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

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Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Effectiveness and Safety of Moderna COVID-19 Vaccine (mRNA-1273) Booster Dose *Emergency Use Authorization Amendment*

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October 14, 2021

Outline

- Background
- Study Design
- Immunogenicity Data
- Safety Data
- Summary

Outline

Background

Study Design

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Safety Data

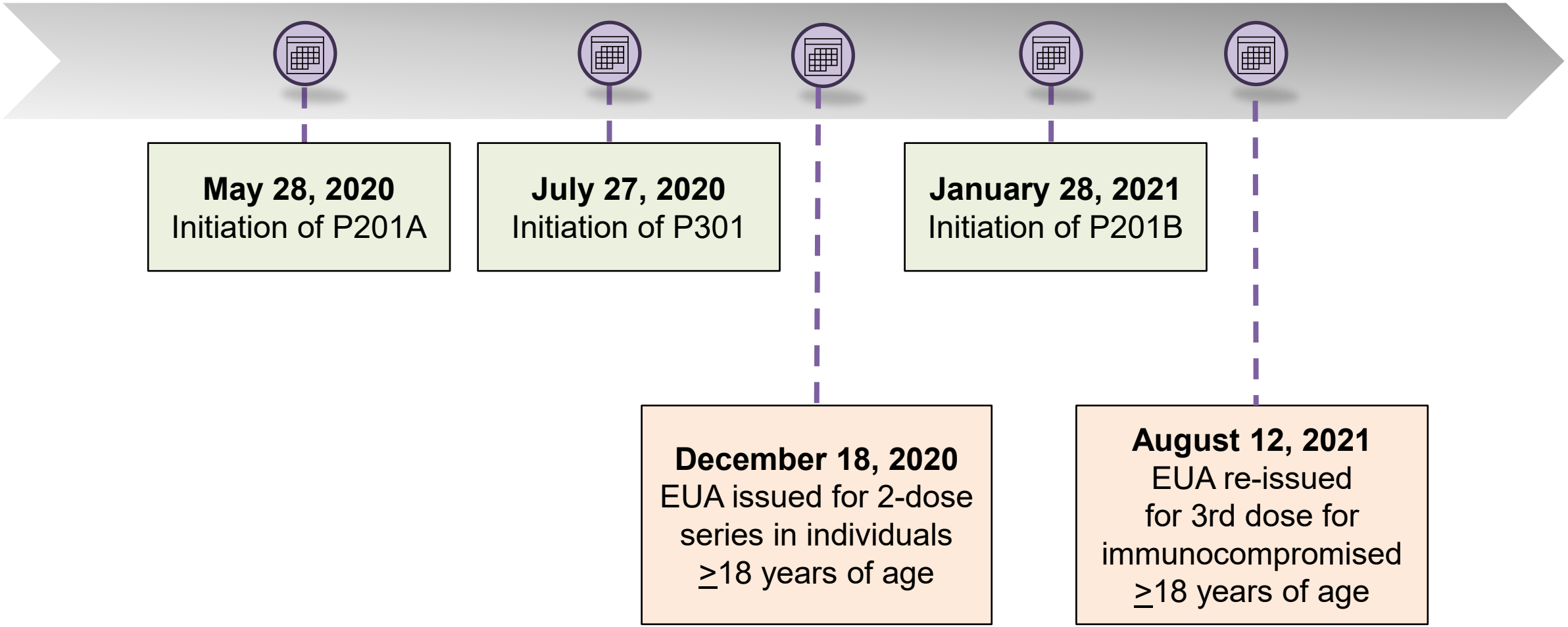
Summary

Moderna COVID-19 Vaccine (mRNA-1273)

Vaccine composition	Dosing Regimen
• Based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA • Formulated in lipid particles • Based on Wuhan strain	• Intramuscular 2-dose series, administered 1 month apart; 100 µg mRNA in each 0.5 mL dose • Third 0.5 mL dose in individuals with certain immunocompromising conditions

- Moderna COVID-19 Vaccine (mRNA-1273) has been available under EUA since December 18, 2020.
- The EUA amendment is intended to support authorization for booster administration of Moderna COVID-19 Vaccine (mRNA-1273) at a **50 µg dose** (0.25 mL) at least 6 months following a 2-dose series in the following populations:
  - individuals 65 years of age and older,
  - individuals 18 through 64 years of age at high risk of severe COVID-19, and
  - individuals 18 through 64 years of age 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.

Regulatory background



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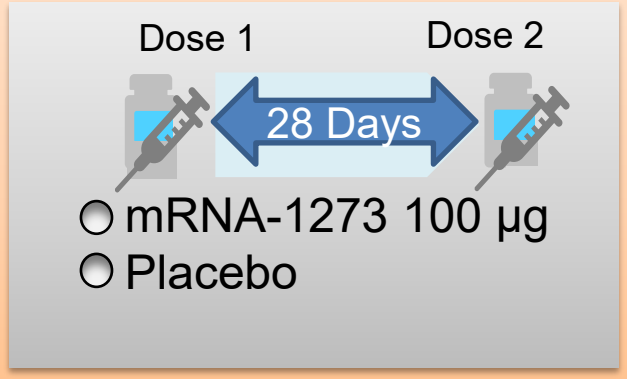
P301: Study Overview

Observer-blinded, randomized, stratified, placebo-controlled Phase 3 efficacy study

30,351 participants stratified by age and health risk

- Group 1: ≥18 to < 65 years (no health risk)
- Group 2: ≥18 to < 65 years (health risk)
- Group 3: ≥ 65 years

Randomized 1:1



15,184 recipients of 100 µg mRNA-1273 two-dose series

1,080 subjects randomly selected as subcohort for booster dose comparison population

P201: Study Overview

PART A
Observer-blinded, randomized, placebo-controlled 2-dose series phase

600 participants stratified by age
- Cohort 1: ≥18 to < 55 years
- Cohort 2: ≥55 years

Randomized 1:1:1

Dose 1 — 28 Days — Dose 2
- mRNA-1273 50 µg
- mRNA-1273 100 µg
- Placebo

Part A participants who received open-label booster dose in Part B (N=344):
- mRNA 50 µg group (n= 173)
- **mRNA 100 µg group (n= 171)**

PART B
Open label booster phase

Booster: mRNA-1273 50 µg at least 6 months (median interval ~7.2 months [range 5.9, 8.6]) after completion of 2-dose series

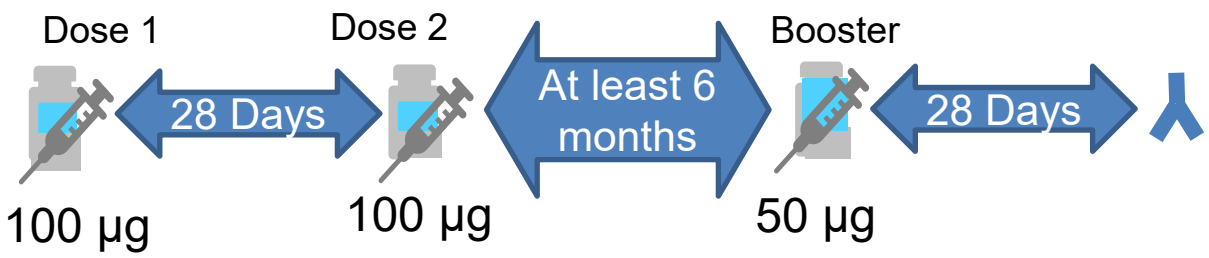
Booster Dose Effectiveness

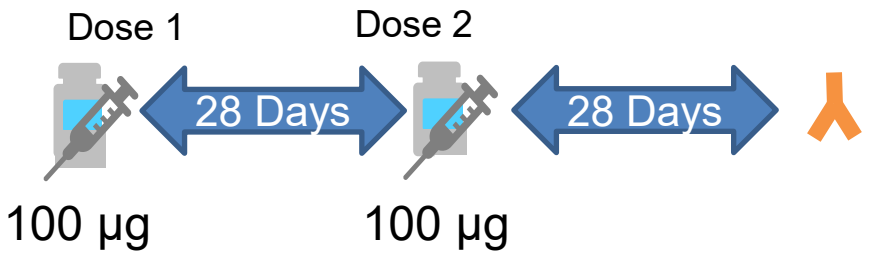
Booster dose effectiveness is being inferred by immunobridging analyses comparing geometric mean neutralizing antibody titers*(GMT) and seroresponse rate* against a pseudovirus expressing the SARS-CoV-2 spike protein from a USA_WA1/2020 isolate carrying the D614G mutation [D614G strain]*

28 days after a single 50 µg booster dose in Study P201 Part B (100 µg prime group)

TO

28 days after the second 100 µg priming dose (Day 57) in random subset from efficacy Study P301





*50% inhibitory dose (ID50) titers measured with a validated pseudovirus neutralization assay against the D614G strain by Duke University Medical Center

Immunobridging Analysis of GMT Co-Primary Endpoint

Co-Primary Endpoint: Geometric mean neutralizing antibody titer (GMT) against a pseudovirus expressing SARS-COV-2 spike protein from the D614G strain

Geometric mean titer (GMT) ratio of SARS-CoV-2 neutralizing titers

$$\frac{\textbf{GMT 28 days Post Booster Dose (P201B)}}{\textbf{GMT 28 days Post Dose 2 (P301)}}$$

Immunobridging success criteria:

- lower limit of the 2-sided 95% CI for GMT ratio ≥ 0.67
- point estimate of GMT ratio ≥1.0

*Given the lack of randomization between studies P201B and P301, an analysis of covariance (ANCOVA) model was used to estimate the GMT ratio that adjusts for differences in age groups (<65 years, ≥65 years).

Immunobridging Analysis of Seroresponse Co-Primary Endpoint

Co-Primary Endpoint: % of participants with seroresponse defined as a ≥4-fold rise in neutralizing titers (from baseline) against a pseudovirus expressing SARS-COV-2 spike protein from the D614G strain* (baseline titers < LLOQ* are set to LLOQ)

Percentage difference between seroresponse at 28 days post booster dose (P201B) and at 28 days post Dose 2 (P301)

% with 4-fold rise from pre-Booster to 28 days post Booster Dose

MINUS

% with 4-fold rise from pre-Dose 1 to 28 days post Dose 2

Immunobridging success criterion: lower limit of the 95% CI for the difference in % of participants with seroresponse is ≥ -10%

*The lower limit of quantitation (LLOQ) is defined as the lowest sample concentration that can be measured by the assay with acceptable accuracy, linearity and precision.

Booster Dose Immunogenicity Co-Primary Endpoints B.1.617.2 (Delta) Variant

Endpoints

- Neutralizing antibody titer (ID50) against pseudovirus expressing SARS-COV-2 Spike protein from USA_WA1/2020 isolate carrying the D614G mutation
- Neutralizing antibody titer (ID50) against pseudovirus expressing SARS-COV-2 Spike protein from B.1.617.2 variant (unvalidated)
- % of participants with seroresponse

Geometric mean titer (GMT)* ratio

$$\frac{\text{GMT (B.1.617.2) 28 days Post Booster Dose (P201B)}}{\text{GMT (D614G) 28 days Post Dose 2 (P301)}}$$

Percentage difference between seroresponse at 28 days post booster dose (P201B) and at 28 days post Dose 2 (P301)

% 4-fold rise pre-Booster to 28 days post Booster Dose (B.1.617.2)
MINUS
% 4-fold rise pre-Dose 1 to 28 days post Dose 2 (D614G)

Results of hypothesis testing pending; descriptive data available for review

*Given the lack of randomization between studies P201B and P301, the statistical analysis plan pre-specified an analysis of covariance (ANCOVA) model for estimating the GMT ratio that adjusts for differences in age groups (<65 years, ≥65 years)

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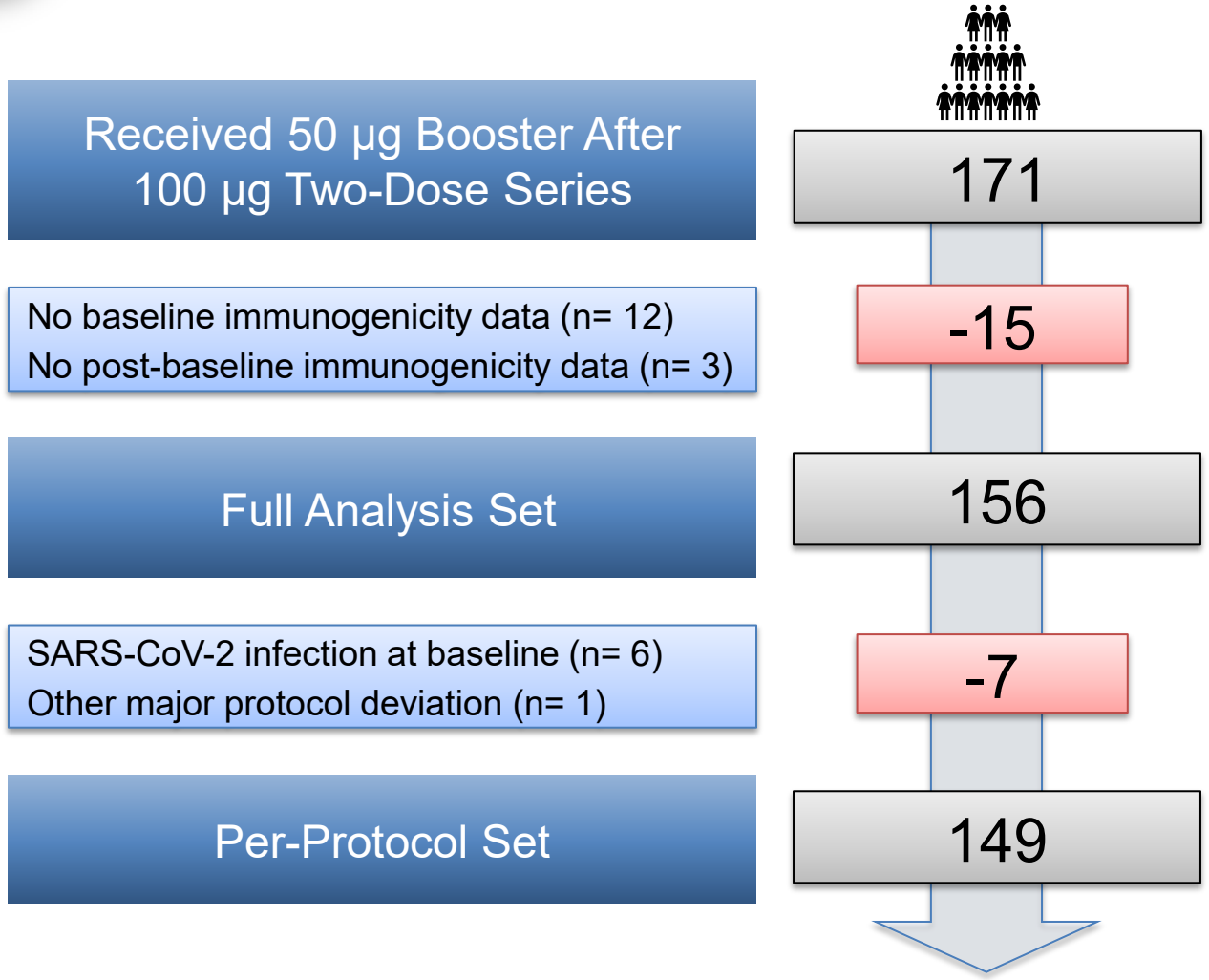
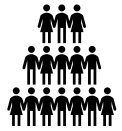
Immunogenicity Analysis Population P201B



Full Analysis Set: All subjects who received any booster injection in Part B and had immunogenicity data available at both baseline (Part B Day 1) and at least 1 post-booster visit

Per-Protocol Set: All subjects in the Full Analysis Set who did not have SARS-CoV-2 infection 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

Immunogenicity Analysis Population P301



Subjects Selected for Random Subcohort
(Baseline SARS-CoV-2 Negative)

1,080

Human Immunodeficiency Virus Infection (n= 18)
Received dose 2 out of window for PPS (n= 5)
Did not receive dose 2 per schedule (n= 1)
Had other major protocol deviation (n= 1)

-25

Per-protocol Set

1,055

Per-protocol Set: All subjects in the Random Subcohort who received 2 doses, did not have SARS-CoV-2 infection at baseline (pre-Dose 1), did not have a major protocol deviation that impacted immune response, had post-injection immunogenicity assessment at timepoint of primary interest (Day 57).

Demographics (Per-protocol Immunogenicity Subset)

Characteristic	Study P201B 50 µg Booster After 100 µg Two-Dose Series N=149	Study P301 100 µg Two-Dose Series N=1,055
Age (Years) Median (Min, Max)	56 (18, 82)	57 (18, 87)
Age Group, n (%) ≥18 and <65 years old	112 (75.2)	700 (66.4)
Age Group, n (%) ≥65 years old	37 (24.8)	355 (33.6)
Sex, n (%) Female	90 (60.4)	495 (46.9)
Sex, n (%) Male	59 (39.6)	560 (53.1)
Race, n (%) White	142 (95.3)	767 (72.7)
Race, n (%) Black or African American	5 (3.4)	188 (17.8)
Race, n (%) Asian	1 (0.7)	26 (2.5)
Race, n (%) American Indian or Alaska Native	1 (0.7)	17 (1.6)
Race, n (%) Native Hawaiian or Other Pacific Islander	0	5 (0.5)
Race, n (%) Multiple	0	15 (1.4)
Race, n (%) Other	0	27 (2.6)
Race, n (%) Not reported/unknown	0	10 (1.0)
Ethnicity, n (%) Hispanic or Latino	10 (6.7)	334 (31.7)
Ethnicity, n (%) Not Hispanic or Latino	139 (93.3)	717 (68.0)
Ethnicity, n (%) Not Reported/Unknown	0	4 (0.4)
Body Mass Index (kg/m^2) Median	25.74	29.62
Obesity (≥30.0 kg/m^2)	14 (9.4)	500 (47.2)

Note: P201 excluded individuals with pre-existing medical conditions that increase the risk of severe COVID-19.

Immunogenicity Results: Immunobridging based on GMT ratios (USA_WA1/2020 carrying the D614G mutation)

Study P201B 50 µg Booster After 100 µg Two-Dose Series Day 29 GMT* (95% CI) N=149	Study P301 100 µg Two-Dose Series Day 57 GMT* (95% CI) N=1053	GMT* Ratio (P201B/P301)
1802 (1548, 2099)	1027 (968, 1089)	1.8 (1.5, 2.1)

Success criteria met as the lower bound of the 2-sided 95% CI for the GMT ratio was ≥0.67 and the point estimate of the GMR was ≥1.0.

*Given the lack of randomization between studies P201B and P301, the statistical analysis plan pre-specified an analysis of covariance (ANCOVA) model for estimating the GMT ratio that adjusts for differences in age groups (<65 years, ≥65 years)

Immunogenicity Results: Immunobridging based on seroresponse (USA_WA1/2020 isolate carrying the D614G mutation)

Study P201B 50 µg Booster After 100 µg Two-Dose Series Day 29[a] Seroresponse n (%) (95% CI) N=149	Study P301 100 µg Two-Dose Series Day 57 Seroresponse n (%) (95% CI) N=1050	Difference in Seroresponse Rate (P201B-P301) % (95% CI)
131 (**87.9**) (81.6, 92.7)	1033 (**98.4**) (97.4, 99.1)	-10.5 (**-16.7**, -6.1)

Study P201B participants who met the ≥4-fold increase in titer post-booster dose had a baseline GMT of 109 (range of individual titers 9, 4393); whereas P201B participants who did not meet the ≥4-fold increase in titers post-booster had a baseline GMT of 492 (range of individual titers 162, 2239).

Success criterion **NOT** met as the lower limit of the 95% CI for the difference in percentages of participants with seroresponse was not greater than -10%.

Immunogenicity Results: B.1.617.2 (Delta) Variant GMTs* 28 Days After Booster Dose and 2-Dose Series (Exploratory Analysis)

	≥18 to <65 Years Study P201B Booster Dose N=112	≥65 Years Study P201B Booster Dose N=37	≥18 to <65 Years Study P301 Dose 2 N=434	≥65 Years Study P301 Dose 2 N=146
Pre-Vaccination GMT (95% CI)	54.8 (44.0, 68.3)	31.8 (22.6, 44.7)	NA	NA
1 month post-vaccination GMT (95% CI)	872 (730, 1043)	706 (524, 951)	427 (390, 468)	277 (238, 322)
1 month post-vaccination Seroresponse % (95% CI)	n=98 87.5 (79.9, 93.0)	n=35 94.6 (81.8, 99.3)	NA	NA

Note: P201B participants received a 50 µg booster dose of mRNA-1273 ≥6 months after completing a 2-dose series of 100 mRNA-1273. P301 participants received a 2-dose series of 100 µg mRNA-1273.
*50% inhibitory dose (ID50) titers measured with a unvalidated pseudovirus neutralization assay against the Delta variant

P201B SARS-CoV-2 Infection: Exploratory Analysis

Study P201 Part B, through the August 16, 2021 cutoff date

- SARS-CoV-2 infection was measured by RT-PCR, Roche Elecsys Anti-SARS-CoV-2 N assay or a COVID-19 local diagnostic test at scheduled visits or for potential SARS-CoV-2 exposure and/or symptoms.
- 38 positive tests after the booster dose (20 in 50 µg-primed booster recipients and 18 in 100 µg-primed booster recipients).
- Limitations: Incidence of SARS-CoV-2 infection was an exploratory endpoint and there was no control group. Collection of information related to potential COVID-19 cases was not systematic as case definitions of COVID-19 were not provided to study sites nor used in the analysis.

P301 Post-hoc analysis of efficacy: Delta surge

P301 protocol-specified COVID-19 cases accrued during the current delta variant surge
01 July 2021 through 27 August 2021
Participants ≥18 years of age

Participants who completed the 2-dose vaccination series **early in the study** (i.e., those who were originally randomized to mRNA-1273; n= 15209)

Incidence **77.1 cases per 1,000 person years** (13 severe cases*: 6.2 per 1,000 person years)

Median of **13 months (7.8-13.3) post-Dose 2** at the beginning of the analysis period

Participants who completed the 2-dose vaccination series **later in the study** (i.e., those who were originally randomized to placebo and then crossed over to mRNA-1273; n= 15206)

Incidence **49.0 cases per 1,000 person years** (6 severe cases*: 3.3 per 1,000 person years)

Median of **7.9 months (4.4-7.7) post-Dose 2** at the beginning of the analysis period

*15 of the 19 severe cases occurred among participants ≥65 years of age and/or who had a risk factor for severe COVID- 19. The 4 remaining cases occurred in participants aged 42, 59, 63 and 64 years who were not at risk for severe disease.

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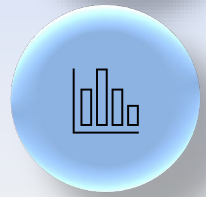

Safety Data

Summary

Length of Safety Follow-up in Booster Recipients

	P201B 50 µg Booster After 50 µg Two-Dose Series N=173	P201B 50 µg Booster After 100 µg Two-Dose Series N=171	P201B All Booster Dose Recipients N=344
Booster dose to August 16, 2021 cut-off date*			
<2 months, n (%)	4 (2.3)	0 (0.0)	4 (1.2)
≥2 - <4 months, n (%)	3 (1.7)	2 (1.2)	5 (1.5)
≥4 to <6 months, n (%)	135 (78.0)	134 (78.4)	269 (78.2)
≥6 to <8 months, n (%)	31 (17.9)	35 (20.5)	66 (19.2)
Mean	5.5	5.7	5.6
Median	5.7	5.7	5.7
Min, max	0.3, 6.4	3.1, 6.4	0.3, 6.4

*P201B data were provided through study day 29 post-booster vaccination (June 10, 2021 database lock date); additional data subject to additional cleaning were provided through August 16, 2021.

Safety: Immediate Reactogenicity

Proportion of participants ≥18 years of age with immediate local and systemic reactions

P201A (5.1%) 100 µg two-dose series	P201B (13.2%) 100 µg-primed booster recipients	P301 (9.9%) 100 µg two-dose series

22 reported any immediate adverse reaction, including one severe case of injection site pain.

<u>Immediate local reactions</u>

Seventeen (10.2%) participants:

- pain (n=16)
- erythema (n=1)
- axillary swelling or tenderness of the vaccination arm (n=3)

<u>Immediate systemic reactions</u>

Eight (4.8%) participants:

- headache (n=5)
- fatigue (n=3)
- arthralgia (n=3)
- myalgia (n=1)
- nausea/vomiting (n=1)

Local Reactogenicity 7 Days After Dose 2 of 100 µg Two-Dose Series in P201A and 7 Days After Booster Dose (following 100 µg Two-Dose Series) in P201B

	≥18 to <65 years		≥65 years	
	P201A Dose 2 ≥18 to <65 years N[a]=155 n[b] (%)	P201B Booster Dose ≥18 to <65 years N[a]=129 n[b] (%)	P201A Dose 2 ≥65 years N[a]=43 n[b] (%)	P201B Booster Dose ≥65 years N[a]=38 n[b] (%)
Any Injection Site Pain[c]	137 (88.4)	111 (86.0)	32 (74.4)	29 (76.3)
Severe	1 (0.7)	4 (3.1)	0	2 (5.3)
Any axillary swelling or tenderness of the vaccination arm[c]	18 (11.6)	32 (24.8)	2 (4.7)	2 (5.3)
Severe	0 (0.0)	1 (0.8)	0	0
Any Swelling (>2.5 cm)[d]	16 (10.3)	8 (6.2)	5 (11.6)	1 (2.6)
Severe	0	0	1 (2.3)	1 (2.6)
Any Redness (>2.5 cm)[d]	12 (7.7)	7 (5.4)	3 (7.0)	1 (2.6)
Severe	2 (1.3)	1 (0.8)	3 (7.0)	0

P201B participants received a 50 µg booster dose of mRNA-1273 ≥6 months after completing a 2-dose series of 100 mRNA-1273. P201A participants received a 2 dose series of 100 µg mRNA-1273.
a. N = # of participants reporting ≥1 yes or no response for the specified reaction after the specified dose.
b. n = # of participants with the specified reaction.
c. Severe: prevents daily activity or any use of prescription pain reliever.
d. Severe: >10.0 cm.

Systemic Reactogenicity 7 Days After Dose 2 of 100 µg Two-Dose Series in P201A and 7 Days After Booster Dose (following 100 µg Two-Dose Series) in P201B

	≥18 to <65 years		≥65 years	
	P201A Dose 2 ≥18 to <65 years Na=155 nb (%)	P201B Booster Dose ≥18 to <65 years Na=129 nb (%)	P201A Dose 2 ≥65 years Na=43 nb (%)	P201B Booster Dose ≥65 years Na=38 nb (%)
Any Fatigue[c]	105 (67.7)	80 (62.0)	23 (53.5)	18 (47.4)
Severe	16 (10.3)	4 (3.1)	2 (4.7)	3 (7.9)
Any Headache[d]	87 (56.1)	76 (58.9)	17 (39.5)	16 (42.1)
Severe	8 (5.2)	1 (0.8)	1 (2.3)	1 (2.6)
Myalgia[c]	89 (57.4)	64 (49.6)	15 (34.9)	18 (47.4)
Severe	15 (9.7)	4 (3.1)	0	1 (2.6)
Arthralgia[c]	66 (42.6)	54 (41.9)	11 (25.6)	15 (39.5)
Severe	8 (5.2)	4 (3.1)	0 (0.0)	1 (2.6)
Chills[c]	71 (45.8)	52 (40.3)	7 (16.3)	7 (18.4)
Severe	1 (0.6)	0	0	0
Nausea/vomiting[e]	36 (23.2)	16 (12.4)	5 (11.6)	3 (7.9)
Severe	0	0	0	0
Fever ≥38.0°C	24 (15.5)	9 (7.0)	2 (4.7)	2 (5.4)
Fever ≥38.0℃ to 38.4°C	18 (11.6)	5 (3.9)	1 (2.3)	1 (2.7)
Fever >38.4℃ to 38.9A°C	3 (1.9)	2 (1.6)	0 (0.0)	1 (2.7)
Fever >38.9 to 40.0°C	3 (1.9)	2 (1.6)	1 (2.3)	0
Fever > 40.0°C	0	0	0	0
Any Rash[f]	5 (3.2)	3 (2.3)	1 (2.3)	0 (0.0)
Use of antipyretic/pain medication[f]	86 (55.5)	64 (49.6)	11 (25.6)	11 (28.9)

Note: P201B participants received a 50 µg booster dose of mRNA-1273 ≥6 months after completing a 2-dose series of 100 mRNA-1273. P201A participants received a 2-dose series of 100 µg mRNA-1273.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Severe: prevents daily activity.
d. Severe: prevents daily activity or any use of prescription pain reliever.
e. Severe: requires outpatient intravenous hydration or prevents daily activity.
f. Severity was not collected for rash or for use of antipyretic or pain medication

P201B Unsolicited Adverse Events/Serious Adverse Events

- Through the August 16, 2021 cutoff date, there were no unsolicited adverse events (AEs) not already captured as solicited local and systemic reactions that were considered causally related to Moderna COVID-19 vaccine.
- A total of 20 subjects (11.7%) reported unsolicited AEs through 28 days after the booster dose. The most common unsolicited AEs (reported by >1 participant) included headache (n= 4; 2.3%) and fatigue (n= 4; 2.3%).
- An event of Bell's palsy (5 hours after booster dose) was reported and considered unlikely to be related based on temporal implausibility.
- There were no serious adverse events (SAEs) reported within 28 days after booster vaccination.
- As of the August 16, 2021 cutoff date, five SAEs were reported in four participants with time to onset more than 30 days following the booster dose (tendon rupture, spontaneous abortion, deep vein thrombosis/pulmonary embolism, pericarditis). None of these SAEs were considered likely to be related to the vaccine because the timing of the events in relation to vaccination did not suggest a causal relationship and/or a more likely alternative etiology was identified.
- No participants were withdrawn due to AEs.

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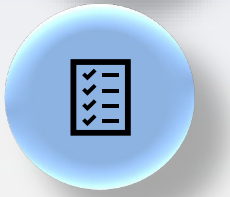

Summary

Summary of P201 data

Immunogenicity

- Immunobridging analyses against the D614G strain met the pre-specified success criteria for the GMT ratio (P201B/P301) but not for seroresponse rates.
- In post-hoc analyses, participants with lower pre-booster neutralizing antibody titers were more likely to achieve a ≥4-fold rise in neutralizing antibody titers after booster vaccination compared to participants with higher pre-booster neutralizing antibody titers.
- Immunogenicity data to support effectiveness of the booster dose against the Delta variant are limited to exploratory analyses using a non-validated assay.

Safety

- There was no evidence of increased reactogenicity following a booster dose relative to Dose 2, with the exception of axillary swelling or tenderness of the vaccination arm in participants ≥18 to <65 years of age.
- Unsolicited adverse events did not reflect any new safety concerns.
- Through the August 16, 2021 cut-off date, there were no deaths or SAEs considered causally related to Moderna COVID-19 vaccine.

Thank you