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

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Safety and Immunogenicity of a 50 µg Booster Dose of mRNA-1273 (Moderna COVID-19 Vaccine)

ModernaTX, Inc.

Vaccines and Related Biological Products Advisory Committee
October 14, 2021
Safety and Immunogenicity of a 50 µg Booster Dose of mRNA-1273 (Moderna COVID-19 Vaccine)

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Therapeutic Area Head, Infectious Diseases
ModernaTX, Inc.
Proposed Use of Moderna Vaccine as a Booster

- Administration of a single 50 µg (0.25 ml) booster dose at least 6 months after completion of a primary series in:
  - Individuals 65 years of age and older;
  - Individuals 18 - 64 years of age at high risk of severe COVID-19; and
  - Individuals 18 - 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
Proposed mRNA Vaccination Schedules

**Individuals ≥ 18 Years**
- **Dose 1**: 100 µg (0.5 mL)
- **Dose 2**: 100 µg (0.5 mL)
- **Booster**: 50 µg (0.25 mL)

4 Weeks → ≥ 1 Month → ≥ 6 Months Post Dose 2

**Immunocompromised ≥ 18 Years**
- **Dose 1**: 100 µg (0.5 mL)
- **Dose 2**: 100 µg (0.5 mL)
- **Dose 3**: 100 µg (0.5 mL)

4 Weeks → ≥ 1 Month → ≥ 6 Months Post Dose 2
Outline of Presentation

- Background
- Update on vaccine efficacy (Study 301)
- Antibody persistence 6-8 months after vaccination
- Breakthrough disease in vaccinated individuals from July – August, 2021
- 50 µg booster dose (Study 201B)
  - Rationale for dose selection
  - Study design
  - Safety data
  - Immunogenicity of 50 µg booster dose vs the original virus (D614G) and Delta variant
- Summary
Background
Review of Safety and Efficacy from Phase 3 Study 301

- 30,375 subjects who received at least one dose
  - 15,180 mRNA-1273 recipients
  - 15,166 placebo recipients
- 94.1% vaccine efficacy in per protocol cohort\(^1\)
  - Based on 9-week median follow-up post-dose 2
- Observed to have acceptable safety profile\(^1\)
- 100 µg 2-dose regimen authorized for emergency use for individuals ≥ 18 years old

1. Baden et al NEJM, 2020
Use of Moderna COVID-19 Vaccine in US Since December 2020 EUA

- Doses Distributed: 191,245,660
- Fully Vaccinated: 69,075,289
- Received Third Dose: 1,495,618

Adapted from CDC COVID Data Tracker (as of October 11, 2021)
Update on mRNA-1273 Efficacy through End of Blinded Phase

Phase 3 Study 301
Participants unblinded and placebo recipients offered vaccine shortly after EUA

Subjects followed for any signs of COVID-19 through
- Weekly e-diary contact
- Monthly phone calls

If subject had symptoms of COVID-19, examination and PCR testing conducted by site

Efficacy results updated through end of blinded phase (March 2021)

Primary data to support BLA (rolling submission completed August 25, 2021)
mRNA-1273 Vaccine Efficacy to Prevent COVID-19 Disease was 93.2% through 5.3 Months of Follow-up

*Per Protocol Set*

![Graph showing cumulative event rate over time from randomization](image)

Median 5.3 months of follow-up
mRNA-1273 Vaccine Efficacy to Prevent Severe COVID-19 Disease was 98.2% through 5.3 Months of Follow-up

Per Protocol Set

Cumulative Severe Event Rate, %

Time from Randomization (days)

Median 5.3 months of follow-up
Exploratory Analysis of Antibody Persistence and Boosting

Study 201B
Exploratory Analysis Against Variants of Concern
Study 201B 50 µg Booster after 100 µg Primary Series

23 to 44-Fold Increase After Booster

NAb Titer (ID$_{50}$)

<table>
<thead>
<tr>
<th>GMT</th>
<th>WT</th>
<th>Beta</th>
<th>Gamma</th>
<th>WT</th>
<th>Beta</th>
<th>Gamma</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1 Post-Dose 2</td>
<td>1,210</td>
<td>84</td>
<td>188</td>
<td>198</td>
<td>27</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Month 6-8 Post-Dose 2</td>
<td>4,588</td>
<td>864</td>
<td>1,308</td>
<td>1,268</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 14 Post-Booster</td>
<td>5,268</td>
<td>6,164</td>
<td>1,308</td>
<td>1,268</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WT: original strain (D614G)
Research VSV pseudoneutralization assay used
Adapted from Choi et al., Nature Medicine 2021
Breakthrough Disease in Vaccinated Individuals from July – August, 2021

Phase 3 Study 301
Breakthrough COVID-19 Cases by Month

Study 301

<table>
<thead>
<tr>
<th>Initial Randomization</th>
<th>mRNA-1273</th>
<th>Early Vaccination</th>
<th>EUA and Cross-over</th>
<th>Later Vaccination</th>
<th>Placebo</th>
<th>Per Protocol Cases of COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oct 2020</td>
<td>Mar 2021</td>
<td>Aug 2021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nov 2020</td>
<td>Apr 2021</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dec 2020</td>
<td>May 2021</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increase in Breakthrough Cases

mITT Population
Incidence Rates of Breakthrough COVID-19 in Early and Later Vaccinated Groups, July – August 2021

**Study 301**

Incidence rates were higher in the group vaccinated earlier.

<table>
<thead>
<tr>
<th>Group</th>
<th>Person years</th>
<th>COVID-19 Cases / 1000 Person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2,102</td>
<td>77.1 (n=162)</td>
</tr>
<tr>
<td>18 - 64</td>
<td>1,558</td>
<td>87.3 (n=136)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>544</td>
<td>47.8 (n=26)</td>
</tr>
</tbody>
</table>

Early (13-month median follow-up) vs Later (8-month median follow-up)

Baden et al., MedRxiv, 2021

Analysis of breakthrough cases observed from July 1 to August 27, 2021, mITT population
50 μg Booster of mRNA-1273 in Previously Vaccinated Individuals

Study 201B
Rationale for Booster Dose Selection

- Goal was to use optimal effective dose for boosting
- Lower booster doses than those used for primary series of other vaccines shown to reactivate immune memory
- Lower booster dose increases worldwide vaccine supply of mRNA-1273
## Design of Booster Dose Study 201B

<table>
<thead>
<tr>
<th>N</th>
<th>Previous Dose of mRNA-1273</th>
<th>Booster Dose</th>
<th>Interval Between Dose 2 &amp; Booster Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doses 1 &amp; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>173</td>
<td>50 µg</td>
<td>50 µg</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td>171</td>
<td>100 µg</td>
<td>50 µg</td>
<td></td>
</tr>
</tbody>
</table>

**Study 201B** (boost with mRNA-1273)
## Demographic Characteristics
**Study 201B Safety Set**

<table>
<thead>
<tr>
<th></th>
<th>50 µg Booster After 100 µg Primary Series N = 171</th>
<th>50 µg Booster Pooled N = 344</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>18-64</td>
<td>78%</td>
<td>76%</td>
</tr>
<tr>
<td>≥ 65</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>61%</td>
<td>66%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Asian</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>94%</td>
<td>94%</td>
</tr>
</tbody>
</table>
Safety Data for 50 µg Booster After 100 µg Primary Series

Study 201B
Follow-up Period for Safety Data Collection

**Median 5.7 Months Safety Follow-up**

**Booster Dose**

**Active Surveillance**

- Solicited Adverse Reactions: 7 Days
- Unsolicited AEs: 28 Days
- SAEs, MAAEs, Deaths, and AEs Leading to Discontinuations
Solicited Local Adverse Reactions within 7 Days

**Study 201B 50 µg Booster Dose After 100 µg Primary Series vs Study 301**

No Grade 4 solicited local adverse reactions were reported.

Solicited safety set:
- Pain: 84% (Study 201B), 88% (Study 301)
- Erythema:
  - Grade 1: 5% (Study 201B), 5% (Study 301)
  - Grade 2: 9% (Study 201B), 12% (Study 301)
- Swelling:
  - Grade 1: 5% (Study 201B), 5% (Study 301)
  - Grade 2: 12% (Study 301)
- Axillary Swelling or Tenderness:
  - Grade 1: 20% (Study 301), 14% (Study 301)

Local reactions were generally similar for booster dose and Dose 2 of primary series.
Solicited Systemic Adverse Reactions within 7 Days

Study 201B 50 µg Booster Dose After 100 µg Primary Series vs Study 301

Grade 4 fever & nausea/vomiting occurred in < 0.1% of subjects in Study 301. No Grade 4 solicited systemic adverse reactions reported in Study 201B.

Solicited safety set

Systemic reactions were generally similar after booster dose compared to Dose 2 of primary series
**Solicited Local Adverse Reactions by Age**

**Study 201B 50 µg Booster Dose After 100 µg Primary Series**

No Grade 4 solicited local adverse reactions were reported

Solicited safety set

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pain</th>
<th>Erythema</th>
<th>Swelling</th>
<th>Axillary Swelling or Tenderness</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-64</td>
<td>86%</td>
<td>5%</td>
<td>6%</td>
<td>25%</td>
</tr>
<tr>
<td>≥ 65</td>
<td>76%</td>
<td>3%</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Most solicited AEs were mild in severity regardless of age

N = 129 38 129 38 129 38 129 38
Solicited Systemic Adverse Reactions by Age

Study 201B 50 µg Booster Dose After 100 µg Primary Series

No Grade 4 solicited systemic adverse reactions were reported

Solicited safety set

Systemic reactions were generally less frequent after a booster dose among older adults
# Unsolicited Adverse Events

## Study 201B 50 µg Booster Dose vs Study 301

<table>
<thead>
<tr>
<th></th>
<th>Participants Reporting at Least One Event, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 µg Booster After 100 µg Primary Series</td>
</tr>
<tr>
<td></td>
<td>N = 171</td>
</tr>
<tr>
<td>Medically attended AEs (MAAE)</td>
<td>41 (24%)</td>
</tr>
<tr>
<td>Vaccine-related MAAE</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Vaccine-related SAE</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event leading to study discontinuation</td>
<td>0</td>
</tr>
</tbody>
</table>

As of August 16, 2021 (median 5.7 months safety follow-up)

No vaccine-related SAEs or deaths in Study 201B to date
Immunogenicity of 50 μg Booster Dose vs Original Virus (D614G)

Study 201B
Co-primary Endpoints to Demonstrate Noninferiority of Immune Response

Study 201B vs Study 301

- Pre-specified immunogenicity endpoints based on pooled primary series groups
- Immunogenicity was compared 1-month post-booster (Study 201B) to 1-month post-dose 2 (Study 301) using neutralization assays against original virus (D614G) and Delta variant
- 2 co-primary endpoints
  - Geometric mean ratio (GMR)
    - Lower bound of the corresponding 95% CI ≥ 0.67 (non-inferiority margin of 1.5)
    - Point estimate ≥ 1
  - Difference of seroresponse rates (SRR)
    - Lower bound of the 95% CI ≥ -10%
  - Consistent with relevant FDA guidance

## Vaccine Effectiveness of 50 μg Booster Dose Inferred by Immunobridging to Study 301

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Previous Dose of mRNA-1273</th>
<th>Booster Dose</th>
<th>Interval between Dose 2 &amp; Booster Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>201B (boost with mRNA-1273)</td>
<td>146</td>
<td>50 μg</td>
<td>50 μg</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td></td>
<td>149</td>
<td>100 μg</td>
<td>50 μg</td>
<td>-</td>
</tr>
<tr>
<td>301 Immunogenicity Subset</td>
<td>1,055</td>
<td>100 μg (primary series only)</td>
<td>None</td>
<td>-</td>
</tr>
</tbody>
</table>

Per protocol set
# Geometric Mean Ratio (GMR) of Neutralization Titers

**Study 201B (Pooled) vs Study 301**

<table>
<thead>
<tr>
<th></th>
<th>Geometric Mean Titer (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 days Post Booster</td>
</tr>
<tr>
<td>Study 201B Pooled</td>
<td>Study 301</td>
</tr>
<tr>
<td>N = 295</td>
<td>N = 1,053</td>
</tr>
<tr>
<td>1,768</td>
<td>1,033</td>
</tr>
<tr>
<td>(1,586, 1,970)</td>
<td>(974, 1,095)</td>
</tr>
</tbody>
</table>

*First co-primary endpoint of GMR non-inferiority margin of 1.5 and point estimate of ≥ 1.0 met*
Geometric Mean Ratio (GMR) of Neutralization Titers

Study 201B 50 µg Booster Dose After 100 µg Primary Series vs Study 301

Co-primary endpoint of GMR non-inferiority margin of 1.5 and point estimate of ≥ 1.0 also met for 100 µg Primary Series followed by 50 µg Booster

<table>
<thead>
<tr>
<th>Geometric Mean Titer (95% CI)</th>
<th>Post Booster / Post Dose 2 GMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 201B 28 days Post 50 µg Booster after 100 µg Primary Series N = 149</td>
<td>Study 301 28 days Post Dose 2 N = 1,053</td>
</tr>
<tr>
<td>1,802 (1,548, 2,099)</td>
<td>1,027 (968, 1,089)</td>
</tr>
</tbody>
</table>

Per protocol set
Measured as pseudovirus neutralization ID$_{50}$
## Seroresponse Rates based on 3.3-Fold Definition (Prespecified Hypothesis)

### Study 201B (Pooled) vs Study 301

<table>
<thead>
<tr>
<th></th>
<th>Study 201B 50 µg Booster Pooled</th>
<th>Study 301 100 µg Primary Series</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Geometric Mean Titer (GMT)</strong></td>
<td>126</td>
<td>10</td>
</tr>
<tr>
<td><strong>GMT 28 days post dose</strong></td>
<td>1,893</td>
<td>1,081</td>
</tr>
<tr>
<td><strong>Participants achieving seroresponse, n (%)</strong></td>
<td>275 (94%)</td>
<td>1,038 (99%)</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>90.1, 96.1</td>
<td>98.0, 99.4</td>
</tr>
<tr>
<td><strong>Difference in seroresponse rate (SRR)</strong></td>
<td>-5.3</td>
<td></td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>-8.8, -2.9</td>
<td></td>
</tr>
</tbody>
</table>

**Co-primary endpoint of SRR met (lower bound of 95% CI ≥ -10%)**
Observed Seroresponse Rates Using Three Definitions

Study 201B (Pooled) vs Study 301/Study 201A (Pooled)

Regardless of definition, a ≥ 90% seroresponse rate was achieved after 50 µg booster dose in the pooled group.
### Seroresponse Rates Based on 4-Fold Rise from Pre-Booster Titers

**Study 201B 50 µg Booster after 100 µg Primary Series vs Study 301**

<table>
<thead>
<tr>
<th></th>
<th>50 µg Booster After 100 µg Primary Series</th>
<th>Study 301 100 µg Primary Series</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 149</td>
<td>N = 1,050</td>
</tr>
<tr>
<td>Baseline Geometric Mean Titer (GMT)</td>
<td>150</td>
<td>10</td>
</tr>
<tr>
<td>GMT 28 days post dose</td>
<td>1,952</td>
<td>1,081</td>
</tr>
<tr>
<td>Participants achieving seroresponse, n (%)</td>
<td>131 (88%)</td>
<td>1,033 (98%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>81.6, 92.7</td>
<td>97.4, 99.1</td>
</tr>
<tr>
<td>Difference in seroresponse rate (SRR)</td>
<td>-10.5</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-16.7, -6.1</td>
<td></td>
</tr>
</tbody>
</table>

SRR success criteria not met (lower bound of 95% CI ≥ -10%)
Titer Comparison for Subjects Who Had ≥ 4-Fold Rise vs < 4-Fold Rise after Booster Dose

Study 201B (Pooled)

Subjects who did not meet 4-fold rise had 4 times higher pre-booster titers compared to those who did meet 4-fold rise.
Older adults, who are at greater risk of complications of COVID-19, achieve high post-booster titers.
Seroresponse Rate Based on 4-Fold Rise from Pre-Booster by Age

Study 201B 50 µg Booster after 100 µg Primary Series vs Study 301

Consistently high seroresponse rate in participants 18-64 and those ≥ 65 years of age
Immune Response to Delta Variant

Study 201B
Geometric Mean Titers of Neutralization Titers Against Delta Variant

**Study 201B 50 µg Booster after 100 µg Primary Series**

Substantial increase in post-boost titers against Delta was achieved in both age groups

- **18-64**
  - N = 112
  - GMFR = 15.9
  - Pre-Booster: 55
  - 28 Days After Boost Dose: 872

- **≥ 65**
  - N = 37
  - GMFR = 22.2
  - Pre-Booster: 32
  - 28 Days After Boost Dose: 706

- **Overall**
  - N = 149
  - GMFR = 17.3
  - Pre-Booster: 48
  - 28 Days After Boost Dose: 828

GMFR = Geometric Mean Fold Rise
Seroresponse Rates to Delta Variant Based on 4-Fold Rise from Pre-Booster

*Study 201B 50 µg Booster after 100 µg Primary Series*

- 18 - 64 years: 88% (N = 112)
- ≥ 65 years: 95% (N = 37)
- Overall: 89% (N = 149)

4 weeks post booster
Summary
Safety Summary of 50 µg Booster Dose

- Rates of adverse reactions (ARs) with 50 µg booster dose comparable to those observed after Dose 2 of primary series
  - Pain at injection site most common solicited local AR in both groups
  - Headache, fatigue and myalgia most common systemic ARs in both groups
  - Majority of ARs were mild-to-moderate in severity
  - Axillary swelling or tenderness was the only AR more frequently reported after booster dose
- No vaccine-related SAEs or deaths in Study 201B
Immunogenicity Summary of 50 µg Booster Dose

- Pre-specified co-primary hypotheses (GMR & SRR difference) were met on pooled dataset
- 50 µg booster dose following 100 µg primary series results in
  - Higher antibody responses to original virus (D614G) than post-Dose 2 in Phase 3 Study 301 (GMR = 1.8)
  - 13-fold rise from pre-booster titers for original virus
  - 17-fold rise from pre-booster titers for Delta variant
- Consistently high antibody titers in both age groups (18-64 and ≥ 65)

GMR = geometric mean ratio
SRR = seroresponse rate
Proposed Use of Moderna Vaccine as a Booster

- Administration of a single 50 µg (0.25 ml) booster dose at least 6 months after completion of a primary series in:
  - Individuals 65 years of age and older;
  - Individuals 18 - 64 years of age at high risk of severe COVID-19; and
  - Individuals 18 - 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
Thank you

NIH/COVPN
Investigators and study site personnel
BARDA
Montefiori laboratory at Duke University

Most importantly, the many individuals who participated in these trials
Safety and Immunogenicity of a 50 µg Booster Dose of mRNA-1273 (Moderna COVID-19 Vaccine)

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