Vaccine, following the eligible population(s) and interval authorized for a homologous booster dose of that vaccine.

We therefore recommend authorization of the Moderna COVID-19 Vaccine for a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine.

[1] CBER's review and analysis of the use of homologous booster doses, including the eligible population(s) and dosing interval for a homologous booster, is documented in separate review memoranda. Those three review memoranda, Emergency Use Authorization (EUA) Amendments for an Unapproved Product Review Memorandum: EUA 27073 (Amendment 250) for the Moderna COVID-19 Vaccine; Emergency Use Authorization (EUA) Amendments for an Unapproved Product Review Memorandum: EUA 27205 (Amendment 194) for the Janssen COVID-19 Vaccine; and Emergency Use Authorization (EUA) Amendments for an Unapproved Product Review Memorandum: EUA 27034 (Amendment 305) for the Pfizer-BioNTech COVID-19 Vaccine, are incorporated here by reference.