Vaccines and Related Biological Products Advisory Committee October 14-15, 2021 Meeting Presentation

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mRNA-1273
BOOSTER DOSE

SPONSOR BRIEFING DOCUMENT

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

MEETING DATE: 14 OCTOBER 2021

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Acronym	Definition
Ab	antibody
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
bAb	binding antibodies
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CNS	central nervous system
CoVs	Coronaviruses
COVID-19	Coronavirus disease 2019
CSR	clinical study report
DMID	Division of Microbiology and Infectious Diseases
DTaP	Diphtheria, Tetanus, and acellular Pertussis
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GLSM	geometric least squares mean
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
GMR	geometric mean ratio
HIV	human immunodeficiency virus
IA	interim analysis
ID_{50}	median infectious dose
IgG	immunoglobulin
IM	intramuscular
KPSC	Kaiser Permanente Southern California
LLOD	lower limit of detection
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically-attended adverse events
MERS	Middle East respiratory syndrome
mITT	modified intent-to-treat
mRNA	messenger ribonucleic acid
mRNA-1273e	mRNA-1273 group vaccinated earlier
mRNA-1273p	mRNA-1273 group vaccinated later
MSD	MesoScale Discovery

Acronym	Definition
nAb	neutralizing antibody
NIH	National Institutes of Health
NIM	noninferiority margin
PolyA	polyadenylated
PP	per-protocol
PsVNA	pseudotyped virus neutralizing assay
PT	preferred term
RMP	Risk Management Plan
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SD	standard deviation
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SRR	seroresponse rate
Study P201	Study mRNA-1273-P201
Study P301	Study mRNA-1273-P301 (COVE)
TEAE	treatment-emergent adverse event
Tdap	Tetanus, Diphtheria, Pertussis
ULOQ	upper limit of quantification
US	United States
UTR	untranslated region
VE	vaccine efficacy
VoC	variant of concern
VSV	vesicular stomatitis virus
WHO	World Health Organization

1 EXECUTIVE SUMMARY

Following an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 and declaration by the World Health Organization (WHO) of the outbreak as a Public Health Emergency of International Concern (its highest level of international public health emergency) on 11 March 2020, ModernaTX, Inc. (Moderna), leveraged its mRNA vaccine platform and previous research into coronaviruses (CoVs) to rapidly develop mRNA-1273. mRNA-1273 is a novel, lipid nanoparticle (LNP) encapsulated, mRNA-based vaccine against SARS-CoV-2. The safety and efficacy of mRNA-1273 to prevent COVID-19 was demonstrated in adults 18 years and older in Study mRNA-1273-P301 (Study P301), leading to emergency use authorization (EUA) in the United States (US) on 18 December 2020, and supporting filing of a Biologics License Application (BLA), which is currently under review. On 13 August 2021, the EUA was amended to include a third dose of the vaccine (at 100 µg) for individuals who have undergone solid organ transplantation or have conditions with an equivalent level of immunocompromise.

Since December 2020, mRNA-1273 and other COVID-19 vaccines have been available under EUA in the US and have obtained marketing licenses in countries around the world, including in EU, Canada, and Japan. Overall, mRNA-1273 is authorized for use in 46 countries and as of 26 September 2021, > 510 million doses of mRNA-1273 have been distributed worldwide.

The efficacy of mRNA-1273 to prevent COVID-19 was demonstrated to be 94.1% (95% CI: 89.3%, 96.8%) in November 2020 with 9 weeks median follow-up (Baden et al 2021) and 93.2% (95% CI: 91.0%, 94.8%) after 5.3 months median follow-up (El Sahly et al 2021), when the original strain (D614G) and the Alpha variant were the major circulating SARS-COV-2 strains (Pajon et al 2021 [in review]). However, in recent evaluations of antibody persistence 6 to 8- months after completion of the two-dose primary series, neutralization titers against variants of concern (VoCs) including Beta, Gamma, and Delta were observed to be 6- to 7-fold lower compared with those observed 1-month post-dose 2. The waning of antibody titers against VoCs is particularly concerning as peak antibody titers post-dose 2 were lower than those to the original strain, resulting in an increased proportion of individuals with antibody titers below the limit of detection of the assays (Choi et al 2021).

Subsequently, with the increasing Delta variant circulation, more cases of COVID-19 among fully-vaccinated individuals have been observed in the US (Bruxvoort et al 2021a [in review]). An increase in the number of breakthrough cases was reported during the open-label follow-up period of Study P301, (the pivotal safety and efficacy trial of mRNA-1273, during July-August 2021) with the vast majority due to the Delta variant. Further analysis showed that participants with a median follow-up of 13 months had significantly higher rates of breakthrough (77.1/1000 person-years) compared to participants with a median follow-up time of 7.9 months (49.0/1000 person-years). This

suggests that a combination of lower antibody persistence and the increased transmissibility of the Delta variant could be contributing to higher breakthrough rates.

Taken together, these data support the public health benefit of a booster dose of mRNA-1273 approximately 6 months after the second dose of mRNA-1273 to restore antibody titer levels and reduce the number of breakthrough cases, particularly against VoCs.

To address this emerging medical need, the immunogenicity of a 50 µg booster dose of mRNA-1273 was evaluated based on the 25 May 2021 FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 and discussions with the FDA and other health authorities. The success criteria proposed for the acceptability of a booster dose included demonstration of non-inferiority of the immune responses elicited by the booster dose compared with the immune response following the second dose of the primary series of the prototype vaccine. Specifically:

- The point estimate of the geometric mean ration (GMR), booster dose of 50 µg mRNA-1273 P201 (Study P201) Part B against the original virus strain vs. primary series of 100 µg mRNA-1273 P301 against the original virus strain, ≥ 1, with the lower bound of the corresponding 95% CI ≥ 0.67, based on the NIM of 1.5.
- The lower bound of the 95% CI of the difference in seroresponse rate (SRR) (SRR in P201 Part B against the original virus strain – SRR in P301 against the original virus strain) is ≥ -10%, based on the NIM of 10%.

Dose Selection

Immunogenicity and safety data presented in this briefing document support the use of a 50 µg booster dose of mRNA-1273 in adults 18 years and older who received primary COVID-19 vaccination at least 6 months prior. These data are derived from Study P201 Part B, where participants who previously received either a 100 µg or 50 µg primary series of mRNA-1273 in Study P201 Part A were given the opportunity to receive a 50 µg booster dose of mRNA-1273 at least 6 months thereafter. In total, 344 participants received the 50 µg booster dose, 171 of whom received two doses of the vaccine in the authorized dosage (100 µg) and interval as their primary series. Eighty-four participants (out of 344, 24.4%) were adults ≥ 65 years of age, who represent a demographic group at increased risk for the complications of severe COVID-19. Safety and immunogenicity after a booster dose were compared to the response after the primary series in study P301, where vaccine efficacy of 94.1% was demonstrated.

A 50 µg dose was selected as the candidate booster vaccine dose for the following reasons:

- Our objective was to use the optimal effective dose for boosting. As part of initial dose ranging of mRNA-1273 (P201 Part A), both 50 and 100 µg were evaluated.

Both doses induced at least a 66-fold rise from pre-dose 1 antibody titers. It was postulated that a 50 µg booster dose would be effective in quickly activating immune memory recall responses. The trend toward lower reactogenicity observed for the 50 µg dose in P201 Part A also supported this selection.

- Lower doses of antigen have been shown to be safe and immunogenic for other booster vaccines, such as diphtheria.
- Reducing the booster dose to 50 µg would result in a substantial increase in the world-wide vaccine supply of mRNA-1273.

Immunogenicity

Administration of a booster dose of 50 µg at least 6 months after the mRNA-1273 primary series (including the pooled data from recipients of the 50 and 100 µg primary series) increased neutralizing antibody titers by 15-fold one month after vaccination compared to pre-boost levels. The ratio of geometric mean titers (GMTs) one month after the booster dose in P201 Part B compared to one month after the 2-dose mRNA-1273 primary series in Study P301 was 1.7. The lower limit of the 95% CI was 1.5, exceeding the prespecified lower bound of 0.67, indicating statistically significantly higher post-booster GMTs (Table 1).

As a second measure of immunogenicity, SRR was evaluated using three definitions. The primary definition specified in the SAP was a 3.3-fold rise in SRR from pre- to post-booster, which was based on a fold rise criterion which statistically distinguishes titers based on the variability of the assay (USP General Chapter <1033> *Biological Assay Validation)*. The SRR was also evaluated as a 4-fold rise pre-booster to post-booster (P201B compared to P301 SRR pre-vaccination to post-dose 2). Both of these SRR definitions have a limitation when comparing to the SRR after the primary series. Pre-booster titers are substantially higher than pre-dose 1 titers, and thus achieving a 3.3 or 4-fold rise is more challenging. To address this limitation, SRR was also evaluated as a 4-fold rise from pre-dose 1 (pre-vaccination) to post-booster (P201B) compared to P201A pre-vaccination to post-dose 2 (within study comparison).

Using each of the three SRR definitions, the post-boost SRR was greater than 90%. Based on the primary definition, the difference in post-boost SRR in P201B compared to the SRR observed after the primary series in Study P301 was -5.3% (-8.8, -2.9), meeting the prespecified noninferiority margin [NIM] of 10%. Using a 4-fold rise definition of seroresponse, the point estimate SRR difference when comparing to the pre-boost titers was -8.2% and the lower bound was –12.2%, exceeding the NIM. This SRR difference was a result of high pre-booster nAb titers in previously primed participants versus those of Study P301 participants who were largely PsVNA seronegative. The third analysis performed showed that 100% of participants met the seroresponse criteria post-boost in P201B, with a SRR difference of 1.7% (0.4, 4.0) compared to P201A, indicating a statistically significantly higher seroresponse rate when comparing the SRR post-booster versus post-dose 2 titers.

Table 1: Co-primary Immunobridging Hypotheses from Study P201 Part B

	P201 Part B Pooled 50 µg mRNA-1273 Booster	P301 mRNA-1273 100 µg Primary Series
Baseline GMT	**125.7**	**9.6**
28 Days After Booster (P201 Part B) or Completion of Primary Series		
n	295	1053
GMT Observed	**1892.7**	**1081.1**
GMFR (95% CI)	**15.06 (13.43, 16.89)**	**112.30 (105.42, 119.62)**
GMT (model based)	1767.9	1032.7
95% CI	(1586.4, 1970.2)	(974.2, 1094.7)
GMR (P201 Part B vs. P301; model-based, 95% CI)	1.7 (1.5, 1.9)	
-3.3-Fold Definition of Achieving Seroresponse		
Participants achieving seroresponse, n (seroresponse rate %)	275/294 (93.5)	1038/1050 (98.9)
95% CI[a]	90.1, 96.1	98.0, 99.4
Difference in seroresponse rate (P201 Part B vs. P301) (%, 95% CI[b])	-5.3 (-8.8, -2.9)	

Abbreviations: GMT estimated by model based geometric least squares mean; CI = confidence interval.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
n=number of participants with available data at the corresponding timepoint
GMT: Geometric Mean Titer
GMFR: Geometric Mean Fold Rise
GMR: Geometric Mean Ratio
Seroresponse of the booster is defined based on pre-booster titer; seroresponse of the primary series is defined based on pre-vaccination (Dose 1) titer
[a] 95% CI is calculated using the Clopper-Pearson method.
[b] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Due to the epidemiology data showing the importance of the Delta variant as well as the protection inferred by neutralizing antibodies, samples from P201 Part B and P301 were tested in a validated PsVNA median infectious dose (ID50) assay against the Delta variant. The results demonstrated a 19-fold increase from pre-booster titers, as well as a 2.1-fold GMR between the Day 29 GMT one-month post-boost in participants vaccinated in P201 Part B vs the GMT one-month post-dose 2 in participants vaccinated in Study P301, suggesting benefit of a mRNA-1273 booster by increasing immunity against the Delta variant.

Safety

The reactogenicity and adverse event profile observed after the booster in P201B was generally similar to that observed following Dose 2 of the initial two-dose regimen in P301, which suggests no potentiation of reactogenicity or any new safety signals arising from administration of a third dose. The solicited local and systemic events reported during the 7-day period after booster were typically mild-to-moderate in severity, arose within the first 1 to 2 days after dosing, with median duration of 2-3 days. No related

SAEs, deaths, or AEs leading to study discontinuation were reported in the follow-up period after vaccination in P201 Part B (~5 months post-booster).

Data using a 100 µg booster dose of mRNA-1273 administered ~4 months after priming with two doses of 100 µg of mRNA-1273 have also been generated and demonstrated a profile consistent with these findings. These supportive data will be presented to the Vaccines and Related Biological Products Advisory Committee by colleagues from the Division of Microbiology and Infectious Diseases (DMID) of the National Institutes of Health, which is the Sponsor of the study, on Friday, 15 October 2021.

Conclusion

Based on the cumulative evidence, the benefit-risk profile of a 50 µg booster dose of mRNA-1273 administered at least 6 months after completion of the primary series is favorable in individuals ≥ 18 years of age, particularly in light of increasing breakthrough disease with the emergence of the Delta variant.

On 22 September 2021, FDA amended the authorization for the BNT162b2 mRNA vaccine to allow for a single booster at least 6 months after completion of the primary series in:

- individuals ≥ 65 years of age,
- individuals aged 18–64 years at high risk for severe COVID-19, and
- individuals aged 18–64 years whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

In the interest of public health, Moderna is requesting an amendment to the EUA for mRNA-1273 for administration of a 50 µg booster dose consistent with the amendment issued by the Agency for the BNT162b2 mRNA vaccine.

2 COVID-19 BACKGROUND

Summary

- Confirmed COVID-19 mortality has surpassed 700,000 deaths in the US, with more than 38 million cases of COVID-19 in the US (Dong et al 2020; Johns Hopkins University 2021).
- As of 26 September 2021, > 510 million doses of mRNA-1273 have been distributed worldwide for use in adults 18 years of age and older with more 305 million doses distributed in the US.
- Observational studies demonstrate high effectiveness of mRNA-1273 against most VoCs; however, decreased effectiveness of mRNA-1273 against the Delta variant has been shown, particularly in individuals ≥ 65 years old (Bruxvoort et al 2021a [in review], Bruxvoort et al 2021b [in review]).
- Low or undetectable neutralization antibody titers have been observed in individual against some VoCs ~6 months after vaccination, which, coupled with the increased transmissibility of the Delta variant, places vaccinated individuals at increased risk of breakthrough disease (Choi et al 2021).
- Recent analysis also demonstrates that neutralizing antibodies likely have utility in predicting mRNA-1273 vaccine efficacy against COVID-19 (Gilbert et al 2021). Therefore, booster vaccination may restore neutralizing antibody titers to a level affording greater protection against breakthrough disease, particularly against VoCs.

2.1 Clinical/Pathophysiology of Condition

Early in 2020, the WHO declared COVID-19 to represent a Public Health Emergency of International Concern, denoting its highest level of public health emergency. Confirmed COVID-19 mortality has surpassed 4.8 million deaths worldwide and 702,360 deaths in the US as of 05 October 2021, with COVID-19 cases numbered over 235 million worldwide and more than 43 million in the US (Dong et al 2020; Johns Hopkins University 2021).

The majority of individuals with COVID-19 have mild symptoms or moderate illness. Approximately 10-15% of COVID-19 cases progress to severe disease, and approximately 5% become critically ill (WHO 2021). Long-term sequelae in COVID-19 patients with persistent symptoms after recovery from acute COVID-19 have been reported. Fatigue, dyspnea, joint pain, chest pain, and neuropsychiatric symptoms have been reported as common and persistent sequelae (Carfi et al 2020; Halpin et al 2021). Myocardial injury has been reported among patients with severe COVID-19 (Shi et al 2020). Additionally, some patients develop serious medical complications such as ventricular dysfunction, pulmonary function abnormalities, and acute kidney injury (Puntmann et al 2020; Rajpal et al 2021; Sardari et al 2021; Huang et al 2020; Zhao et

al 2020; Peleg et al 2020). While more serious long-term health complications appear to be less common, they have individual, global health, and severe socioeconomic consequences.

Individuals at highest risk of severe COVID-19 are older adults (≥ 65 years old) and people of any age who have certain underlying medical conditions, such as cancer, chronic kidney disease, chronic lung diseases, dementia or other neurological conditions, diabetes, Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state, liver disease, obesity, pregnancy, sickle cell disease, solid organ transplant, and stroke or cerebrovascular disease (CDC 2021). Smokers and individuals with substance use disorders are also at increased risk for severe COVID-19 (CDC 2021).

2.2 Currently Available COVID-19 Vaccines

It is widely acknowledged that the key to controlling this pandemic and mitigating its impact is primary prevention through vaccination. Currently available COVID-19 vaccines in the US include mRNA-1273 (December 2020), BNT162b2 (December 2020), and Ad26.COV2.S (February 2021). As of 26 September 2021, > 510 million doses of mRNA-1273 have been distributed worldwide, of which 305 million have been distributed in the US.

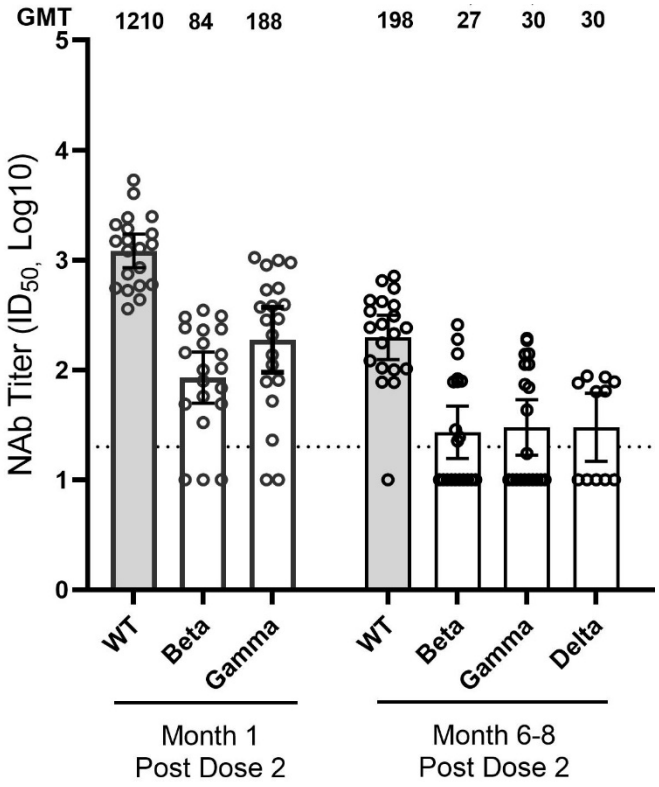
2.3 Unmet Need due to Variants of Concern and Waning Immunity

Moderna has been evaluating the persistence of antibody titers in its ongoing clinical studies. Data from Studies P201 and P301 support persistence of immunogenicity and effectiveness, respectively, through at least 6 months. Results from the P301 final blinded analysis were consistent with results of the interim and primary analyses, confirming persistence of high rates of efficacy over a median of 5.3-month blinded observation period. These final efficacy results were obtained during the blinded phase of the study, prior to widespread circulation of the Delta variant in the US. In P201, the Day 209 immunogenicity analysis demonstrated persisting immunogenicity, albeit at reduced titers. Neutralizing titers against the original virus strain D614G using the qualified microneutralization assay are reduced by about 3.3-fold from Day 43 (peak titers) at Day 209.

Given the potential for waning immunity from the primary series and the emergence of SARS-CoV-2 variants with increased transmissibility, serum nAb titers from vaccine recipients were assessed over time. A subset of participants vaccinated in P201 were tested 6-8 months after the primary series and nAb results (using a research-grade vesicular stomatitis virus [VSV]-based pseudoviral assay [VSV-PsVNA] [D614G]) were compared with those obtained 1 month after the primary series (2 doses of 100 µg). Preliminary data show that 6-8 months after the primary series, nAb titers against the original D614G virus waned 6- to 7-fold compared with 1-month post-dose 2 primary series. Similarly, by 6-8 months after the primary series, neutralizing titers against the

Beta and Gamma strains as well as Delta strains declined ~40-fold versus peak (1 month post) titers measured against the original D614G virus (Figure 1; Choi et al 2021).

Figure 1: Neutralization of Original Virus Strain D614G and Variants by Participant Serum Collected 1 Month After Primary Vaccination Series and 6 Months Later as Measured by the VSV-Based PsVNA



Neutralization of D614G (WT), Beta, and Gamma SARS-CoV-2 virus strains 1 month after the primary series and neutralization of D614G, Beta, and Gamma SARS-CoV-2 virus strains approximately 6 months after the primary vaccination series (D614G, n = 20; B.1.617.1, n = 11; B.1.617.2, n = 11). The horizonal dotted lines indicate the lower limit of quantification (LLOQ). GMT, geometric mean titer; ID50, 50% inhibitory dilution; nAb, neutralizing antibody.
Source: Choi et al 2021

While a definitive immune correlate of protection has not been established, analysis of pre-Delta breakthrough cases in Phase 3 (COVE) by Gilbert et al identified a 6-fold higher disease risk among participants with PsVNA ID50 titers < 100 compared to participants with PsVNA ID50 titers between 100 and 1000 (Gilbert et al 2021). Low or undetectable neutralization titers particularly against VOCs after ~6 months may place vulnerable populations at a greater risk of infection or disease.

An interim analysis (IA) from Moderna Study P901 with Kaiser Permanente Southern California (KPSC) (Long-term Effectiveness study, prospective cohort with individuals ≥ 18 years old vaccinated starting in December 2020 and followed through end June 2021 for the IA) showed effectiveness of 2 doses of mRNA-1273 against COVID-19

diagnosis was 87.4% (99.3% CI: 84·8-89·6%). VE against COVID-19 hospitalization and hospital death was 95.8% (99.3% CI: 90.7-98.1%) and 97.9% (99.3% CI: 66.9-99.9%), respectively. VE was higher against symptomatic (88.3% [98.3% CI: 86.1%-90.2%]) than asymptomatic SARS-CoV-2 infection (72.7% [98.3% CI: 53.4%-84.0%]), but was generally similar across age, sex, and racial/ethnic subgroups (Bruxvoort et al 2021b [in review]). The most common variants circulating in the KPSC population during this analytic period were Delta, Alpha, Epsilon, and Gamma.

Additionally, a test-negative case-control analysis was conducted using SARS-CoV-2 positive specimens collected during 3/1/2021 to 7/27/2021 from all KPSC members ≥ 18 years old. Two-dose VE (95% CI) was 86.7% (84.3-88.7%) against Delta infection, 98.4% (96.9-99.1%) against Alpha, 90.4% (73.9-96.5%) against Mu, and 96-98% against other identified variants. VE against Delta declined from 94.1% (90.5-96.3%) 14-60 days after vaccination to 80.0% (70.2-86.6%) 151-180 days after vaccination. Waning was less pronounced for non-Delta variants. VE against Delta was lower among individuals aged ≥ 65 years (75.2% [59.6-84.8%]) than those aged 18-64 years (87.9% [85.5-89.9%]). VE against Delta hospitalization was 97.6% (92.8-99.2%) (Bruxvoort et al 2021a [in review]).

2.3.1 Summary of COVID-19 Cases From July-August 2021 in Ongoing Study P301

The efficacy of mRNA-1273 to prevent COVID-19 was demonstrated to be 94.1% (95% CI: 89.3%, 96.8%) after 9 weeks median follow-up in November 2020 and 93.2% (95% CI: 91.0%, 94.8%) after 5.3 months of follow-up, when the original strain and the Alpha variant were the major circulating lineages. Covid-19 cases from the beginning of the open-label phase through June 2021 were low with an increase observed in July and August 2021, corresponding to the Delta variant surge in the US. The surveillance of Covid-19 through the protocol-defined illness visits remained unchanged through the open label phase. An analysis was conducted of COVID-19 incidences during a portion of the open-label phase 01 July through 27 August 2021, in participants initially randomized to the mRNA-1273 group (vaccinated from July-December 2020) and those initially randomized to the placebo group (vaccinated December 2020-April 2021) in the mITT population (that includes all randomized participants who received at least 1 dose of mRNA-1273 and were SARS-CoV-2 negative at baseline of study entry). Included in this analysis were 14,746 participants in the earlier vaccinated group and 11,431 in the later vaccinated group The baseline characteristics of the participants were similar between the groups. Median follow-up times from the first dose were 13 months in the earlier group (including double-blind and open-label phases) and 7.9 months in the later group (only open-label phase) groups.

Results of this analysis of COVID-19 cases occurring from 01 July to 27 August 2021 show statistically significant lower incidence rates of COVID-19 in more recently vaccinated P301 participants than those more remotely vaccinated and also numerically

fewer severe COVID-19 cases in more recently vaccinated recipients, with the vast majority of COVID-19 cases in both groups attributed to the Delta variant.

Table 2 presents the number of cases and calculated incidence rates from 01 July through 27 August 2021. To assess the difference in incidence rates of COVID-19 between the two groups, 1 – the ratio of the two incidence rates was calculated and provided with the 95% CI. Further, the proportion of the observed COVID-19 cases attributed to the Delta variant (including B.1.617.2, AY.1, AY.2, and AY.3 sequences) was assessed.

Sequencing results confirm that the surge in COVID-19 cases observed in July and August was largely driven by the Delta variant. There were 162 COVID-19 cases in the mRNA-1273 group vaccinated earlier (mRNA-1273e) and 88 COVID-19 cases in the mRNA-1273 group vaccinated later (mRNA-1273p). Of the cases sequenced, 144/149 (97%) in the mRNA-1273e and 86/87 (99%) in the mRNA-1273p groups were caused by the delta variant, highlighting that both groups were similarly exposed to the Delta variant-related surge. The incidence rate of all COVID-19 (calculated for the interval 01 July to 27 August 2021 for each group) among the more recent vaccine recipients (mRNA-1273p) was 49.0 per 1000 person-years compared with 77.1 per 1000 person-years among the more remotely vaccinated (mRNA-1273e) (Baden et al 2021 [in review]). The incidence rates were found to be statistically significantly different (1 – incidence rate ratio = 36.4%; 95% CI: 17.1%, 51.5%, excluding 0%), demonstrating greater protection against COVID-19 by more recent vaccination. It should be noted that both vaccinated groups had lower observed incidence rates than the placebo group at the time of final analysis (136.7 per 1000 person-years), demonstrating the value of primary series vaccination even with the increase in breakthrough cases (El Sahly et al 2021).

A small group of the COVID-19 cases occurring during this period met the protocol definition of severe COVID-19 based on the ongoing tracking of cases. There were 13 severe COVID-19 cases observed in the mRNA-1273e group and 6 in the mRNA-1273p group during the time period (6.2 per 1000 person-years vs. 3.3 per 1000 person-years). While these incidence rates are not statistically significantly different (they are based on only a small number of cases), the incidence rate in the more remotely vaccinated group is numerically higher than that in the more recently vaccinated group. Additionally, only 3 study participants were hospitalized, all of whom were in the original mRNA-1273 group. Two of these hospitalized participants, males 71 and 79 years of age, both with underlying pulmonary disease and vaccinated more than 10 months earlier, subsequently died with acute respiratory failure.

Results of this analysis of COVID-19 cases occurring from 01 July to 27 August 2021 show statistically significant lower incidence rates of COVID-19 in more recently vaccinated P301 participants than those more remotely vaccinated and also numerically fewer severe COVID-19 cases in more recently vaccinated recipients, with the vast majority of COVID-19 cases in both groups attributed to the Delta variant.

Table 2: COVID-19 and Severe COVID-19 Cases Starting 14 Days After Dose 2 of mRNA-1273 During 01 July 2021 to 27 August 2021 - mITT Population

mRNA-1273e (N= 14746)			mRNA-1273p (N=11431 at Risk in Open-Label Phase*)			mRNA-1273p vs. mRNA-1273e	
Cases	Person-Years	Rate/1000 Person-Years	Cases	Person-Years	Rate/1000 Person-Years	1 – Incidence Rate Ratio	95% CI
COVID-19 cases starting 14 days after Dose 2							
162	2102	77.1	88	1796	49.0	36.4%	(17.1%, 51.5%)
Severe COVID-19 cases starting 14 days after Dose 2							
13	2102	6.2	6	1796	3.3	46.0%	(-52.4%, 83.2%)

Participants at risk at the start of the analysis period (01 July 2021 to 27 August 2021) are included, and the incidence rate per 1000 person-years is calculated in this analysis. Incidence rate is defined as the number of COVID-19 cases divided by the number of participants at risk at the beginning of the time period (01 July 2021) and adjusted by person-years in each group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
*mRNA-1273p participants not considered at risk in the Open-Label phase were excluded from this analysis: those who (i) were diagnosed with COVID-19 or SARS-CoV-2 infection during the blinded phase, (ii) did not enter open-label or received off-study COVID-19 vaccine, or (iii) had a case prior to first dose of mRNA in the open-label phase.

Taken together, the observed decline in circulating nAb levels over time, combined with the emergence of highly transmissible VOC, clinical trial data and real world evidence support interventions to restore or enhance circulating nAb against both the original strain and particularly VOCs. An additional vaccine dose that boosts circulating nAb against the original strain and against critical VOCs may be highly valuable in efforts to contain this dynamic global pandemic. Dose-sparing strategies, such as the use of **50 µg rather than a 100 µg of mRNA-1273**, not only reduce overall exposure to antigen but can make additional doses available for distribution worldwide.

Moderna has requested an amendment to the current EUA to include a 50 µg booster dose of mRNA-1273 to be administered at least 6 months after the primary vaccination in:

- individuals ≥ 65 years of age
- individuals aged 18–64 years at high risk for severe COVID-19
- individuals aged 18–64 years whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

3 OVERVIEW OF CLINICAL DEVELOPMENT OF mRNA-1273 BOOSTER

Summary

- The 50 µg booster dose was selected for the following reasons:
  - Our objective was to use the optimal effective dose for boosting. As part of initial dose ranging of mRNA-1273 (P201 Part A), both 50 and 100 µg were evaluated. Both doses induced at least a 66-fold rise from pre-dose 1 antibody titers. It was postulated that a 50 µg booster dose would be effective in quickly activating immune memory recall responses. The trend toward lower reactogenicity observed for the 50 µg dose in P201 Part A also supported this selection.
  - Lower doses for boosters have been shown to be safe and immunogenic for other vaccines, such as diphtheria.
  - Reducing the booster dose to 50 µg increases world-wide vaccine supply.
- Effectiveness of the mRNA-1273 booster was inferred by comparing the antibody titers and SRR from P201 Part B to the pivotal adult study (P301), in which 94.1% VE against COVID-19 was demonstrated.

3.1 mRNA-1273 Booster Vaccine Dose Rationale

Preliminary data suggest that 6-8 months after administration of the 2-dose regimen of 100 µg of mRNA-1273, nAbs and binding antibodies (bAbs) against both the original strain and against VOCs wane (Choi et al, 2021; Pegu et al 2021). Accordingly, Moderna initiated investigations of booster doses. As part of initial dose ranging of mRNA-1273 (P201 Part A), both 50 and 100 µg were evaluated. Both dosages induced substantial neutralizing antibodies. While the 100 µg dosage was advanced to the pivotal trial (P301), it was postulated that a 50 µg booster dose would be effective in quickly activating immune memory recall responses. The trend toward lower reactogenicity observed for the 50 µg dose in P201 Part A also supported this selection. Finally, there is precedence for a booster dose to be lower than the priming vaccine dose. For example, Tetanus, Diphtheria, Pertussis (Tdap), the booster for the Diphtheria, Tetanus, and acellular Pertussis (DTaP) vaccine, has a reduced dose of the diphtheria and pertussis vaccines and is intended to boost the immunity that wanes after primary vaccination.

The interval between primary and booster doses selected for the clinical studies was at least 6 months after the completion of the primary immunization series. This interval was selected based on the data of waning of immunogenicity against VoCs demonstrated at 6-8 months. Furthermore, given the urgency of investigating the safety and effectiveness of booster doses as the epidemiological landscape of the pandemic

evolves, it was too early to evaluate participants primed more than 9 months ago. Moderna considers, however, that it is reasonable to assume that the booster effect will be similar in people who received their primary series more than 6-8 months prior to their booster.

3.2 Studies Supporting Development of mRNA-1273 Vaccine Booster

Multiple strategies for a booster vaccine have been and are currently being assessed in Moderna's clinical development plan and through collaborations with the National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIH).

The data in this briefing document are intended to support the use of a 50 µg booster of mRNA-1273 to adults 18 years and older who received a primary vaccination series at least 6 months prior. Effectiveness of the mRNA-1273 booster was inferred by comparing the antibody titers and SRRs from P201 Part B to the pivotal adult study (P301), in which VE against COVID-19 was demonstrated. Data from a study sponsored by DMID evaluating a 100 µg booster dose are also included as supportive safety and immunogenicity data (Table 3).

Table 3: Clinical Studies Supporting the Development of mRNA-1273 50 µg Booster

Study	Primary Series	Booster Dose (Dose 3)	Interval Between Dose 2 and 3	N
P201 B	2 dose 50 µg – mRNA-1273	50 µg – mRNA-1273	≥ 6 months	173
	2 dose 100 µg – mRNA-1273	50 µg – mRNA-1273	≥ 6 months	171
	Pooled	50 µg – mRNA-1273	≥ 6 months	344
DMID 21-0012	Multiple	100 µg – mRNA-1273	12-20 weeks	154

DMID = Division of Microbiology and Infectious Diseases.

3.2.1 Study P201 Part B Design

P201 Part B is the open-label part of the randomized, controlled P201 study (which aided in dose-selection during the clinical development of mRNA-1273 [Chu et al 2021]) assessing immunogenicity responses following administration of a 50 µg booster of mRNA-1273 to participants primed with 2 doses of mRNA-1273 in P201 Part A (50 µg or 100 µg of mRNA-1273).

After the primary analysis for Study P201 was completed, the study was amended to include an open-label interventional phase Part B. Part B provided the opportunity for study participants who previously received placebo to receive 2 doses of mRNA-1273 (100 µg) vaccine. In addition, all participants who previously received mRNA-1273 (50 µg or 100 µg) vaccine at least 6 months earlier received a single booster dose of mRNA-1273 (50 µg).

Solicited local and systemic adverse reactions (ARs) were collected for the 7 days following the booster injection (i.e., the day of injection and 6 subsequent days), and unsolicited AEs were collected for the 28 days following each injection (i.e., the day of injection and 27 subsequent days). SAEs, MAAEs, and AEs leading to study discontinuation were recorded for the duration of follow-up. After the booster dose, participant sera were collected on Days 8, 15, 29, and 57 and Month 6-7 to assess nAb and bAb titers against the original D614G virus strain.

In Part B, a preplanned analysis for the booster dose at Day 29 has been conducted (database lock date 10 June 2021). Additional safety data including SAEs, MAAEs, and AEs leading to study discontinuation were analyzed through August 16th, representing approximately 5 months of safety follow-up. A total of 344 participants received a 50 µg booster dose in Study P201 Part B.

3.2.2 Study DMID 21-0012 Design

DMID Study 21-0012 is a Phase 1/2 heterologous SARS-CoV-2 vaccine dosing (mRNA-1273 booster) study of the various EUA vaccines (Ad26.COV2.S, mRNA-1273, BNT162b2) in participants ≥ 18 years old (NCT04889209). A total of 154 participants have been enrolled and received an mRNA-1273 boost injection (intramuscular [IM]; 100 µg) approximately 12-20 weeks after receiving primary vaccination under EUA. Safety data from all participants boosted with 100 µg mRNA-1273 (N=154) and PsVNA data for participants who received a 2-dose primary series of mRNA-1273 followed by the 100 µg booster dose of mRNA-1273 (N=51) are presented. Heterologous boost data will be presented by the NIH and are not included in this briefing document.

3.2.3 Study P301 Overview

Study P301 is an ongoing pivotal randomized, observer-blind, placebo-controlled, stratified study to evaluate efficacy, immunogenicity, and safety in adults ≥ 18 years of age. In this study, more than 30,000 participants were randomized and > 96.7% participants received dose 2 of mRNA-1273. Data from this study supported the US EUA (18 December 2020). These data also supported the US BLA, which is under review.

The safety and efficacy of mRNA-1273 to prevent COVID-19 was demonstrated in adults 18 years and older in Study P301. Three analyses of efficacy have been conducted (Table 4), confirming persistent, high efficacy over a substantially larger case database and over a median 5.3-month blinded observation period from randomization in Part A (Baden et al 2021; El Sahly et al 2021).

Table 4: Primary Efficacy Endpoint Analyses of Study 301, Part A, Starting 14 Days After Second Injection (11 Nov 2020, 25 Nov 2020, and 04 May 2021 Datasets; Adjudicated Cases, Per-Protocol Sets)

	11 Nov 2020 Dataset, Interim Analysis		25 Nov 2020 Dataset, Primary Analysis		04 May 2021 Dataset, Final Analysis	
	Placebo (N=13,883)	mRNA-1273 (N=13,934)	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Placebo (N=14,164)	mRNA-1273 (N=14,287)
Number of participants with COVID-19, n (%)	90 (0.6)	5 (< 0.1)	185 (1.3)	11 (< 0.1)	744 (5.3)	55 (0.4)
Vaccine efficacy based on hazard ratio (95% CI)[a]	0.945 (0.865, 0.978)		0.941 (0.893, 0.968)		0.932 (0.910, 0.948)	
p value[b]	< 0.0001		< 0.0001		< 0.0001	
Person-years[c]	2697.5	2716.9	3273.7	3304.9	5445.2	5729.9
Incidence rate per 1,000 person-years (95% CI)[d]	33.365 (26.829, 41.011)	1.840 (0.598, 4.295)	56.510 (48.660, 65.266)	3.328 (1.662, 5.955)	136.633 (126.991, 146.814)	9.599 (7.231, 12.494)
Vaccine efficacy based on incidence rate (95% CI)[e]	0.945 (0.87, 0.98)		0.941 (0.892, 0.971)		0.930 (0.908, 0.948)	

[a] Vaccine efficacy is defined as 1 − hazard ratio (mRNA-1273 vs placebo), and 95% CI was estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

[b] One-sided *p* value from stratified Cox proportional hazard model to test the null hypothesis VE ≤ 0.3.

[c] Person-years is defined as the total years from randomization date to the date of COVID-19, last date of study participation, or efficacy cutoff date, whichever is earlier.

[d] Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI was calculated using the exact method (Poisson distribution) and adjusted by person-years.

[e] Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio was calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

In this briefing document, to support use of 50 µg mRNA1273 as a booster for the mRNA-1273, immunogenicity data from adults ≥ 18 years in Study P301, based on a database lock date of 04 May 2021, were used as a comparator group to infer efficacy based on the immunogenicity response of a single 50 µg booster (Study P201 Part B).

3.3 Bioassays for the Assessment of Clinical Endpoints

The clinical biomarker strategy to support clinical development includes an extensive panel of assays to assess SARS-CoV-2 infection and characterize the immune response induced by mRNA-1273. Immunoassays for Study P201 were validated or considered qualified for use in the assessment of clinical samples for P201 Part A. In P201 Part B as well as P301, PsVNA (original strain and Delta strain) and binding assays Anti-S and Anti-N enzyme-linked immunosorbent assays (ELISAs) utilized were validated and considered acceptable for use in the assessment of clinical samples.

3.4 Statistical Methods Used for P201 Part B and P301 Comparison

The primary immunogenicity objective of the P201 Part B protocol was to assess levels of Spike specific Ab following a 50 µg booster dose of mRNA-1273 vaccine to participants previously receiving 2 doses of either 50 or 100 µg of mRNA-1273.

A standalone P201 Part B Statistical Analysis Plan (SAP) of immune response to a single 50 µg booster described a new primary immunogenicity objective to infer effectiveness of the 50 µg booster by establishing noninferiority of the booster dose using the coprimary endpoints: (i) geometric mean (GM) titers of serum nAb and (ii) SRR (Table 5). In the prespecified analysis, the immunogenicity data of P201 Part B participants at Day 29 after receiving a single booster dose of 50 µg mRNA-1273 was compared with immunogenicity data at Day 57 post-primary series from the pivotal efficacy study P301. The primary analysis population of these coprimary endpoints (in Study P201 Part B) included all PP participants who received a single booster dose of 50 µg mRNA-1273 in Study P201 Part B, regardless of the dose level (50 or 100 µg) received in the primary series during Study P201 Part A. The SAP also described an assay-specific seroresponse definition for PsVNA ID50: a seroresponse is a titer change from below the LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above (≥) the LLOQ (referred as assay-specific definition (3.3-fold rise) onwards in this document).The seroresponse of the booster was based on from the pre-booster titer; and the seroresponse of the primary series was based on from the pre-vaccination (Dose 1) titer.

This SAP was amended per comments received from the FDA on 02 July 2021 (Version 2.0, dated 06 August 2021). In the amended SAP, for each assay, a 4-fold rise definition of seroresponse was added. Participants with a titer change from below the LLOQ to equal or above (≥) 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above (≥) the LLOQ are considered achieving seroresponse. In addition, a sensitivity analysis, by excluding the 20 participants who were included in a Day 15 exploratory analysis, was

also added in this amendment (referred as SAP-specified sensitivity analysis onwards in this document).

The primary immunogenicity objective is considered met if the noninferiority based on both GM titers and SRR at Day 29 in P201 Part B compared with Day 57 in P301 is demonstrated, at a 2-sided alpha of 0.05. The null hypotheses based on GM titers and SRR and the criterion of success include: noninferiority is based on the GMR (Study P201 Part B at Day 29 vs Study P301 Part A at Day 57) with a NIM of 1.5 and a point estimate of GMR ≥ 1; and noninferiority based on difference in SRR (Study P201 Part B at Day 29 – Study P301 Part A at Day 57) with a NIM of 10% are described in Table 5.

Table 5: Coprimary Endpoints to Demonstrate Immunogenicity Noninferiority

	Coprimary endpoint 1[a]	Coprimary endpoint 2[a]
	Ab GM titers	**Ab SRR**
Null Hypothesis	H_{10}: immunogenicity response to a single booster dose of 50 µg mRNA-1273 against the original virus strain as measured by Ab GM at Day 29 in P201 Part B is inferior compared with that at Day 57 in participants receiving the primary series of 100 µg mRNA-1273 against the original virus strain using Study P301 data.	H_{20}: immunogenicity response to a single booster dose of 50 µg mRNA-1273 against the original virus strain as measured by SRR at Day 29 in P201 Part B is inferior compared with that at Day 57 in participants receiving the primary series of 100 µg mRNA-1273 against the original virus strain using Study P301 data.
Noninferiority Criteria	• The point estimate of the GMR, booster dose of 50 µg mRNA-1273 P201 Part B against the original virus strain vs. primary series of 100 µg mRNA-1273 P301 against the original virus strain, ≥ 1, and • The lower bound of the corresponding 95% CI is ≥ 0.67, based on the NIM of 1.5	• The lower bound of the 95% CI of the difference in SRR (SRR in P201 Part B against the original virus strain – SRR in P301 against the original virus strain) is ≥ -10%, based on the NIM of 10%.

Abbreviations: Ab = antibody; CI = confidence interval; GM = geometric mean; GMR = geometric mean ratio; NIM = noninferiority margin.
[a] The primary immunogenicity objective was considered met if noninferiority was demonstrated based on both coprimary endpoints.

Seroresponse of the booster (in participants who received the booster vaccination in Study P201 Part B) was defined based on the fold-rise from pre-booster titer; whereas seroresponse of the primary series was assessed from pre-vaccination titer. The difference in SRR, is defined as SRR at Day 29 in Study P201 Part B participants receiving 50 µg mRNA-1273 booster minus the SRR at Day 57 for participants receiving the primary series of 100 µg mRNA-1273 in Study P301 Part A.

To assess the magnitudes of the differences in immune response 28 days after a single booster dose of 50 µg mRNA-1273 (P201 Part B) and the immune response 28 days after the completion of the primary series of mRNA-1273 100 µg (P301 Part A), an analysis of covariance (ANCOVA) model was used. The model included log-transformed antibody titers at Day 29 in P201 Part B, and Day 57 in P301 Part A as the

dependent variable, treatment groups (P201 Part B 50 µg mRNA-1273 booster, P301 mRNA-1273 100 µg primary series) as an explanatory variable, adjusting for age groups (< 65, ≥ 65). The geometric least squares mean (GLSM, GMT [model-based]) and corresponding 2-sided 95% CI for the antibody titers for each treatment group were provided. The GLSM, and the corresponding 95% CI results in log-transformed scale estimated from the model were back-transformed to obtain these estimates in the original scale. GMR, estimated by the ratio of GLSM and the corresponding 2-sided 95% CI were provided to assess the treatment difference.

4 OVERVIEW OF IMMUNOGENICITY

Summary

- Administration of a booster dose of 50 µg at least 6 months after administration of the second of 2 doses of the mRNA-1273 primary series produced robust immune responses compared to pre-boost levels, suggesting that the B-cell memory generated by mRNA-1273 50 µg booster can be quickly and potently enhanced.
- Measuring nAb responses in the validated PsVNA ID50 assay demonstrated a 1.71-fold ratio of GMR between the Day 29 GMT in participants vaccinated in P201 Part B vs the Day 57 GMT in participants who received the 2 dose mRNA-1273 primary series in Study P301, in which robust efficacy was demonstrated.
- SRR difference, using an assay-specific definition (i.e., 3.3-fold rise for PsVNA) of post-boost seroresponse in P201B, compared to the seroresponse observed after the primary series in Study P301, was -5.3% (95% CI: 8.8%, -2.9%).
- The mRNA-1273 50 µg booster dose increases neutralization titers against the original virus stain and against the Delta variant.
- In spite of the lower pre-boost titers among the more vulnerable ≥ 65 years age group, the 50 µg booster enhanced nAb titers (PsVNA ID50) to similar levels in both age groups.

4.1 Study Populations

4.1.1 Study P201 Part B

4.1.1.1 Disposition

Following Study P201 Part A, 344 participants received a booster dose in Part B (Table 6). Of these 344, 173 received 2 doses of 50 µg and 171 received 2 doses of 100 µg in Part A. The interval between the prime series in Part A and the booster ranged from 177-269 days overall (or 5.8-8.8 months), with a mean (standard deviation [SD]) of 216.9 (19.12) days (or approximately 7.1 months). As of the database lock date for the Day 29 planned analysis, all participants had completed the Day 29 visit.

Table 6: Study P201 Part B Participant Disposition Safety Set 50 µg and 100 µg Priming Groups (Safety Set[a])

	mRNA-1273 50 µg Primary Series N=200 n (%)	mRNA-1273 100 µg Primary Series N=200 n (%)	mRNA-1273 Pooled N=400 n (%)
Consented to Part B - Boost	188 (94.0)	185 (92.5)	373 (93.3)
Agreed to be Unblinded	187 (93.5)	186 (93.0)	373 (93.3)
Agreed to Receive mRNA-1273 in Part B	174 (87.0)	171 (85.5)	345 (86.3)
Actually Received Booster Injection	173 (86.5)	171 (85.5)	344 (86.0)
Discontinued Study Vaccine in Part B	0	0	0
Discontinued from Study in Part B	9 (4.5)	6 (3.0)	15 (3.8)
Completed Study[b]	0	0	0
Discontinued from Study in Part B Reason for Discontinuation of Study in Part B			
Adverse Event (COVID-19 Infection)	0	0	0
Adverse Event (Other)	0	0	0
Death	0	0	0
Lost to Follow-up	3 (1.5)	2 (1.0)	5 (1.3)
Withdrawal of Consent (Other)	5 (2.5)	3 (1.5)	8 (2.0)
Other	1 (0.5)	1 (0.5)	2 (0.5)

Abbreviations: COVID-19 = coronavirus disease 2019.
Percentages are based on the number of safety participants in Part A. Only participants who received mRNA-1273 in Part A are included and are summarized under the vaccination groups which they actually received in Part A.
[a] Safety Set included all randomized participants who received any mRNA-1273 primary series during Part A.
[b] Study completion is defined as a participant who completed 6 months of follow-up after the last injection received in Part B (Open-Label Phase).

4.1.1.2 Analysis Sets

The planned Day 29 analysis in Part B evaluated the safety, reactogenicity and immunogenicity of mRNA-1273 50 µg administered as a single booster dose given 6-8 months after completing the 2-dose mRNA-1273 50 µg or 100 µg prime series in Part A.

Relevant P201 Part B analysis populations include: Safety Set, Solicited Safety Set, and Per-Protocol (PP) Set (Table 7).

Table 7: Study P201 Part B Number of Participants in Each Analysis Set by Prime Series Group (50 µg and 100 µg mRNA-1273)

	mRNA-1273 50 µg Primary Series + 50 µg Booster n (%)	mRNA-1273 100 µg Primary Series + 50 µg Booster n (%)	P201 Part B mRNA-1273 Pooled 50 µg Booster Total n (%)
Safety Set[a]	173	171	344
Solicited Safety Set[b]	163 (94.2)	167 (97.7)	330 (95.9)
Per-Protocol Set[c]	146 (84.4)	149 (87.1)	295 (85.8)

Only participants who received booster injection in Part B are included and are summarized under the vaccination groups which they actually received in Part A. Percentages are based on the number of safety participants.
[a] All participants who are randomized in Part A and received any booster injection during Part B.
[b] All participants who are randomized in Part A and received any booster injection during Part B, and contribute any solicited AR data, i.e., have at least 1 post-baseline solicited safety assessment in Part B.
[c] All participants in the Full Analysis Set who did not have SARS-CoV-2 infection (positive reverse transcription polymerase chain reaction [RT-PCR] result or positive Elecsys result) at baseline (Part B Day 1), did not have a major protocol deviation that impacted immune response, had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for booster injection).

The Solicited Safety Set was used for the analyses of solicited ARs for Part B booster dose, and the Safety Set was used for analysis of safety for Part B booster dose except for the solicited ARs. For the immunogenicity analyses to compare the post-booster responses in P201 Part B with the Day 57 response in P301, the PP Set of P201 Part B and the P301 PP Immunogenicity Set were evaluated. Among 306 participants in Part B of P201 who received a booster injection and had both baseline and Day 29 immunogenicity assessment, 11 were excluded from the PP Set: 10 because of SARS-CoV-2 infection at baseline, and 1 because of a major protocol deviation.

4.1.1.3 Demographics and Baseline Characteristics

In the Part B Safety Set for Study P201, across both 50 µg and 100 µg prime series groups, participants were predominantly female (Table 8), had a mean age of approximately 52 years and were predominantly white (95%) and not Hispanic or Latino (94%). Other than a slightly larger proportion of females in the 50 µg prime series group than in the 100 µg prime series group, no apparent differences were observed in baseline demographics across the prime series groups.

Table 8: Study P201 Part B Demographics and Characteristics in P201 Part B of 50 µg and 100 µg Priming Groups (Safety Set)

Characteristic	mRNA-1273 50 µg Primary Series + 50 µg Booster N=173 n (%)	mRNA-1273 100 µg Primary Series + 50 µg Booster N=171 n (%)	P201 Part B mRNA-1273 Pooled 50 µg Booster N=344
Sex			
Female	124 (71.7)	104 (60.8)	228 (66.3)
Male	49 (28.3)	67 (39.2)	116 (33.7)
Age			
Mean (SD)	52.0 (15.79)	52.0 (15.11)	52.0 (15.44)
Median	56.0	55.0	56.0
Min, Max	18, 87	18, 87	18, 87
Age Group			
≥ 18 and < 65 years old	127 (73.4)	133 (77.8)	260 (75.6)
≥ 65 years old	46 (26.6)	38 (22.2)	84 (24.4)
Race			
White	164 (94.8)	164 (95.9)	328 (95.3)
Black or African American	3 (1.7)	5 (2.9)	8 (2.3)
Asian	2 (1.2)	1 (0.6)	3 (0.9)
American Indian or Alaska Native	1 (0.6)	1 (0.6)	2 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0	1 (0.3)
Multiracial	1 (0.6)	0	1 (0.3)
Other	1 (0.6)	0	1 (0.3)
Ethnicity			
Hispanic or Latino	10 (5.8)	10 (5.8)	20 (5.8)
Not Hispanic or Latino	162 (93.6)	161 (94.2)	323 (93.9)
Not reported	1 (0.6)	0	1 (0.3)
Body mass index (kg/m^2)			
Mean (SD)	25.68 (3.309)	25.46 (3.185)	25.57 (3.245)
Median	26.12	25.59	25.76

Abbreviations: SD = standard deviation.
Baseline height was defined as the assessment performed on Day 1 pre-dose in Part A and baseline weight was defined as the assessment performed on Day 1 pre-dose in Part B.
Age was defined at Part A screening.
Percentages are based on the number of safety participants.

4.1.2 Study P301

This section discusses the Study P301 Immunogenicity Subset used as the comparator for the primary immunogenicity endpoint in Study P201.

4.1.2.1 Disposition

1080 participants with negative baseline SARS-CoV-2 status were randomly selected from Study P301 participants in the mRNA-1273 group to form an Immunogenicity Subset in Study P301, which was used as the comparator arm for the P201 Part B immunobridging analysis.

Of the 1080 selected participants from the Study P301 mRNA-1273 group, 25 were further excluded from the PP Immunogenicity Subset for the following reasons: had HIV infection (18 participants), received dose 2 outside of [21, 42] days after dose 1 (5 participants), did not receive dose 2 per schedule (1 participant), or had major protocol deviations (1 participant). Thus, 1055 participants were included in the PP Immunogenicity Subset from Study P301.

4.1.2.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics of the PP Immunogenicity Subsets for P201 Part B and P301 were compared (Table 9).

Table 9: Demographic and Baseline Characteristics in Study P201 Part B and Study P301: Per-Protocol Immunogenicity Subset

Statistic	P201 Part B mRNA-1273 Pooled 50 µg Booster (N=295)	P301 mRNA-1273 100 µg Primary Series (N=1055)
Age (Years)		
n	295	1055
Mean (SD)	52.77 (15.170)	54.51 (15.329)
Median	56	57
Min, Max	18.0, 87.0	18.0, 87.0
Age Group		
≥ 18 and < 65 years old	219 (74.2)	700 (66.4)
≥ 65 years old	76 (25.8)	355 (33.6)
Gender, n (%)		
Male	103 (34.9)	560 (53.1)
Female	192 (65.1)	495 (46.9)
Race, n (%)		
White	281 (95.3)	767 (72.7)
Black or African American	7 (2.4)	188 (17.8)
Asian	3 (1.0)	26 (2.5)
American Indian or Alaska Native	2 (0.7)	17 (1.6)
Native Hawaiian or Other Pacific Islander	1 (0.3)	5 (0.5)
Multiple	1 (0.3)	15 (1.4)
Other	0	27 (2.6)
Not Reported	0	5 (0.5)

Unknown	0	5 (0.5)
Ethnicity, n (%)		
Hispanic or Latino	20 (6.8)	334 (31.7)
Not Hispanic or Latino	274 (92.9)	717 (68.0)
Not Reported	1 (0.3)	2 (0.2)
Unknown	0	2 (0.2)
Body Mass Index (kg/m^2)		
n	290	1050
Mean (SD)	25.65 (3.210)	30.96 (7.758)
Median	26.05	29.62
Min, Max	18.0, 34.9	14.0, 79.2
Positive Baseline SARS-CoV-2 Status [a]	0	0

Percentages are based on the number of Per-Protocol Immunogenicity Subset participants.
Age in P201 is defined at P201 Part A screening.
a Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1 in P201 Part B or Day 1 in P301.

4.1.3 Study DMID 21-0012

4.1.3.1 Disposition

As of the data snapshot date, a total of 154 participants have been enrolled into Cohort 1 and received the 100 µg mRNA-1273 Boost, with 51 participants in Group 2E (EUA dosed mRNA-1273). All 154 enrolled participants received the study boost vaccination and have remained in the study.

4.1.3.2 Demographics

Of the 154 enrolled participants across the 3 initial dosing groups, 72 (46.8%) were 18-55 years old, and 82 (53.2%) were 56 years old or older. The population included 67 males (43.5%) and 87 females (56.5%); the study population included 130 white participants (84.4%), 13 Asian (8.4%), 6 Black or African American (3.9%), 4 multiracial (2.6%) and 1 reported other (0.6%). Eleven (7.1%) participants reported Hispanic or Latino ethnicity and 2 (1.3%) unknown ethnicity.

4.2 Vaccine Effectiveness and Immunogenicity

This section contains an overview of immunogenicity data for Study P201 Part B, including a noninferiority analysis using immunogenicity data from Study P301 as a comparator based on PsVNA ID50 (infectious dose 50) for both the original strain and the Delta strain. Binding antibody data were also submitted to support the regulatory filing but are not presented here.

This section also includes immunogenicity for DMID Study 21-0012. Results of neutralization titers specific to the validated PsVNA are presented. Data reported include results from samples obtained at Day 1 (pre-boost) and Day 29 (post-boost) visits.

4.2.1 Results

Based on the data, booster vaccination with mRNA-1273 induced robust anamnestic responses against original virus strain (D614G), suggesting that the B-cell memory generated by mRNA vaccines can be quickly and potently enhanced. Within 28 days of booster injection, combining the groups of participants previously receiving either 50 or 100 µg doses demonstrated a 15.1 (95% CI: 13.4, 16.9) fold increase in GMT from pre-booster values. Importantly, potent serum neutralizing titers were measured after the 50 µg booster vaccination, meeting prespecified criteria for noninferiority in terms of GMTs and SRRs (relative to neutralizing titers observed after a 2-dose primary series with 100 µg mRNA-1273 in P301). Similarly, a 19.0 GM fold increase (95% CI: 16.7, 21.6) was observed against the Delta variant from the pre-booster values.

The potent responses observed compared with those following the primary series, suggest that booster inoculations are likely to address waning immunogenicity and emerging SARS-CoV-2 variants.

4.2.1.1 Pseudovirus Neutralizing Antibody (ID50) Titers against Original Virus Strain in Study P201 Part B

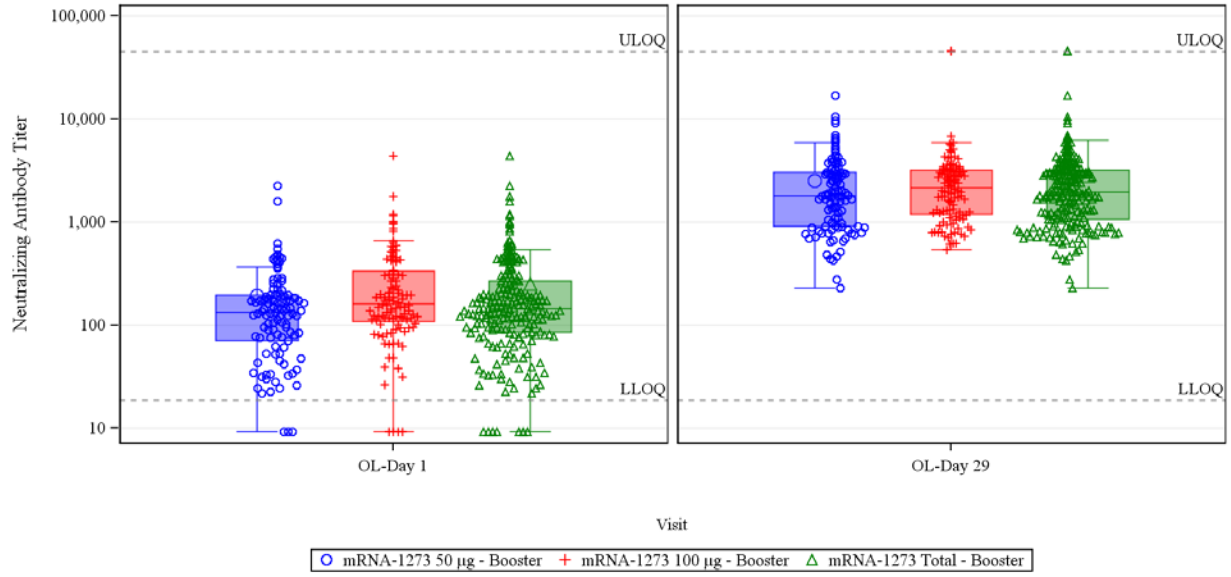
Administration of a booster dose of 50 µg at least 6 months after the mRNA-1273 primary series (including the pooled data from recipients of the 50 and 100 µg primary series) increased neutralizing antibody titers by 15-fold one month after vaccination compared to pre-boost levels. Among participants previously receiving the 100µg mRNA-1273 primary series, the 50 µg booster led to an increase in titers compared to pre-boost levels, resulting in a geometric mean fold rise (GMFR) of 12.99 (Table 10). The distribution of titers post-boost in the 100 µg and 50 µg priming groups were similar (Figure 2), supporting the pooling of these data.

Table 10: Summary of Pseudovirus Neutralizing Antibody ID50 Titers After 50 µg Booster Injection (by Primary Series Groups)

	mRNA-1273		
	50 µg Primary Series + 50 µg Booster N=146 n (%)	100 µg Primary Series + 50 µg Booster N=149 n (%)	Pooled 50 µg Booster N=295 n (%)
Baseline (OL-Day 1; pre-booster), n[a]	145	149	294
GMT	104.658	150.224	125.696
95% CIb	88.282, 124.070	125.726, 179.495	111.011, 142.325
OL-Day 29, nc	146	149	295
GMT	1834.309	1951.735	1892.708
95% CIb	1600.233, 2102.623	1729.606, 2202.392	1728.800, 2072.157
N1	145	149	294
GMFR	17.53	12.99	15.06
95% CIb	14.94, 20.56	11.04, 15.29	13.43, 16.89

Abbreviations: nAb = neutralizing antibody. GMT = geometric mean titer; GMFR = geometric mean fold rise (post-baseline vs. baseline titers); CI = confidence interval; LLOQ = lower limit of quantification; OL = Open-Label; N1 = Number of participants with nonmissing data at baseline and the corresponding visit; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values that are greater than the ULOQ are converted to the ULOQ if actual values are not available. Percentages are based on the number of participants in the Per-Protocol Set with nonmissing data at baseline and the corresponding visit (N1).
[a] Number of participants with nonmissing baseline.
[b] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back-transformed to the original scale for presentation.
[c] Number of participants in the Per-Protocol Set with nonmissing data at the corresponding visit.

Figure 2: Box Plot of PsVNA ID50 Titers: Per-Protocol Set



Abbreviations: LLOQ = lower limit of quantification. ULOQ = upper limit of quantification. OL=Open-Label. LLOQ: 18.5, ULOQ: 45118
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.

4.2.1.2 Immunobridging: Comparison of P201 Part B Booster to P301 Primary Series Against the Original Virus Strain

4.2.1.2.1 Coprimary Endpoint: GMR as Assessed by PsVNA ID50 Titers

The primary analysis population for this coprimary endpoint (in Study P201 Part B) included all PP participants who received a single booster dose of 50 µg mRNA-1273 in Study P201 Part B (i.e., all participants combined regardless of whether they received 50 µg or 100 µg of mRNA-1273 in the primary series).

In comparison to the peak PsVNA ID50 titers in P301 Part A (Day 57), where efficacy was demonstrated, the GMR (P201 Part B Day 29 vs. P301 Day 57, against the original virus strain) was 1.71 (95% CI: 1.519, 1.929; Table 11). This estimate was above the prespecified threshold of 1.0, with the lower bound of the 95% CI greater than 0.67

(corresponding to NIM=1.5). Hence, this GMR successfully met the prespecified noninferiority criterion. This criterion was met for the pooled 50 µg group as well as for the 100 µg priming group only (Table 12).

Table 11: Analysis of PsVNA ID50 Titers against Original Virus Strain: mRNA-1273 Post-Booster Compared with the P301 Primary Series Peak Titers (PP Immunogenicity Set)

	P201 Part B Pooled 50 µg mRNA-1273 Booster	P301 mRNA-1273 100 µg Primary Series
28 Days After Booster (P201 Part B) or Completion of Primary Series		
n	295	1053
GMT (model based)	1767.936	1032.698
95% CI	(1586.445, 1970.189)	(974.207, 1094.701)
GMR (P201 Part B vs. P301; model-based)	1.712	
95% CI	(1.519, 1.929)	

Abbreviations: ANCOVA = analysis of covariance; ID50 = 50% inhibitory dilution; GMT (model based) = geometric least squares mean; CI = confidence interval; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
n= number of participants with nonmissing data at the corresponding timepoint

Table 12: Analysis of PsVNA ID50 Titers against Original Virus Strain: mRNA-1273 Post-Booster Compared with the P301 Primary Series Peak Titers - by Primary Series Groups (PP Immunogenicity Set)

	P201 Part B 50 µg mRNA-1273 Booster After 50 µg Primary Series N=146	P301 mRNA-1273 100 µg Primary Series N=1055	P201 Part B 50 µg mRNA-1273 Booster After 100 µg Primary Series N=149	P301 mRNA-1273 100 µg Primary Series N=1055
28 Days after Booster (P201 Part B) or Completion of Primary Series				
n	146	1053	149	1053
GMT (model-based)	1716.185	1031.948	1802.426	1026.854
95% CI	(1469.496, 2004.286)	(971.974, 1095.622)	(1548.020, 2098.643)	(967.880, 1089.420)
GMR (P201 Part B vs. P301; model-based)	1.66		1.76	
95% CI	(1.412, 1.958)		(1.496, 2.060)	

Abbreviations: ANCOVA = analysis of covariance; ID50 = 50% inhibitory dilution; GMT (model based) = geometric least squares mean; CI = confidence interval; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.

Separate ANCOVA modes were used for the two analyses comparing each P201 priming group to P301: P201 50 µg priming + 50 µg booster (group variables: P201 50 µg priming, and P301) and P201 100 µg priming + 50 µg booster (group variables: P201 100 µg priming, and P301).

4.2.1.2.2 Coprimary Endpoint: SRR as Assessed by PsVNA ID50 Titers

The primary analysis population for this coprimary endpoint (in Study P201 Part B) included all PP participants who received a single booster dose of 50 µg mRNA-1273 in Study P201 Part B (i.e., all participants pooled regardless of whether they received 50 µg or 100 µg of mRNA-1273 in the primary series).

The calculated SRR difference (for PsVNA ID50 titers) between P201 Part B Day 29 post-booster and P301 Part A Day 57 was assessed. This analysis was performed using 3 definitions of SRR: (i) an assay-specific definition (3.3-fold rise) proposed by Moderna, (ii) a 4-fold rise definition compared to pre-boost, and (iii) 4-fold rise definition compared to pre-vaccination baseline. The assay-specific seroresponse definition is based on a fold rise criterion derived which statistically distinguishes titers based on the variability of the assay USP General Chapter <1033> *Biological Assay Validation*.

Using the assay-specific definition (3.3-fold rise), the calculated difference in SRR between P201 Part B Day 29 post-boost and P301 Part A Day 57 is -5.3% (95% CI: -8.8%, -2.9%; Table 13). The lower bound of the 95% CI is -8.8%, meeting the prespecified success criterion of a NIM of 10%.

Using the 4-fold rise definition, the calculated difference in SRR between P201 Part B Day 29 post-boost and P301 Part A Day 57 is -8.2% (95% CI: -12.2%, -5.2%) (Table 13). The lower bound of the 95% CI is slightly less than -10% (the prespecified NIM of 10%).

Seroresponse, by definition, reflects the fold rise from baseline and accordingly may be influenced by baseline titers. In the pivotal P301 study, the vast majority of participants were seronegative at baseline, clearly contrasting with baseline or pre-booster titers for participants in P201 Part B who had previously received 2 doses of mRNA-1273 (9.62 vs. 125.7, respectively). These differences in baseline titers make it challenging to meet the SRR difference criterion if using a 4-fold rise definition for SR. This is further borne out by assessing individual baseline serum nAb titers of participants in P201 Part B: participants who successfully met the 4-fold increase in titer post-booster had a baseline GMT of 108.64 (range 9.25, 4393.49). This contrasts with participants who did not meet the 4-fold increase in titers post-booster who had substantially higher baseline GMT of 492.28 (range 162.43, 2238.93). Moreover, participants who did not technically meet the 4-fold increase in titer from baseline to post 50 µg boost, nonetheless achieved substantial increase with a GMT of 1354 post-booster (range 540.0, 5050.6). Accordingly, we provide analysis of SRR difference using both definitions of seroresponse in this document.

The third analysis was performed using a seroresponse definition using the respective baseline titers of the participants (measured in P201 Part A). This analysis showed that

100% of participants met the seroresponse criteria, confirming the robust response of the 50 µg boost.

Table 13: Analysis of SRR by PsVNA ID50 Assay: mRNA-1273 Post-Booster Compared with the P301 Primary Series Peak Titers - by Primary Series Groups (PP Immunogenicity Set)

	Seroresponse Rate per Assay-Specific Definition*		Seroresponse Rate per 4-Fold Definition†		Seroresponse Rate per 4-Fold Rise from Baseline Definition‡	
Statistic	P201 Part B Pooled 50 µg Booster§ (N=295)	P301 100 µg Primary Series (N=1055)	P201 Part B Pooled 50 µg Booster§ (N=295)	P301 100 µg Primary Series (N=1055)	P201 Part B, Pooled 50 µg Booster‖ (N=294)	P201 Part A, After Dose 2 of Primary Series (N=294)
N1	294	1050	294	1050	289	289
Participants achieving seroresponse, n (seroresponse rate %)	275 (93.5)	1038 (98.9)	265 (90.1)	1033 (98.4)	289 (100.0)	284 (98.3)
95% CI¶	90.1, 96.1	98.0, 99.4	86.1, 93.3	97.4, 99.1	98.7, 100.0	96.0, 99.4
Difference in seroresponse rate# (P201 Part B vs. P301) (%)	-5.3		-8.2		1.7	
95% CI**	-8.8, -2.9		-12.2, -5.2		0.4, 4.0	

Abbreviations: CI = confidence interval; ID50 = 50% inhibitory dilution; LLOQ = lower limit of quantification.
N1 = Number of participants with nonmissing data at both post-baseline timepoint of interest and baseline.
For participants who received the primary series in Phase 3 COVE, seroresponse was defined based on the fold-rise at Day 57 (28 days after the second dose of mRNA-1273) compared to the baseline titer (prior to first dose of primary dose).
* Seroresponse specific to the ID50 titer in the D614G pseudovirus neutralizing antibody assay at a participant level was defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline was equal to or above LLOQ.
§ For participants who received a booster vaccination in Phase 2, Part B, seroresponse was defined based on the fold-rise at OL-D29 (28 days after the booster dose of mRNA-1273) compared to the pre-booster titer (OL-D1; at least 6 months after completion of the primary series).
† Seroresponse at participant level was defined as a change of titer in the D614G pseudovirus neutralizing antibody assay from below the lower limit of quantification (LLOQ) to equal to or above 4 × LLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
‡ Seroresponse at participant level was defined as a change of titer in the D614G pseudovirus neutralizing antibody assay from below the lower limit of quantification (LLOQ) to equal to or above 4 × LLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
‖ For participants who received a booster vaccination in Phase 2, Part B, seroresponse was defined based on the fold-rise at OL-D29 (28 days after the booster dose of mRNA-1273) compared to the baseline titer (prior to first dose of primary dose).
¶ 95% CI was calculated using the Clopper-Pearson method.
# For the 4-Fold Rise from Baseline Definition, the difference in seroresponse rate was the fold rise in Phase 2 Part B at OL-D29 (28 days after the booster dose of mRNA-1273) compared to 28 days after the second dose during the primary series in Phase 2 Part A.
** 95% CI was calculated using the Miettinen-Nurminen (score) confidence limits.

4.2.1.2.3 Subgroup Analysis by Age Groups

In general, the subgroup analysis (by the primary series) and the SAP-specified sensitivity analysis yielded similar results.

In a preplanned analysis of younger (≥ 18 to < 65 years) versus older (≥ 65 years) adults, the 50 µg booster enhanced nAb titers (PsVNA ID50) to similar levels in each age group. This was observed in spite of the lower pre-boost titers among the more vulnerable ≥ 65 years age group (82.51; 95% CI: 64.25, 105.96) compared with pre-boost titers in the younger group (145.57; 95% CI: 126.68, 167.27). The GMR (P201 Part B vs. P301) in the ≥ 65 years of age group was 2.02 (95% CI: 1.59, 2.57), comparable to the GMR of 1.61 (95% CI: 1.40, 1.84) achieved for younger adults (≥ 18 to < 65 years) (Table 14). In addition, the 95% CIs for the post-booster GMTs overlapped (1761.77 [95% CI: 1458.19, 2128.56] for the ≥ 65 years of age group as compared with 1940.39 [95% CI:1749.49, 2152.12] for the ≥ 18 to < 65 years of age group]), indicating administration of a booster dose may help the older age group compensate for the greater waning in antibody titers.

Analyses of SRR by the 4-fold rise definition yielded consistent results.

Table 14: Analysis of Neutralizing Antibody ID50 Titers and Seroresponse Rate 28 Days After mRNA-1273 Boost (Both Primary Series Groups Combined) by Age Group Compared with the P301 Primary Series Peak Titers

	Age ≥ 18 to < 65 Years		Age ≥ 65 Years	
	P201 Part B Pooled 50 µg mRNA-1273 Booster N=219	P301 mRNA-1273 100 µg Primary Series N=700	P201 Part B Pooled 50 µg mRNA-1273 Booster N=76	P301 mRNA-1273 100 µg Primary Series N=355
Baseline				
n	218	699	76	353
GMT	145.57	9.77	82.51	9.35
95% CI	126.68, 167.27	9.37, 10.18	64.25, 105.96	9.16, 9.54
28 Days after Booster (P201 Part B) or Completion of Primary Series				
n	219	698	76	355
GMT	1940.39	1206.59	1761.77	871.20
95% CI	1749.49, 2152.12	1125.71, 1293.28	1458.19, 2128.56	785.48, 966.29
GMR (P201 Part B vs. P301; model based)	1.608		2.022	
95% CI	1.403, 1.844		1.591, 2.570	
Participants Achieving Seroresponse, n (Seroresponse Rate %)				
N1	218	697	76	353
n (%)	202 (92.7)	687 (98.6)	73 (96.1)	351 (99.4)
95% CI	88.4, 95.7	97.4, 99.3	88.9, 99.2	98.0, 99.9
Seroresponse Rate Difference	-5.9		-3.4	
95% CI	-10.2, -2.9		-10.4, -0.5	

ANCOVA = analysis of covariance; CI = confidence interval; Est. = estimate; GMT (model based) = geometric least squares mean; GMT = geometric mean titer; ID50 = 50% inhibitory dilution; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available. Separate ANCOVA modes were used for P201 50 µg priming + 50 µg booster (group variables: P201 50 µg priming, and P301) and P201 100 µg priming + 50 µg booster (group variables: P201 100 µg priming, and P301). Seroresponse specific to pseudovirus nAb ID50 titer at a participant level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.

4.2.1.2.4 Results from Boosted Study P201 Part B Participants Against the Delta (B.1.617.2) Variant

Serum samples were obtained from participants in Study P201 Part B (at least 6 months after receiving 2 primary doses of either 50 or 100 µg of mRNA-1273) pre-booster and on Day 29 post-booster. Results of the PsVNA against the Delta variant (B.1.617.2) are presented in Table 15. Administration of the mRNA-1273 booster (50 µg) induced an 18-fold rise in neutralizing titers against the Delta variant compared with pre-booster levels (GMFR=18.97; 95% CI, 16.72, 21.53; overall group, n=295). Over 90% of booster recipients in the overall group (92.2%; 95% CI: 88.5-95.0%; n=293) met the definition of a seroresponse for the Delta variant (using a 4-fold increase from pre-booster baseline).

As noted in Section 4.2.1.1 the 50 µg booster mRNA-1273 resulted in robust increases in nAb responses against prototype virus, regardless of the priming dose (2 doses of 50 or 100 µg). Similarly, administration of the 50 µg mRNA-1273 prototype booster resulted in robust increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 100 µg had a GMFR of 17.28 (95% CI: 14.38, 20.77).

Additional analyses of Delta variant nAb GMT by age group have been conducted. nAb responses in older adults, are numerically similar to those observed in the younger groups (Table 16**,** 749.94 vs. 822.98). These data are reassuring, considering the higher risk for severe COVID-19 among older adults.

The GMFR (Day 29 post-booster: pre-booster) achieved by mRNA-1273 booster, measured by the Delta (B.1.617.2) pseudovirus assay (18.97; 95% CI: 16.72, 21.53), points to the ability of the prototype vaccine booster to enhance a breadth of nAb responses, including against the highly transmissible Delta variant. Just as the mRNA-1273 booster generated enhanced nAb levels against the original strain (GMFR 15.06 [95% CI: 13.43, 16,89], it also was able to broaden and increase nAb levels against the Delta variant.

Table 15: Summary of Pseudovirus Neutralizing Antibody ID50 Titers Against Delta Strain (B.1.617.2) - Per-Protocol Immunogenicity Subset

Timepoint Date Category Statistic	P201 Part B 50 µg mRNA-1273 Booster After 50 µg Priming N=146	P201 Part B 50 µg mRNA-1273 Booster After 100 µg Priming N=149	P201 Part B Pooled 50 µg mRNA-1273 Booster N=295
Pre-Booster			
n[1]	144	149	293
GMT	37.14	47.89	42.27
95% CI[2]	31.25, 44.15	39.68, 57.79	37.19, 48.04
Median	35.40	38.81	36.87
Min, Max	9.3, 818.3	9.3, 2730.5	9.3, 2730.5
28 Days After Boost Dose			
n[3]	146	149	295
GMT	779.48	827.77	803.51
95% CI[2]	670.05, 906.78	738.48, 927.86	731.42, 882.70
Median	819.12	792.27	801.12
Min, Max	43.5, 9720.8	124.2, 5587.5	43.5, 9720.8
GMFR	20.89	17.28	18.97
95% CI[2]	17.54, 24.87	14.38, 20.77	16.72, 21.53
Participants Achieving Seroresponse Comparing to Pre-booster, n (Seroresponse Rate %)[4]			
N1	144	149	293
n (%)	137 (95.1)	133 (89.3)	270 (92.2)
95% CI[5]	90.2, 98.0	83.1, 93.7	88.5, 95.0

CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; max = maximum; min = minimum; N1 = number of participants with non-missing data at pre-booster and the corresponding visit; nAb = neutralizing antibody.

Note: Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of participants in the Per-Protocol Set with non-missing data at baseline and the corresponding visit (N1).

[1] Number of participants with non-missing data at pre-booster.

[2] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back- transformed to the original scale for presentation.

[3] Number of participants in the Per-Protocol Set with non-missing data at the corresponding visit.

[4] Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4 × LLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.

[5] 95% CI is calculated using the Clopper-Pearson method.

Table 16: Summary of Pseudovirus Neutralizing Antibody ID50 Titers Against Delta Strain (B.1.617.2) - By Age Group (18 to < 65 years old vs ≥ 65 years old) - Per-Protocol Immunogenicity Subset

Timepoint	P201 Part B Pooled 50 µg mRNA-1273 Booster		
Date Category Statistic	18 to < 65 Years Old N=219	≥ 65 Years Old N=76	Overall N=295
Pre-Booster			
n[1]	218	75	293
GMT	47.20	30.67	42.27
95% CI[2]	40.64, 54.81	24.20, 38.88	37.19, 48.04
28 Days After Boost Dose			
n[3]	219	76	295
GMT	822.98	749.94	803.51
95% CI[2]	743.49, 910.97	600.87, 935.99	731.42, 882.70
Median	829.23	690.44	801.12
Min, Max	43.5, 5587.5	76.8, 9720.8	43.5, 9720.8
GMFR	17.38	24.45	18.97
95% CI[2]	14.98, 20.18	19.33, 30.92	16.72, 21.53
Participants Achieving Seroresponse Comparing to Pre-booster, n (Seroresponse Rate %)[4]			
N1	218	75	293
n (%)	197 (90.4)	73 (97.3)	270 (92.2)
95% CI[5]	85.7, 93.9	90.7, 99.7	88.5, 95.0

CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; max = maximum; min = minimum; N1 = number of participants with non-missing data at pre-booster and the corresponding visit; nAb = neutralizing antibody.
Note: Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of participants in the Per-Protocol Set with non-missing data at baseline and the corresponding visit (N1).
[1] Number of participants with non-missing data at pre-booster.
[2] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back- transformed to the original scale for presentation.
[3] Number of participants in the Per-Protocol Set with non-missing data at the corresponding visit.
[4] Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4 × LLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
[5] 95% CI is calculated using the Clopper-Pearson method.

4.2.1.2.5 Noninferiority Analyses: Comparison of P201 Part B Booster to P301 Primary Series Against the Delta (B.1.617.2) Variant

A noninferiority analysis was also conducted comparing nAb responses observed post-booster (P201 Part B, Day 29 post-booster) to those observed post-primary series (P301, Day 57) against the Delta variant.

The nAb titers against the Delta variant (measured using the validated PsVNA assay [ID50]), were available from P201 Part B participants, Day 29, and a random subset of the Per-Protocol Immunogenicity Set for Study P301, Day 57. As shown in Table 17, the GMT post-booster was 743.886 (95% CI: 663.745, 833.703), markedly higher than the GMT observed after the primary series, 353.980 (325.041, 385.496). The GMR of these GMT against the Delta variant was 2.1 (95% CI: 1.84, 2.40) (Table 17).

Table 17: Analysis of Pseudovirus Neutralizing Antibody ID50 Titers – Study P201 Against Delta [B.1.617.2] Versus Study P301 Against Delta [B.1.617.2] - Per-Protocol Immunogenicity Set

Statistic	P201 Part B Pooled 50 µg mRNA-1273 Booster (N=295)	P301 mRNA-1273 100 µg Primary Series (N=580)
n	295	580
GMT (model based) (95% CI)	743.886 (663.745, 833.703)	353.980 (325.041, 385.496)
Ratio of GMT (model based) [P201 Part B vs. P301] (95% CI)	2.101 (1.839, 2.401)	

CI = confidence interval; GMT (model based) = geometric least squares mean.
n = Number of participants with non-missing data at the corresponding timepoint.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 × LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (P201 Part B and P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
Note: Antibody: Pseudovirus Neutralizing Antibody ID50 Titers [P201: LLOQ=18.5, ULOQ=45118; P301=18.5, ULOQ=45118]

The comparison described above utilized the post-booster GMT from the combined or overall P201 Part B group (participants receiving either 50 or 100 µg in their primary series). This capacity for prototype mRNA-1273 to markedly boost nAb responses against the Delta variant was similarly observed for each dose group as illustrated in the prime dose subgroup analysis (Table 18). Participants primed with 2 doses of 100 µg showed a GMR of 2.0 (95% CI: 1.71, 2.45); participants primed with 2 doses of 50 µg had a GMR of 2.2 (95% CI: 1.81, 2.56).

Table 18: Analysis of Pseudovirus Neutralizing Antibody ID50 Titers – Study P201 Against Delta [B.1.617.2] Versus Study P301 Against Delta [B.1.617.2] - Per-Protocol Immunogenicity Set

Statistic	P201 Part B 50 µg mRNA-1273 Booster After 50 µg Priming (N=146)	P301 mRNA-1273 100 µg Primary Series (N=580)	P201 Part B 50 µg mRNA-1273 Booster After 100 µg Priming (N=149)	P301 mRNA-1273 100 µg Primary Series (N=580)
n	146	580	149	580
GMT (model based) (95% CI)	720.296 (610.200, 850.257)	352.141 (321.568, 385.621)	750.543 (640.715, 879.197)	347.792 (318.782, 379.440)
Ratio of GMT (model based) [P201 Part B vs. P301] (95% CI)	2.045 (1.708, 2.450)		2.158 (1.818, 2.562)	

CI= confidence interval; GMT (model based) = geometric least squares mean; LLOQ= lower limit of quantification; N= number of participants in analysis group; ULOQ= upper limit of quantification.
Note: Antibody: Pseudovirus Neutralizing Antibody ID50 Titers [P201: LLOQ=18.5, ULOQ=45118; P301=18.5, ULOQ=45118]
n = Number of participants with non-missing data at the corresponding timepoint.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 × LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
Separate analysis of covariance (ANCOVA) modes were used for P201 50 µg priming + 50 µg booster (group variables: P201 50 µg priming, and P301) and P201 100 µg priming + 50 µg booster (group variables: P201 100 µg priming, and P301).

The capacity for mRNA-1273 booster to enhance nAb responses against Delta variant in older adults (≥ 65 years) was assessed in a by-age subgroup analysis. Adults ≥ 65 years showed an even more robust response to the mRNA-1273 booster, with a GMR of 2.7 compared with a GMR of 1.9 for adults ≥ 18 and < 65 years (Table 19). Whereas post-primary series anti-Delta nAb responses among older adults (GMT [model based] 276.8; 95% CI: 236.98, 323.24) were lower than those of younger adults (GMT [model based] 427.334; 95% CI: 390.90, 467.17), administration of mRNA-1273 booster yielded post-booster anti-Delta nAb titers in adults ≥ 65 years (GMT [model based] 749.94; 95% CI: 604.79, 929.93) comparable to those achieved post-booster in younger adults (GMT [model based] 822.98; 95% CI: 725.94, 932.99; Table 19).

Table 19: Subgroup Analysis of Pseudovirus Neutralizing Antibody ID50 Titers – Study P201 Against Delta [B.1.617.2] Versus Study P301 Against Delta [B.1.617.2] - Per-Protocol Immunogenicity Set

	≥ 18 and < 65 years		≥ 65 years	
Statistic	**P201 Part B 50 µg mRNA-1273 Booster (N=219)**	**P301 mRNA-1273 100 µg Primary Series (N=434)**	**P201 Part B 50 µg mRNA-1273 Booster (N=76)**	**P301 mRNA-1273 100 µg Primary Series (N=146)**
n	219	434	76	146
GMT (model based)	822.980	427.334	749.937	276.767
95% CI	(725.944, 932.987)	(390.897, 467.166)	(604.785, 929.927)	(236.979, 323.236)
Ratio of GMT (model based) (P201 Part B vs. P301)	1.926		2.710	
95% CI	(1.651, 2.246)		(2.078, 3.533)	

CI = confidence interval; GMT (model based) = geometric least squares mean.
n = Number of participants with non-missing data at the corresponding timepoint.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 × LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (P201 Part B and P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
Note: Antibody: Pseudovirus Neutralizing Antibody ID50 Titers [P201: LLOQ=18.5, ULOQ=45118; P301=18.5, ULOQ=45118]

4.2.1.3 DMID 21-0012 Immunogenicity Data 100 µg mRNA-1273 Booster Dose

Results of this study of a boosting dose of mRNA-1273, at a dose of 100 µg, reinforces findings observed after the 50 µg boosting dose (P201 Part B, above). Comparing GMT obtained 12-20 weeks after 2 doses of 100 µg mRNA-1273 with GMT obtained 29 days after a 100 µg booster dose, show a significant increase in nAb titers with a GMFR of 7.46 (5.92-9.39) (Table 20). Consistent with the results from P201 Part B, the older adult cohort aged ≥ 56 years had a GMFR consistent with the younger age cohort 18-55 years of age (Table 21).

Table 20: DMID 21-0012 Cohort 1 Immunogenicity Endpoint Report: Neutralization Antibody Titers by PsVNA ID50 Assay to Pseudovirus D614G[1], by Timepoint

Parameter	**Group 2E [Dosed Moderna, Boost Moderna] (N = 51)**
Day 1 Visit (pre-boost)	
N (nonmissing)	50
Geometric mean (95% CI)	366.31 (280.09-479.06)
Day 29 Visit (28 days post-boost)	
N (nonmissing)	48
Geometric mean (95% CI)	2892.62 (2349.52-3561.26)

N* (nonmissing pre- and post-boost)	47
Participants with ≥ 4-fold rise[2], 95% CI	80.9% (66.7%-90.9%)
Geometric mean fold rise[2], 95% CI	7.46 (5.92-9.39)

Report date 16 September 2021.
CI = confidence interval; ID50 = median infectious dose.
[1] Values below the lower limit of detection (LLOD = 10) were assigned the value of LLOD/2. Values between the LLOD and the lower limit of quantification (LLOQ = 18.5) are taken as reported, or a value of LLOQ/2 is assigned if observations are reported as <LLOQ but no value is provided. Values greater than the upper limit of quantification (ULOQ = 45118) are taken as reported, or a ceiling value equivalent to the ULOQ is assigned if values are not provided
[2] Relative to pre-vaccination (Day 1 Visit) levels, among participants with no missing observations at both pre- and post-boost timepoints.

Table 21: DMID 21-0012 Cohort 1 Immunogenicity Endpoint Report: Neutralization Antibody Titers by PsVNA ID50 Assay to Pseudovirus D614G[1], by Age and Timepoint

Parameter	Group 2E [Dosed Moderna, Boost Moderna] Age 18-55 yo	Group 2E [Dosed Moderna, Boost Moderna] Age ≥ 56 yo
Day 1 Visit (pre-boost)		
N (nonmissing)	26	24
Geometric mean (95% CI)	381.82 (265.23-549.68)	350.21 (229.06-535.43)
Day 29 Visit (28 days post-boost)		
N (nonmissing)	25	23
Geometric mean (95% CI)	2858.71 (2113.84-3866.06)	2929.94 (2150.22-3992.40)
N* (nonmissing pre- and post-boost)	25	22
Participants with ≥ 4-fold rise[2], 95% CI	80.0% (59.3%-93.2%)	81.8% (59.7%-94.8%)
Geometric mean fold rise[2], 95% CI	7.16 (5.30-9.67)	7.81 (5.35-11.42)

Report date 16 September 2021.
CI = confidence interval; ID50 = median infectious dose; yo = years old.
[1] Values below the lower limit of detection (LLOD = 10) were assigned the value of LLOD/2. Values between the LLOD and the lower limit of quantification (LLOQ = 18.5) are taken as reported, or a value of LLOQ/2 is assigned if observations are reported as <LLOQ but no value is provided. Values greater than the upper limit of quantification (ULOQ = 45118) are taken as reported, or a ceiling value equivalent to the ULOQ is assigned if values are not provided.
[2] Relative to pre-vaccination (Day 1 Visit) levels, among participants with no missing observations at both pre- and post-boost timepoints.

4.2.1.4 Comparison of Neutralization Titers Between 100 µg Booster Dose and 50 µg Booster Dose

While the observed GMT after the 100 µg boost in the DMID Study 21-0012 was higher than that observed after a 50 µg boost in P201 Part B (2892.62 vs 1892.71), both boost doses resulted in robust increases in immune responses, measured by PsVNA ID50, compared with pre-boost titers. The 50 µg boost in P201 Part B resulted in a 15.06 GMFR and the 100 µg boost in the DMID Study 21-0012 resulted in a 7.46 GMFR. Both

boost doses also resulted in marked higher titers compared with the Day 28 post-primary series titer in P301 (1081.1, 95% CI: 1019.80, 1146.14), where efficacy was established.

There are several caveats that may contribute to the higher immunogenicity in the 100 µg boost group in the DMID Study 21-0012, including higher pre-boost titers (366.31, 95% CI: 280.09, 479.06 in DMID Study 21-0012 compared with 125.70, 95% CI: 111.01, 142.32) and administering of the booster at ~4 months post-primary series in the DMID study versus 6 months or more in Study P201.

Overall, in the absence of a threshold of protection, it appears that the immunogenicity provided by the 50 µg booster dose will be sufficient to restore the immunogenicity of the primary series, which should be efficacious against COVID-19, particularly caused by VOC such as the Delta variant.

4.2.2 Conclusion

While a specific nAb threshold conferring protection remains to be defined, published data confirm that higher rates of VE correspond with higher levels of nAb (Gilbert et al 2021). Data presented here show that the mRNA-1273 booster sharply increases nAb responses against the highly transmissible Delta variant compared with those nAb responses achieved post-primary series. This was seen for younger adults (18 to < 65 years) and for older adults (≥ 65 years), and the booster allowed older adults to achieve nAb responses against Delta variant comparable to those of younger adults. Overall, these data continue to highlight the capacity for the prototype mRNA-1273 booster to generate robust immune responses against the original strain as well as VoCs.

5 OVERVIEW OF SAFETY

Summary

- No new safety signals emerged upon administration of the booster dose in Study P201 Part B, and the safety profile of mRNA-1273 booster was similar to that observed following the second dose of the primary series (in Study P301 Part A).
- Most solicited local ARs were grade 1 to grade 2 in severity; no grade 4 solicited local or systemic ARs were reported in either prime series group.
- Unsolicited TEAEs were infrequent and mild to moderate in severity, and no SAEs or AEs lead to study discontinuation up to Day 29 in P201 Part B.
- No cases of myocarditis, pericarditis, or relevant AEs suggestive of any of these conditions were observed up to Day 29 in P201 Part B.
- In the post-authorization period, a total of 301,035,380 doses have been distributed worldwide, and the data show that mRNA-1273 has an acceptable safety profile.

This section contains a summary of solicited ARs and unsolicited AEs up to study Day 29 for Study P201 Part B. For P201 Part B, results are provided for recipients of (i) 100 µg Prime + 50 µg Boost and (ii) 50 µg Prime + 50 µg Boost; and (iii) the combined "50 + 100 µg" Prime + 50 µg Boost. Relevant reference data (as noted below) are also provided from P201 Part A 100 µg prime series and P301 Part A:

- Solicited ARs and unsolicited AEs for P201 Part B up to Day 29 (data extracted on 11 June 2021);
- Solicited ARs (post-dose 2) from P201 Part A (100 µg prime series group) and P301 Part A;
- Unsolicited AEs for 28 days post any dose from P201 Part A (100 µg prime series group) and P301 Part A;

Updated listings of cumulative unsolicited AEs, SAEs, and MAAEs from participants who received a single booster dose in Study P201 Part B, were generated from a live ongoing database (data subject to further cleaning; data snapshot date: 16 August 2021) representing ~5 months post-boost follow-up.

This section also contains summaries of solicited AR and unsolicited AE (up to study Day 7) for the supportive Study DMID Study 21-0012.

The safety and reactogenicity profile observed following the 50 µg mRNA-1273 booster in Study P201 Part B was similar regardless of the priming dose (50 µg or 100 µg) and accordingly, combined data (regardless of the priming dose) are considered supportive of the booster indication for this submission.

In addition, the reactogenicity profile observed following the 50 µg mRNA-1273 booster in Study P201 Part B was similar to that observed post-dose 2 of mRNA-1273 in the previously reported Study P201 Part A and in Study P301 Part A. The safety profile reported within a 28-day time window following a 50 µg mRNA-1273 booster observed in Study P201 Part B was also similar to that observed within a 28-day time window after any dose of mRNA-1273 in the previously reported P201 Part A and in Study P301 Part A. No new safety signals were observed in P201 Part B or in supportive DMID Study 21-0012.

5.1 Study P201 Part B, P201 Part A, and P301 Safety Data (Side-by-Side Evaluation)

5.1.1 Solicited Adverse Reactions

Participants recorded solicited local and systemic ARs in the eDiary on the day of each mRNA-1273 injection and during the 7 days after each mRNA-1273 injection. The reactogenicity profile following a 50 µg booster had a comparable profile for solicited local and systemic ARs among participants primed with 50 µg or those 100 µg. Because these 2 groups were comparable, the combined safety data are presented below (Table 22 and Table 23). The reactogenicity profile following a single injection of the 50 µg mRNA-1273 booster observed in Study P201 Part B was similar to that observed after the second dose of mRNA-1273 from the primary series in the previously reported P201 Part A and P301 Part A.

5.1.1.1 Summary of Solicited Local Adverse Reactions

The following local ARs were evaluated in each study within 7 days after injection: pain at injection site, erythema (redness) at injection site, swelling (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm.

The frequency of local ARs in Study P201 Part B following the 50 µg booster dose was numerically similar to that observed following the second injection of the primary series (50 µg or 100 µg) (Table 22).

The most common solicited AR after the 50 µg boost dose was pain. Most solicited local ARs were grade 1 to grade 2 in severity. Pain was the most commonly reported grade 3 local AR in P201 Part B. No grade 4 solicited local ARs were reported in either primary series group in P201. Local ARs were transient, and most resolved by Day 4. The frequency and severity of solicited local ARs was numerically comparable between age cohorts (18 to < 55; ≥ 55 years of age).

Table 22: Solicited Local Adverse Reactions Reported Within 7 Days After Booster vs Within 7 Days After the 2nd Injection in the Primary Series of P201 Part A and P301 (by Grade): Solicited Safety Set

	mRNA-1273				
	P201 50 µg Prime + 50 µg Booster N=163 n(%)	P201 100 µg Prime + 50 µg Booster N=167 n (%)	P201 Part B Pooled 50 µg Booster N=330 n (%)	P201 Part A 100 µg N=198 n (%)	P301 100 µg N= 14691 n (%)
Pain, N1	162	167	329	198	14688
Any	144 (88.9)	140 (83.8)	284 (86.3)	169 (85.4)	12964 (88.3)
Grade 1	111 (68.5)	111 (66.5)	222 (67.5)	140 (70.7)	9508 (64.7)
Grade 2	26 (16.0)	23 (13.8)	49 (14.9)	28 (14.1)	2850 (19.4)
Grade 3	7 (4.3)	6 (3.6)	13 (4.0)	1 (0.5)	606 (4.1)
Erythema (Redness), N1	162	167	329	198	14687
Any	10 (6.2)	8 (4.8)	18 (5.5)	15 (7.6)	1274 (8.7)
Grade 1	4 (2.5)	5 (3.0)	9 (2.7)	7 (3.5)	456 (3.1)
Grade 2	4 (2.5)	2 (1.2)	6 (1.8)	3 (1.5)	531 (3.6)
Grade 3	2 (1.2)	1 (0.6)	3 (0.9)	5 (2.5)	287 (2.0)
Swelling (Hardness), N1	162	167	329	198	14687
Any	12 (7.4)	9 (5.4)	21 (6.4)	21 (10.6)	1807 (12.3)
Grade 1	4 (2.5)	4 (2.4)	8 (2.4)	14 (7.1)	900 (6.1)
Grade 2	7 (4.3)	4 (2.4)	11 (3.3)	6 (3.0)	652 (4.4)
Grade 3	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.5)	255 (1.7)
Lymphadenopathy, N1	162	167	329	198	14687
Any	35 (21.6)	34 (20.4)	69 (21.0)	20 (10.1)	2092 (14.2)
Grade 1	22 (13.6)	30 (18.0)	52 (15.8)	17 (8.6)	1735 (11.8)
Grade 2	13 (8.0)	3 (1.8)	16 (4.9)	3 (1.5)	289 (2.0)
Grade 3	0	1 (0.6)	1 (0.3)	0	68 (0.5)

N1 = Number of exposed participants who submitted any data for the event.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).

5.1.1.2 Summary of Solicited Systemic Adverse Reactions

The following systemic ARs were evaluated in each study: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting,

fever, and chills. Rash was a solicited systemic AR in Study P201 only; therefore, no comparison between P201 and P301 can be made and accordingly rash is not included in Table 23.

The frequency of systemic ARs in Study P201 Part B following the 50 µg booster dose was numerically similar to that observed following the second injection of the primary series in Study P201 Part A and in P301 (Table 22; Table 23). The most common systemic ARs after the 50 µg booster dose in P201 Part B were fatigue, headache, arthralgia, and myalgia, which occurred at a similar rate between the P201 Part B 50 and 100 µg prime series groups. Because these 2 groups were comparable, the combined safety data are presented below (Table 23). No difference in incidence of the solicited AR of rash (3.7% in the 50 µg vs 1.8% in the 100 µg groups) was observed after the booster dose between the 50 µg and 100 µg prime series. Most solicited systemic AR in P201 Part B were grade 1 to grade 2 in severity. Systemic ARs were transient, and most resolved by Day 4. The frequency and severity of solicited systemic ARs was numerically comparable between age cohorts (18 to < 55; ≥ 55 years of age).

Fatigue, myalgia, headache, and arthralgia were the most commonly reported grade 3 systemic ARs (Table 23). No grade 4 solicited systemic ARs were reported in P201.

Table 23: Solicited Systemic Adverse Reactions Within 7 Days After Booster vs Within 7 Days After the 2nd Injection in the Primary Series of P201 Part A and P301 (by Grade): Solicited Safety Set

	mRNA-1273				
	50 µg Prime + 50 µg Booster (N=163) n (%)	100 µg Prime + 50 µg Booster N=167 n (%)	P201 Part B Pooled 50 µg Booster (N=330) n (%)	P201 Part A 100 µg N=198 n (%)	P301 100 µg N=14691 n (%)
Fever, N1	162	166	328	198	14682
Any	13 (8.0)	11 (6.6)	24 (7.3)	26 (13.1)	2276 (15.5)
Grade 1	12 (7.4)	6 (3.6)	18 (5.5)	19 (9.6)	1363 (9.3)
Grade 2	1 (0.6)	3 (1.8)	4 (1.2)	3 (1.5)	697 (4.7)
Grade 3	0	2 (1.2)	2 (0.6)	4 (2.0)	203 (1.4)
Grade 4	0	0	0	0	13 (< 0.1)
Headache, N1	162	167	329	198	14687
Any	97 (59.9)	92 (55.1)	189 (57.4)	104 (52.5)	8637 (58.8)
Grade 1	57 (35.2)	61 (36.5)	118 (35.9)	56 (28.3)	4815 (32.8)
Grade 2	34 (21.0)	29 (17.4)	63 (19.1)	39 (19.7)	3156 (21.5)
Grade 3	6 (3.7)	2 (1.2)	8 (2.4)	9 (4.5)	666 (4.5)
Fatigue, N1	162	167	329	198	14687
Any	103 (63.6)	98 (58.7)	201 (61.1)	128 (64.6)	9607 (65.4)

Grade 1	40 (24.7)	47 (28.1)	87 (26.4)	44 (22.2)	3431 (23.4)
Grade 2	50 (30.9)	44 (26.3)	94 (28.6)	66 (33.3)	4743 (32.3)
Grade 3	13 (8.0)	7 (4.2)	20 (6.1)	18 (9.1)	1433 (9.8)
Myalgia, N1	162	167	329	198	14687
Any	86 (53.1)	82 (49.1)	168 (51.1)	104 (52.5)	8529 (58.1)
Grade 1	40 (24.7)	47 (28.1)	87 (26.4)	35 (17.7)	3242 (22.1)
Grade 2	37 (22.8)	30 (18.0)	67 (20.4)	54 (27.3)	3966 (27.0)
Grade 3	9 (5.6)	5 (3.0)	14 (4.3)	15 (7.6)	1321 (9.0)
Arthralgia, N1	162	167	329	198	14687
Any	66 (40.7)	69 (41.3)	135 (41.0)	77 (38.9)	6303 (42.9)
Grade 1	35 (21.6)	43 (25.7)	78 (23.7)	32 (16.2)	2809 (19.1)
Grade 2	23 (14.2)	21 (12.6)	44 (13.4)	37 (18.7)	2719 (18.5)
Grade 3	8 (4.9)	5 (3.0)	13 (4.0)	8 (4.0)	775 (5.3)
Nausea/Vomiting, N1	162	167	329	198	14687
Any	29 (17.9)	19 (11.4)	48 (14.6)	41 (20.7)	2794 (19.0)
Grade 1	25 (15.4)	16 (9.6)	41 (12.5)	25 (12.6)	2094 (14.3)
Grade 2	4 (2.5)	3 (1.8)	7 (2.1)	16 (8.1)	678 (4.6)
Grade 3	0	0	0	0	21 (0.1)
Grade 4	0	0	0	0	1 (< 0.1)
Chills, N1	162	167	329	198	14687
Any	62 (38.3)	59 (35.3)	121 (36.8)	78 (39.4)	6500 (44.3)
Grade 1	32 (19.8)	36 (21.6)	68 (20.7)	30 (15.2)	2907 (19.8)
Grade 2	28 (17.3)	23 (13.8)	51 (15.5)	47 (23.7)	3402 (23.2)
Grade 3	2 (1.2)	0	2 (0.6)	1 (0.5)	191 (1.3)

N1 = Number of exposed participants who submitted any data for the event. NR = not reported.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).

5.1.2 Unsolicited Adverse Events

In P201 Part B, unsolicited treatment-emergent adverse events (TEAEs) were systematically collected during the 28-day time window after the booster dose. Adverse events leading to discontinuation from study participation, SAEs, MAAEs, and pregnancies are being collected from Day 1 through the entire study period or until the last day of study participation.

In Study P301, unsolicited TEAEs were systematically collected during the 28-day time window after each mRNA-1273 injection; SAEs, MAAEs, pregnancies, and AEs leading to withdrawal were collected throughout the duration of the study.

5.1.2.1 Summary of Unsolicited Adverse Events

The frequency of unsolicited AEs following the booster in Study P201 Part B was similar across the 50 µg and 100 µg prime series groups and numerically comparable to or lower than the rates observed post any dose in P201 Part A and P301 Part A (Table 24). All unsolicited AEs were mild or moderate in severity. No unsolicited AEs led to study discontinuation. TEAEs that were considered by the investigator as related to mRNA-1273 were consistent with PT terms solicited as part of the reactogenicity assessment. There were no SAEs in 201 Part B up to 28 days after booster administration.

Table 25 summarizes TEAEs by Preferred Term (PT) for the 28-day follow-up period after booster vaccination. No unexpected reporting patterns were observed. Some reported TEAEs (e.g., headache and fatigue) are solicited ARs that extended beyond Day 7. The reports with a PT of COVID-19 represent 4 asymptomatic participants who had nasal swabs, collected at scheduled study visits or following potential exposure to SARS-CoV-2, that tested positive for SARS-CoV-2.

Table 24: Summary of Unsolicited Treatment-Emergent Adverse Events up to 28 Days After Booster in P201 Part B or Up to 28 Days After Any Injection in P201 Part A and P301: Safety Set

	mRNA-1273				
	50 µg Prime + 50 µg Booster N=173 n (%)	100 µg Prime + 50 µg Booster N=171 n (%)	P201 Part B Pooled 50 µg Booster (N=344) n (%)	P201 Part A 100 µg N=200 n (%)	P301 mRNA-1273 (N=15184) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination					
All	17 (9.8)	22 (12.9)	39 (11.3)	56 (28.0)	4752 (31.3)
Serious	0	0	0	0	98 (0.6)
Fatal	0	0	0	0	2 (< 0.1)
Medically-attended	8 (4.6)	12 (7.0)	20 (5.8)	17 (8.5)	1819 (12.0)
Leading to study discontinuation	0	0	0	0	9 (< 0.1)
Severe	0	0	0	5 (2.5)	258 (1.7)
Unsolicited TEAEs related to study vaccination					
All	6 (3.5)	7 (4.1)	13 (3.8)	27 (13.5)	2067 (13.6)
Serious	0	0	0	0	8 (< 0.1)
Fatal	0	0	0	0	0
Medically-attended	0	2 (1.2)	2 (0.6)	5 (2.5)	198 (1.3)
Leading to study discontinuation	0	0	0	0	1 (< 0.1)
Severe	0	0	0	2 (1.0)	83 (0.5)

TEAE = treatment-emergent adverse event.

Table 25: Study P201 Part B Incidence of Unsolicited TEAE by Preferred Term up to 28 Days After Booster: Safety Set

Preferred Term	50 µg Prime + 50 µg Booster N=173 n (%)	100 µg Prime + 50 µg Booster N=171 n (%)	P201 Part B Pooled 50 µg Booster (N=344) n (%)
Number of Participants Reporting Unsolicited Adverse Events	17 (9.8)	22 (12.9)	39 (11.3)
Number of Unsolicited Adverse Events	19	27	46
Headache	1 (0.6)	4 (2.3)	5 (1.5)
COVID-19	1 (0.6)	3 (1.8)	4 (1.2)
Fatigue	0	4 (2.3)	4 (1.2)
Arthralgia	1 (0.6)	1 (0.6)	2 (0.6)
Lymphadenopathy	2 (1.2)	0	2 (0.6)
Oropharyngeal pain	1 (0.6)	1 (0.6)	2 (0.6)
Tooth abscess	2 (1.2)	0	2 (0.6)
Abdominal pain	0	1 (0.6)	1 (0.3)
Allergy to arthropod bite	0	1 (0.6)	1 (0.3)
Anxiety	0	1 (0.6)	1 (0.3)
Chills	1 (0.6)	0	1 (0.3)
Dermatitis exfoliative	1 (0.6)	0	1 (0.3)
Dizziness	0	1 (0.6)	1 (0.3)
Facial paralysis	1 (0.6)	0	1 (0.3)
Gastrooesophageal reflux disease	0	1 (0.6)	1 (0.3)
Glycosylated haemoglobin increased	0	1 (0.6)	1 (0.3)
Humerus fracture	0	1 (0.6)	1 (0.3)
Hypertension	1 (0.6)	0	1 (0.3)
Influenza	0	1 (0.6)	1 (0.3)
Injection site erythema	0	1 (0.6)	1 (0.3)
Myalgia	0	1 (0.6)	1 (0.3)
Osteopenia	1 (0.6)	0	1 (0.3)
Pruritus	1 (0.6)	0	1 (0.3)
Rash	0	1 (0.6)	1 (0.3)
Skin laceration	1 (0.6)	0	1 (0.3)
Suspected COVID-19	1 (0.6)	0	1 (0.3)
Tooth fracture	1 (0.6)	0	1 (0.3)
Urinary tract infection	0	1 (0.6)	1 (0.3)
Vertigo	1 (0.6)	0	1 (0.3)
Vitamin D deficiency	0	1 (0.6)	1 (0.3)

Vomiting	1 (0.6)	0	1 (0.3)
Wheezing	0	1 (0.6)	1 (0.3)

Source: P201 Part B: Table 14.3.1.9.3.1.
n/N = number; TEAE = treatment-emergent adverse event.

As of 16 August 2021 in the live database of this ongoing study (data subject to further cleaning), SAEs, MAAEs, and AEs leading to discontinuation are described below (Table 26). There was no clinical pattern observed, and none of the additional cases were considered related to mRNA-1273.

Table 26: Safety Overview After 50 µg mRNA-1273 Booster Vaccination in Study P201 Part B (up to 16 Aug 2020) vs After Any 100 µg mRNA-1273 Primary Series Injection in Study P201 Part A and Study P301 – Participants ≥ 18 Years of Age (Safety Set)

Participants reporting at least one	P201B 50 µg Booster After 50 µg Prime N=173	P201B 50 µg Booster After 100 µg Prime N=171	P201A 100 µg Prime N=200	P301A 100 µg Prime N=15184
Medically attended AEs[a]	37 (21.4)	41 (24.0)	38 (19.0)	3468 (22.8)
Related MAAE	0	2 (1.2)	5 (2.5)	213 (1.4)
Serious Adverse Events[a]	2 (1.2)	2 (1.2)	2 (1.0)	268 (1.8)
Related SAE	0	0	0	12 (< 0.1)
Deaths[a]	0	0	0	17 (0.1)
AE leading to study discontinuation[a]	0	0	0	26 (0.2)

AE = adverse event; MAAE = medically attended adverse event; SAE = serious adverse event.
[a] Through the 16 August 2021 data snapshot for study P201 Part B. Throughout the study for P201 Part A (CSR addendum). Throughout the blinded phase for P301 (Part A)

5.1.2.2 Unsolicited Medically-Attended Adverse Events

An MAAE was an AE that led to an unscheduled visit (including a telemedicine visit) to a healthcare practitioner (including unscheduled visits to the study site). The incidence of MAAEs during the 28-day time window was numerically higher in P201 Part A than in P201 Part B, including when assessed by the investigator as related to treatment (Table 24), which is consistent to the longer follow-up period due to receipt of 2 doses in Part A versus 1 dose in Part B. The rate of MAAEs was similar between the 50 µg and 100 µg prime series groups in P201 Part B, with no participants experiencing MAAE considered related to mRNA-1273 in the 50 µg prime series group and 2 (1.2%) in the 100 µg prime series group (grade 2 headache and grade 1 rash).

The review of cumulative MAAEs among P201 Part B participants who received a booster as of 16 August 2021 in the live ongoing database comprises 110 events, none of which were considered related except for the 2 cases of headache and rash noted above (Table 25). There were 5 serious MAAEs, which are described in Section 5.1.4

5.1.3 Deaths

No deaths were reported in Study P201 Part A or among P201 Part B booster participants (Table 24).

5.1.4 Other Serious Adverse Events

There were no SAEs reported within the 28-day time window post-booster in P201 Part B or within the 28-day time window post any injection in P201 Part A (Table 24).

The review of cumulative SAEs among P201 Part B participants who received a booster in the live clinical database as of 16 August 2021 indicated 5 SAEs in 4 participants (2 in each of the 50 µg and 100 µg priming groups) were reported, and all were considered by the investigator to be not related to mRNA-1273 (Table 26).

In the 100 µg priming group, there was a 23-year-old with a tendon rupture that occurred 93 days after the booster and a 26-year-old female with a history of genital herpes simplex, anxiety, depression, and 2 previous pregnancies resulting in live births who experienced a spontaneous abortion 52 days after vaccination. This participant subsequently became pregnant again 114 days after vaccination and this second pregnancy is ongoing.

Two participants in the 50 µg priming series had SAEs. A 71-year-old-male with relevant past medical history significant for hypertension reported a deep venous thrombosis and pulmonary embolism 79 days after booster. An 87-year-old female with a history of hypothyroidism, hypercholesterolemia, osteoarthritis, grade 1 diastolic dysfunction, and chronic bradycardia developed worsening of chronic bradycardia 44 days post-dose 2 in P201 Part A. Approximately 60 days post-dose 2 of the 50 µg priming series, she was hospitalized for pacemaker placement and was discharged in stable condition. Subsequently, a serious event of pericarditis was reported in this participant 89 days after booster vaccination, which lasted 6 days, along with a grade 2 event of angina lasting 1 day. Of note, the participant also reported grade 2 pericarditis (not reported as serious) again from Day 122-127 after the booster. Both events of pericarditis in the single participant were considered not related to vaccination.

5.1.5 Discontinuation from Investigational Product or Study Participation

There was no study discontinuation due to an adverse event in P201 Part B (Table 24, Table 26).

5.2 Study DMID 21-0012

A total of 154 participants have been enrolled and received an mRNA-1273 boost injection (IM; 100 µg) approximately 12-20 weeks after receiving primary vaccination under EUA. Safety data from all participants boosted with 100 µg mRNA-1273 (N=154) is presented below, regardless of primary vaccination type.

5.2.1 Summary of Solicited Adverse Reactions

5.2.1.1 Solicited Local Adverse Reactions

From the data available up to the data snapshot, the number and proportion of participants reporting severe local solicited events/symptoms (out of the total 154 enrolled in all 3 groups) is as follows: 0 (0%) reported severe erythema/redness, 1 (0.6%) severe induration/swelling and 1 (0.6%) severe pain and/or tenderness. The majority of the events were mild or moderate (Table 27). There were no notable clinical differences between groups.

Table 27: Participants Experiencing Local Solicited Events by Symptom, Maximum Severity, and Group

	mRNA-1273 50 µg Booster Total (N=154) n (%)
Erythema/redness[a]	
None/not gradable	133 (86.4)
Mild	21 (13.6)
Moderate	0
Severe	0
Potentially life-threatening	0
Erythema/redness largest diameter[b] (cm)	
N	26
Mean (SD)	2.1 (3.3)
Induration/swelling[g]	
None/not gradable	107 (69.5)
Mild	39 (25.3)
Moderate	7 (4.5)
Severe	1 (0.6)
Potentially life-threatening	0
Induration/swelling largest diameter[b]	
N	44
Mean (SD)	3.5 (3.1)
Pain and/or tenderness[a]	
None	28 (18.2)
Mild	86 (55.8)
Moderate	38 (24.7)
Severe	1 (0.6)
Potentially life-threatening	0

AE= adverse event; max = maximum; min = minimum; SD = standard deviation.
[a] For a given sign or symptom, each participant's solicited AE was counted once under the maximum severity for all post-administration assessments.

[b] For erythema/redness and induration/swelling, at each assessment time the maximum diameter at the injection site was recoded. For a given largest diameter, each participant was counted once under maximum largest diameter for all post-administration assessments.

5.2.1.2 Solicited Systemic Adverse Reactions

From the data available up to the data snapshot, the number and proportion of participants reporting severe systemic solicited events/symptoms (out of the total 154 enrolled in all 3 groups) are as follows: 5 (3.2%) reported chills, 7 (4.5%) malaise and/or fatigue, 3 (1.9%) myalgia, 2 (1.3%) headache, 1 (0.6%) nausea, 1 (0.6%) arthralgia, and 2 (1.3%) fever (Table 28). No potentially life-threatening systemic solicited events or symptoms have been reported.

Table 28: Participants Experiencing Systemic Solicited Events by Symptom, Maximum Severity, and Group

	Total (N=154) n (%)
Malaise and/or fatigue[a]	
None	41 (26.6)
Mild	59 (38.3)
Moderate	47 (30.5)
Severe	7 (4.5)
Myalgia[a]	
None	60 (39.0)
Mild	53 (34.4)
Moderate	38 (24.7)
Severe	3 (1.9)
Headache[a]	
None	72 (46.8)
Mild	57 (37.0)
Moderate	23 (14.9)
Severe	2 (1.3)
Nausea[a]	
None	123 (79.9)
Mild	25 (16.2)
Moderate	5 (3.2)
Severe	1 (0.6)
Chills[a]	
None	101 (65.6)
Mild	28 (18.2)
Moderate	20 (13.0)
Severe	5 (3.2)

	Total (N=154) n (%)
Arthralgia[a]	
None	108 (70.1)
Mild	29 (18.8)
Moderate	16 (10.4)
Severe	1 (0.6)
Fever[a]	
None	130 (84.4)
Mild	15 (9.7)
Moderate	7 (4.5)
Severe	2 (1.3)

AE = adverse event.
a For a given sign or symptom, each participant's solicited AE was counted once under the maximum severity for all post-administration assessments.

5.2.2 Summary of Unsolicited Adverse Reactions

Most participants experienced mild or moderate AEs. The most commonly reported AE term considered by the investigator to be related to study vaccine was lymphadenopathy. There was 1 grade 3 AE of vomiting and no grade 4 or grade 5 AEs.

5.2.3 Deaths, Other Serious Adverse Events, and Other Significant Unsolicited Adverse Events

In DMID Study 21-0012, no deaths, SAEs, discontinuations from investigational product or study participation, or pregnancies had occurred at the time of the data snapshot.

6 PHARMACOVIGILANCE AND RISK MANAGEMENT PLAN

The Pharmacovigilance Plan for mRNA-1273 addresses the general safety of the booster dose including the further characterization of identified and potential risks and adverse events of interest described in the RMP through continued clinical studies and noninterventional studies as follows:

Clinical studies:

- Ongoing Study P201 Part B, an open-label interventional phase of a Phase 2a, randomized, observer-blind, placebo-controlled, dose confirmation study to evaluate the safety, reactogenicity, and immunogenicity of a 50 µg booster of mRNA-1273 SARS-CoV-2 vaccine in adults aged 18 years and older, collects in the open-label phase AEs leading to discontinuation from study participation, MAAEs, and SAEs through Month 6 or withdrawal from the study.
- Ongoing DMID Study 21-0012, a Phase 1/2 study of delayed heterologous SARS-CoV-2 vaccine dosing (boost) after receipt of EUA vaccines (sponsored by the NIH), which plans to enroll 400 participants and collects MAAEs, SAEs, and AESI from dose 1 on study to 12 months after last dose on study.
- Ongoing Study P205 Part A, an open-label Phase 2/3 study evaluating the immunogenicity, safety, and reactogenicity of 2 dose levels of the mRNA-1273.211 vaccine (a multivalent vaccine containing the prototype and beta variant mRNAs in a 1:1 ratio, at a 50 or 100 µg combined dose level) when administered as a single booster dose to adult participants of the P301 study who have previously received 2 doses of mRNA-1273 as a primary series. Participants who previously received 2 doses of mRNA 1273, 28 days apart, with the second dose being at least 6 months ago, will receive a single booster dose of mRNA 1273.211 (50 or 100 µg). Approximately 300 participants will receive a single booster dose of mRNA-1273.211 50 µg, and approximately 584 participants will receive a single booster dose of mRNA-1273.211 100 µg. P205 Part B will evaluate a single booster of 100 µg mRNA-1273 in participants who received 2 priming doses of mRNA-1273 6 months earlier. In Part C, participants who received 2 priming doses of mRNA-1273 will receive a single booster of 100 µg mRNA-1273.617.2 (Delta vaccine variant).
- Moderna is currently providing a booster dose of 50 µg of mRNA 1273 to the ~25,000 participants remaining in P301 to provide the opportunity to study the safety of the booster dose on a larger scale than the P201 Part B study. The study (P301 Part C) will assess safety, immunogenicity, and the impact of the booster on the incidence rates of COVID-19 (through case surveillance, testing, and sequencing consistent with P301 Part A and Part B). Blood is being collected at ~ Day 4 post-boost for future potential cardiac biomarker testing. Unsolicited AEs, MAAEs, and SAEs will also be collected. Any cases of suspected myocarditis and pericarditis will be evaluated by a Cardiac Endpoint Adjudication

Committee, implemented uniformly across all clinical studies in the mRNA-1273 program in order to further evaluate the risk of myocarditis and pericarditis, in particular after the booster dose.

Non-interventional studies:

The noninterventional studies will capture safety data after any dose, including a booster dose, in the following 2 ongoing studies:

- P903, a post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval signal evaluation in HealthVerity
- P904, a post-authorization active surveillance safety study using secondary data to monitor real-world safety of mRNA-1273 in Europe, as the booster may become authorized in Europe.

Safety surveillance via routine pharmacovigilance and reporting to health authorities will continue post authorization with the booster dose according to the Regulations and the RMP. Moderna will educate vaccinators and vaccination centers of the authorized dosing to prevent potential dosing errors and will monitor this closely via routine pharmacovigilance.

7 BENEFITS AND RISKS CONCLUSIONS

The efficacy of mRNA-1273 to prevent COVID-19 was demonstrated to be 94.1% with 9 weeks median follow-up (Baden 2021) and 93.2% after 5.3 months median follow-up (El Sahly 2021), when the original strain (D614G) and the Alpha variant were the major circulating SARS-COV-2 strains. However, decreased levels of neutralizing antibody titers 6-8 months post-primary series, particularly against VoCs, have been observed. Clinical trial data breakthrough infections as well as real world evidence of reduced effectiveness against the Delta variant indicate that a booster dose of mRNA-1273 for those vaccinated more than 6 months previously could be beneficial to restore antibody titers to higher than post-dose 2 levels and reduce the number of breakthrough cases particularly against VoCs.

Following receipt of a 50 µg booster, study participants had increased neutralizing antibody titers to the original virus strain by 15-fold as compared to pre-booster values. Older adults over 65 years has consistent responses as compared to the younger age group. Responses successfully met the prespecified noninferiority criteria for GMR as well as for SRR difference (if an assay-specific definition of seroresponse was used on the pooled dataset; use of a 4-fold rise definition led to a lower bound of the 95% CI, -12.2%). In addition, if SRR were calculated using pre-dose 1 levels, 100% of participants achieved a 4-fold rise in SRR. Responses were boosted 19-fold higher overall, and 24-fold higher in adults ≥65 years of age, to the Delta virus strain, which is especially relevant given the predominance of Delta variant circulation in the US at this time.

In the analysis of P201 Part B, reactogenicity and unsolicited TEAE data up to Day 29 and SAE and MAAE data up to 5 months follow-up show no unexpected findings for the 50 µg booster. To date, these results appear to be consistent with the safety results of P301 Part A. The initial findings of the ongoing DMID Study 21-0012 further support the safety profile of the booster at the higher 100 µg dose. Post authorization, Moderna will continue expanding the safety database and follow-up duration of the booster dose through continued clinical studies and noninterventional studies. The core contribution to the clinical safety database will be the extension of the P301 study, in which all participants are currently being offered a 50 µg booster dose. The extension of P301 will enable continued active surveillance of breakthrough COVID-19 in a vaccinated population as well as the sequencing of breakthrough isolates. This plan will provide a well-established system for the safety monitoring of the booster dose. In addition, routine pharmacovigilance will monitor the occurrence of new ARs.

Considering the public health impact emergency due to SARS-CoV-2 and the need to date to contain the pandemic, the efficacy and safety results of a booster dose evaluated in the ongoing clinical trial P201 Part B support a booster dose administered IM as a single 50-µg dose of mRNA-1273 at least 6 months after completing a primary series.

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