Vaccines and Related Biological Products Advisory Committee Meeting

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mRNA-1273.214
Moderna COVID-19 Investigational Bivalent Vaccine
(*Original + Omicron*)

Stephen Hoge, MD
President
Moderna, Inc.
Rationale for Variant-Containing Booster Vaccines

- SARS-CoV-2 variants continue to challenge public health in US and globally
- Circulating variants are antigenically distinct from the strain in current vaccines
- Current vaccine boosters increase antibody response against variants, including Omicron
  - Neutralizing antibody titers lower against variants, particularly Omicron
  - Real-world data suggest decrease in effectiveness against infection from Omicron, although effectiveness against severe disease is maintained\(^1\),\(^2\)
- Goals of variant-containing booster vaccines\(^3\),\(^4\)
  - Retain neutralization for ancestral SARS-CoV-2
  - Stronger immune response against current variants
  - Broader cross-neutralization against future variants
  - Extend durability of protection

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Modern COVID-19 Investigational Vaccine Candidates

- Extensive evaluation of 3 monovalent and 3 bivalent variant vaccines in past year
  - >4,300 participants across all vaccines
  - Studied 50 and 100 µg dose levels
- Focus today will be on bivalent candidates at 50 µg dose level

**mRNA-1273.211**
- 25 µg Ancestral SARS-CoV-2
- + 25 µg Beta Variant (B.1.351)

**mRNA-1273.214**
- 25 µg Ancestral SARS-CoV-2
- + 25 µg Omicron Variant (B.1.1.529)
Summary of Results from Prior Studies on Monovalent and Bivalent Variant-Containing Vaccines

- Monovalent Beta vaccine 50 µg elicited numerically lower neutralizing GMTs than bivalent vaccine\(^1\)-\(^3\)
  - At both 1 and 6 months
  - Against ancestral SARS-CoV-2, Beta, and Delta

- Bivalent Beta-containing vaccine (mRNA-1273.211 50 µg) elicited significantly higher neutralizing antibody response than prototype (mRNA-1273 50 µg)\(^1\)
  - At both 1 and 6 months
  - Against ancestral SARS-CoV-2, Beta, Delta, and Omicron
  - Bivalent titers more durable (Beta GMR increased at 6 months vs. 1 month)

- 50 and 100 µg dose levels evaluated for mRNA-1273 and mRNA-1273.211
  - 50 µg dose of both vaccines met all immunobridging criteria
  - 50 µg of mRNA-1273 is the currently authorized booster dose

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3. Moderna unpublished data.
### Clinical Studies with Moderna COVID-19 Investigational Bivalent Vaccine Candidates

<table>
<thead>
<tr>
<th>Bivalent Vaccine</th>
<th>Study (Part)</th>
<th>Dose</th>
<th>N</th>
<th>Median Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1273.211</td>
<td>205 (A)</td>
<td>3rd</td>
<td>300</td>
<td>245 days</td>
</tr>
<tr>
<td>mRNA-1273.214</td>
<td>205 (G)</td>
<td>4th</td>
<td>437</td>
<td>43 days</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>737</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Study (Part)</th>
<th>Dose</th>
<th>N</th>
<th>Median Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1273</td>
<td>201 (B)</td>
<td>3rd</td>
<td>171</td>
<td>176 days</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>205 (F)</td>
<td>4th</td>
<td>377</td>
<td>57 days</td>
</tr>
</tbody>
</table>

- Participants in Parts F/G previously received mRNA-1273 primary series (100 µg) and 3rd dose (50 µg)
- Parts F and G enrolled Feb 18 – Mar 23, 2022

Study 205 Objectives Aligned with Regulatory Guidance

- Pre-specified objectives for modified vaccine vs prototype
  1. Superiority of GMTs against variant of concern (VOC)
  2. Non-inferiority of seroresponse rate (SRR) against VOC
  3. Non-inferiority of GMTs and SRR against ancestral SARS-CoV-2

Hypothesis Testing Strategy for mRNA-1273.214 at Day 29

1. Non-inferiority of GMTs for Ancestral SARS-CoV-2: Yes
2. Non-inferiority of GMTs for Omicron: Yes
3. Non-inferiority of SRR for Omicron: Yes

Superiority of GMTs for Omicron

Study-level Alpha at Day 29 = 0.025

# Demographics and Baseline Characteristics

**Study 205, Safety Set**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mRNA-1273 (N = 377)</th>
<th>mRNA-1273.214 (N = 437)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years) – mean (range)</strong></td>
<td>57.5 (20, 96)</td>
<td>57.3 (20, 88)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>39.8%</td>
<td>39.8%</td>
</tr>
<tr>
<td>Female</td>
<td>50.7%</td>
<td>59.0%</td>
</tr>
<tr>
<td>Non-White Race</td>
<td>14.6%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Hispanic / Latino Ethnicity</td>
<td>9.8%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Interval between 2nd and 3rd Dose (months) – median (range)</td>
<td>8.0 (5.6, 14.4)</td>
<td>8.0 (4.7, 15.0)</td>
</tr>
<tr>
<td>Interval between 3rd and 4th Dose (months) – median (range)</td>
<td>4.4 (3.0, 10.2)</td>
<td>4.5 (2.9, 13.4)</td>
</tr>
<tr>
<td>Prior SARS-CoV-2 Infection</td>
<td>26.8%</td>
<td>22.0%</td>
</tr>
</tbody>
</table>

Local Reactogenicity After 4\textsuperscript{th} Dose of mRNA-1273.214 Similar to 2\textsuperscript{nd} Dose of Primary Series and 3\textsuperscript{rd} Dose of mRNA-1273

\textit{Study 205, Safety Set}

Solicited local adverse reactions within 7 Days after injection.
Sources: 2\textsuperscript{nd} dose mRNA-1273 (Baden et al, \textit{NEJM} 2021); 3\textsuperscript{rd} dose mRNA-1273 (Choi et al, \textit{Nat Med} 2022); 4\textsuperscript{th} dose mRNA-1273.214 (Chalkias et al. \textit{medRxiv} 2022).
Systemic Reactogenicity After 4\textsuperscript{th} Dose of mRNA-1273.214 Similar to 2\textsuperscript{nd} Dose of Primary Series and 3\textsuperscript{rd} Dose of mRNA-1273

\textit{Study 205, Safety Set}

- Fever
  - Grade 3\textsuperscript{a}
  - 16\%
  - Grade 1-2
  - 4\%

- Headache
  - Grade 3\textsuperscript{a}
  - 59\%
  - Grade 1-2
  - 55\%

- Fatigue
  - Grade 3\textsuperscript{a}
  - 65\%
  - Grade 1-2
  - 59\%

- Myalgia
  - Grade 3\textsuperscript{a}
  - 58\%
  - Grade 1-2
  - 49\%

- Arthralgia
  - Grade 3\textsuperscript{a}
  - 40\%
  - Grade 1-2
  - 43\%

- Nausea / Vomiting
  - Grade 3\textsuperscript{a}
  - 31\%

- Chills
  - Grade 3\textsuperscript{a}
  - 24\%

\textbf{Sources:} 2\textsuperscript{nd} dose mRNA-1273 (Baden et al, \textit{NEJM}, 2021); 3\textsuperscript{rd} dose mRNA-1273 (Choi et al, \textit{Nat Med}, 2022); 4\textsuperscript{th} dose mRNA-1273.214 (Chalkias et al. \textit{medRxiv}, 2022).
Omicron Neutralizing Titers After 4th Dose Significantly Higher with mRNA-1273.214 than mRNA-1273

Study 205, Per-Protocol Immunogenicity Set

**All Participants**
- 3.8-fold rise
- 7.1-fold rise

**No Prior Infection**
- 4.4-fold rise
- 8.0-fold rise

**Prior Infection**
- 2.5-fold rise
- 4.8-fold rise

### Omicron Neutralizing Antibody ID50 GMT (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Pre Boost (N)</th>
<th>Day 29 (N)</th>
<th>Pre Boost (N)</th>
<th>Day 29 (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>512 (95% CI)</td>
<td>1933</td>
<td>432 (95% CI)</td>
<td>3070</td>
</tr>
<tr>
<td>mRNA-1273.214</td>
<td>1473 (95% CI)</td>
<td>298</td>
<td>2372 (95% CI)</td>
<td>7676</td>
</tr>
</tbody>
</table>

**4th Dose**
- mRNA-1273
- mRNA-1273.214

Omicron Neutralizing Titers After 4th Dose with mRNA-1273.214 Superior to mRNA-1273

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4th Dose</th>
<th>mRNA-1273 (N = 260)</th>
<th>mRNA-1273.214 (N = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMT Pre-booster</td>
<td></td>
<td>332 (282, 391)</td>
<td>298 (259, 343)</td>
</tr>
<tr>
<td>GMT at Day 29(^1)</td>
<td></td>
<td>1421 (1283, 1574)</td>
<td>2480 (2264, 2716)</td>
</tr>
<tr>
<td>GMT Ratio(^1) (.214 vs Prototype)</td>
<td></td>
<td>1.75 (1.49, 2.04)</td>
<td></td>
</tr>
<tr>
<td>Seroresponse rate at Day 29</td>
<td></td>
<td>99.2% (97.2, 99.9)</td>
<td>100% (98.9, 100)</td>
</tr>
<tr>
<td>Difference in seroresponse rates(^2)</td>
<td></td>
<td>1.5 (-1.1, 4.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Success Criteria Met**

Superiority of GMTs: Lower 97.5% CI of GMT Ratio ≥ 1.0
Non-inferiority of Seroresponse Rates: Lower 97.5% CI of difference > -10%

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1. Based on pre-specified ANCOVA model adjusting for age group (< 65, ≥ 65 years) and pre-booster titer.
2. Common risk difference and 97.5% CI were calculated using stratified Miettinen-Nurminen method adjusting for age group.

Ancestral SARS-CoV-2 (D614G) Neutralizing Titers After 4th Dose Significantly Higher with mRNA-1273.214 than mRNA-1273

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mRNA-1273 (N = 260)</th>
<th>mRNA-1273.214 (N = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMT Pre-booster</td>
<td>1521</td>
<td>1267</td>
</tr>
<tr>
<td>95% CI</td>
<td>(1353, 1710)</td>
<td>(1120, 1432)</td>
</tr>
<tr>
<td>GMT at Day 29¹</td>
<td>5287</td>
<td>6422</td>
</tr>
<tr>
<td>95% CI</td>
<td>(4887, 5719)</td>
<td>(5990, 6886)</td>
</tr>
<tr>
<td>GMT Ratio¹ (.214 vs Prototype)</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>97.5% CI</td>
<td>(1.08, 1.37)</td>
<td></td>
</tr>
<tr>
<td>Seroresponse rate at Day 29</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>95% CI</td>
<td>(98.6, 100)</td>
<td>(98.9, 100)</td>
</tr>
<tr>
<td>Difference in seroresponse rates²</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>97.5% CI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Success Criteria Met

- Non-inferiority of GMTs: Lower 97.5% CI of GMT Ratio ≥ 0.67
- Non-inferiority of Seroresponse Rates: Lower 97.5% CI of difference > -10%

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1. Based on pre-specified ANCOVA model adjusting for age group (< 65, ≥ 65 years) and pre-booster titer.
2. Common risk difference and 97.5% CI can not be estimated between two seroresponse rates of 100%.

4th Dose of mRNA-1273.214 Delivered Higher Neutralizing Titers than mRNA-1273 Across Age Groups, Including Age >65

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection

**Ancestral SARS-CoV-2**

- **18 – < 65 years**
  - Before Boost: 1304 (ID50 GMT), 494 (95% CI)
  - Day 29: 1820
- **≥ 65 years**
  - Before Boost: 5198
  - Day 29: 7378

**Omicron**

- **18 – < 65 years**
  - Before Boost: 300 (ID50 GMT), 1235 (95% CI)
  - Day 29: 2229
- **≥ 65 years**
  - Before Boost: 373
  - Day 29: 319

**mRNA-1273.214** Delivered Higher Neutralizing Titers than **mRNA-1273** Across Age Groups, Including Age >65.
Binding Antibody Titers Against Prior VOC Are Significantly Higher with mRNA-1273.214 than mRNA-1273

Study 205, Per-Protocol Immunogenicity Set

<table>
<thead>
<tr>
<th>Variant</th>
<th>GMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>1.17</td>
<td>1.09, 1.24</td>
</tr>
<tr>
<td>Beta</td>
<td>1.14</td>
<td>1.07, 1.22</td>
</tr>
<tr>
<td>Delta</td>
<td>1.10</td>
<td>1.03, 1.16</td>
</tr>
<tr>
<td>Gamma</td>
<td>1.16</td>
<td>1.09, 1.24</td>
</tr>
</tbody>
</table>

Meso Scale Discovery (MSD) Assay. Nominal alpha = 0.05.
mRNA-1273 N = 350-351; mRNA-1273.214 N = 398-402.
Investigational Bivalent mRNA-1273.214 Vaccine Met All Regulatory Criteria for a Variant-Containing Vaccine

All pre-specified primary and key secondary objectives met:

- ✔ Superiority of GMTs and non-inferiority of SRRs for Omicron (Primary)
- ✔ Non-inferiority of GMTs for Ancestral SARS-CoV-2 (Primary)
- ✔ Non-inferiority of SRRs for Ancestral SARS-CoV-2 (Key Secondary)
- ✔ Safety and tolerability profile consistent with mRNA-1273 booster
Role of mRNA-1273.214 in Addressing Emerging Variants
Predominant SARS-CoV-2 Strains in the US Have Changed During Different Periods of the COVID-19 Pandemic

https://covid.cdc.gov/covid-data-tracker/
4th Dose of Bivalent mRNA-1273.214 Increases Omicron (BA.1) Neutralizing Titers

1 Month After 3rd Dose of mRNA-1273
Among Participants with No Prior Infection

- Omicron Neutralizing Antibody ID50 GMT (95% CI)
- (N = 147)

1 Month After 4th Dose of mRNA-1273.214
Among Participants with No Prior Infection

- (N = 334)

Omicron Subvariants Continue to Emerge

Daily New Cases of SARS-CoV-2 Infection in US

% of Viral Lineages Among Infections

https://covid.cdc.gov/covid-data-tracker/
4th Dose of mRNA-1273.214 Increased BA.4/BA.5 Neutralizing Titers Regardless of Prior SARS-CoV-2 Infection

Study 205, Per-Protocol Immunogenicity Set

<table>
<thead>
<tr>
<th></th>
<th>4th Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Participants (N = 428)</td>
</tr>
<tr>
<td>Pre-Booster GMT (95% CI)</td>
<td>173 (147, 202)</td>
</tr>
<tr>
<td>Observed GMTs at Day 29 (95% CI)</td>
<td>941 (826, 1071)</td>
</tr>
<tr>
<td>Geometric Mean Fold Rise at Day 29 (95% CI)</td>
<td>5.44 (5.01, 5.92)</td>
</tr>
</tbody>
</table>

BA.4/BA.5 assay conducted at Duke/VRC (research grade, validation underway).

4th Dose of mRNA-1273.214 Increased BA.4/BA.5 Neutralizing Titers Regardless of Prior SARS-CoV-2 Infection or Age

Study 205, Per-Protocol Immunogenicity Set

BA.4/BA.5 assay conducted at Duke/VRC (research grade, validation underway).
4th Dose of mRNA-1273.214 Increased BA.4/BA.5 Neutralizing Titers to Levels Observed Against Delta and Omicron After 3rd Dose of mRNA-1273

1 Month After 3rd Dose of mRNA-12731
Among Participants with No Prior Infection

- Delta
  - Day 29: 828

- Omicron
  - Day 29: 629

1 Month After 4th Dose of mRNA-1273.2142
Among Participants with No Prior Infection

- Omicron BA.4/BA.5
  - Pre Boost: 116
  - Day 29: 727

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3rd Dose of mRNA-1273 Increased Real-World Effectiveness Against Delta and Omicron

*Kaiser Permanente Study*

Effectiveness Against Infection After 2 or 3 Doses of mRNA-1273

<table>
<thead>
<tr>
<th></th>
<th>Delta</th>
<th>Omicron</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Doses Adjusted VE (95% CI)</td>
<td>64% ± 1%</td>
<td>14% ± 1%</td>
</tr>
<tr>
<td>3 Doses Adjusted VE (95% CI)</td>
<td>95% ± 1%</td>
<td>70% ± 1%</td>
</tr>
</tbody>
</table>

Effectiveness Against Hospitalization After 2 or 3 Doses of mRNA-1273

<table>
<thead>
<tr>
<th></th>
<th>Delta</th>
<th>Omicron</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Doses Adjusted VE (95% CI)</td>
<td>99% ± 1%</td>
<td>85% ± 1%</td>
</tr>
<tr>
<td>3 Doses Adjusted VE (95% CI)</td>
<td>100% ± 1%</td>
<td>99% ± 1%</td>
</tr>
</tbody>
</table>

1. 3-dose regimen excludes immunocompromised. Follow-up time for 2-doses >270 days, 3-doses >60 days.

Upcoming Data and Plans for mRNA-1273.214
Additional Data Collection Ongoing for mRNA-1273.214

- Immunogenicity for BA.4/BA.5 after 4th dose of mRNA-1273 to provide comparator for mRNA-1273.214
- Durability of immune response with mRNA-1273.214 at 3 and 6 months after the 4th dose
- mRNA-1273.214 in infants and children, 6 months – 5 years of age
  - Primary series study ongoing
  - Booster study ongoing
- Continued safety follow-up of mRNA-1273.214 booster recipients
mRNA-1273.214 Has the Potential to Provide Improved Protection Against COVID-19

- Met pre-specified primary and key secondary objectives
  - Superior neutralizing titers against Omicron
  - Significantly higher neutralizing titers against ancestral strain
  - Favorable safety and tolerability profile
- Significantly higher binding antibodies against Alpha, Beta, Gamma, and Delta
- Robust neutralizing titers against BA.4/BA.5, including adults ≥ 65
- More durable antibody responses demonstrated with bivalent platform

Regulatory submissions completed within next 2 weeks
Pending authorization, vaccine available in late July / early August
THANK YOU to Our Study Collaborators, Investigators, and Participants

• All investigators
• Study site personnel
• Most importantly, the individuals who participated in these trials
mRNA-1273.214
Moderna COVID-19 Investigational Bivalent Vaccine
(Original + Omicron)

Moderna, Inc.
Vaccines and Related Biological Products Advisory Committee
June 28, 2022