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

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.
DMID 21-0012 - Heterologous Platform Boost Study

Mix and Match

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

Kirsten E. Lyke, MD representing Mix and Match Study Team
University of Maryland, School of Medicine
Center for Vaccine Development and Global Health
Disclosures:

The speaker has received funding as co-Principal Investigator for Phase I studies involving the Pfizer COVID-19 vaccine. Additionally, the speaker receives grant funding from NIAID/IDCRC as co-Chair and site PI for the MixNMatch and as an investigator on the Moderna and Novavax Phase III studies.
3 vaccines are available under EUA in US

Key decisions to be made on late boost
   If boost needed?
   Whom to boost?
   When to administer boost?
   What to boost with?

The data needed to make these decisions include:
   Correlates of protection
   Longevity of antibody response after primary vaccination
   Emergence of variants
   Breakthrough infections
   Safety and immunogenicity of boost – primarily homologous boost trials by companies

Understand how to use current vaccines to be used as a boost
   Can one vaccine be used as a boost to a different vaccine?
   Is it safe to mix vaccines?
   What happens to the immune response after booster vaccination?
Study Design

Volunteers received EUA/approved Covid-19 vaccine

- At least 12 weeks since the last vaccine dose
  - Timing driven by need to have data available for the fall
- Approximately 50 participants per group (primary vaccine + booster)
  - Sample size: ~25/age strata -18-55 years of age; ≥ 56 years of age
    - 99.5% probability of observing at least one AE with a true event rate of 10%
    - 63.6% probability of observing at least one AE with a true event rate of 2%
- Designed to inform public health decisions
  - Not powered or designed to compare between the groups
<table>
<thead>
<tr>
<th>Group</th>
<th>Sample Size*</th>
<th>EUA Vaccine</th>
<th>Interval (weeks)</th>
<th>Delayed Booster Vaccination</th>
<th>Strategy Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Previously dosed Janssen – Ad26.COV2-S</td>
<td>≥12</td>
<td>Moderna- mRNA-1273</td>
<td>Same Strain, Heterologous platform</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Previously dosed Moderna – mRNA-1273</td>
<td>≥12</td>
<td>Moderna- mRNA-1273</td>
<td>Control - Same Strain &amp; platform</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Previously dosed Pfizer/BioNTech –BNT162b2</td>
<td>≥12</td>
<td>Moderna- mRNA-1273</td>
<td>Same Strain, Similar platform</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Previously dosed Janssen – Ad26.COV2-S</td>
<td>≥12</td>
<td>Janssen – Ad26.COV2.S</td>
<td>Control - Same Strain &amp; platform</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Previously dosed Moderna – mRNA-1273</td>
<td>≥12</td>
<td>Janssen – Ad26.COV2.S</td>
<td>Same Strain, Heterologous platform</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>Previously dosed Janssen – Ad26.COV2-S</td>
<td>≥12</td>
<td>Pfizer/BioNTech – BNT162b2</td>
<td>Same Strain, Heterologous platform</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>Previously dosed Moderna – mRNA-1273</td>
<td>≥12</td>
<td>Pfizer/BioNTech- BNT162b2</td>
<td>Same Strain, Similar platform</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>Previously dosed Pfizer/BioNTech –BNT162b2</td>
<td>≥12</td>
<td>Pfizer/BioNTech – BNT162b2</td>
<td>Control - Same Strain &amp; platform</td>
</tr>
</tbody>
</table>

Study Visits: Days 1, 8 (call), 15, 29, Months 3, 6, 12

Lyke et al. VRBPAC Oct 14-15, 2021
Volunteer Characteristics
N = 458

2 Participants
- Group 4 (n = 1)
- Group 6 (n = 1)
- High N protein antibody (D1) suggestive of prior infection

1 Participant
- Group 5 (n = 1)
- Covid-19 Study Day 27

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

Lyke et al. VRBPAC Oct 14-15, 2021
<table>
<thead>
<tr>
<th>Time from Vaccination to Boost (Weeks)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen 18-55</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>25th, 75th %tile</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>mRNA-1273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen 18-55</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Median</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ad26.COV2-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen 18-55</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>25th, 75th %tile</td>
</tr>
</tbody>
</table>

Increasing interval with sequential, staged recruitment
Immunogenicity
Summary of Available Immunogenicity through D15/D29

Duke (Montefiori Lab): PsVN (ID50, ID80 and in IU$_{50}$/mL, IU$_{80}$/mL)
- D614G  N=~450 (50/arm)
- VoCs N=60, 20/arm, 10/age group
  - Beta, Delta - In process

VRC (McDermott Lab): IgG Antibody Binding
- 4-plex (validated) (AU/mL)
  - S-2P (Wa-1 and Beta) N=~450 (~50/arm) (AU/mL)
    - S-2P Wa-1: Binding Antibody Units/mL (BAU/mL) (International Standard)
- 10-plex Fit for Purpose (FFP)
  - S-2P (Alpha, Beta, Gamma, Delta, Wa-1) (AUC/m)
Moderna mRNA-1273 Booster Vaccination with 100 mcg
IgG Serum Binding Antibody Response to S-2P-Wa-1 Antigen by 4-plex ECLIA V.2, by Group, Age and Timepoint: mRNA-1273 Booster Vaccination – through Day 29

Study Day

N=52

N=50

N=50
Pseudovirus Neutralization Antibody Titers to Spike D614G through D29 post-mRNA-1273 Boost (100 mcg)

EUA Primary Vaccination(s)

<table>
<thead>
<tr>
<th>EUA Vaccine</th>
<th>Nab Titer (ID50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26.COV2.S</td>
<td>2794 x76 1784 x45</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>3727 x10 2893 x7.5</td>
</tr>
<tr>
<td>BNT162b2</td>
<td>3247 x32 2048 x21</td>
</tr>
</tbody>
</table>

GMFR
GMT
GM IU50/mL

ID50

Group 1E: By Age Group
Group 2E: By Age Group
Group 3E: By Age Group

Age Group: 18-55 years old 56+ years old

N=52 N=50 N=50

IU50/mL = ID50 x 0.242

Lyke et al. VRBPAC Oct 14-15, 2021
Janssen Ad26.COV2.S Booster Vaccination with $5 \times 10^{10}$ vp
IgG Serum Binding Antibody Response to S-2P-Wa-1 Antigen by 4-plex ECLIA V.2, by Group, Age Group and Timepoint: Ad26.COV2.S Booster Vaccination – through Day 29

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Ad26.COV2.S</th>
<th>mRNA-1273</th>
<th>BNT162b2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.6 x10^4, 326</td>
<td>3.4 x10^5, 3029</td>
<td>2.1 x10^5, 1905</td>
</tr>
<tr>
<td>15</td>
<td>4.1 x10^4, 369</td>
<td>5.1 x10^5, 4560</td>
<td>2.9 x10^5, 2600</td>
</tr>
<tr>
<td>29</td>
<td>7.1 x10^4, 639</td>
<td>1.5 x10^6, 3690</td>
<td>3.6 x10^5, 320</td>
</tr>
</tbody>
</table>

**GMFR**

**GMT**

**GM: BAU/mL**

**Group 4E: By Age Group**

- **Group 5E: By Age Group**
- **Group 6E: By Age Group**

**Age Group:**
- 18-55 years old
- 56+ years old

**Study Day**

- N=50
- N=49
- N=51

Lyke et al. VRBPAC Oct 14-15, 2021
Pseudovirus Neutralization Antibody Titers to Spike D614G through 14 days post-Ad26.COV2.S Boost by Group (top) and Age (bottom), and Timepoint

**EUA Primary Vaccination(s)**

<table>
<thead>
<tr>
<th></th>
<th>Ad26.COV2.S</th>
<th>mRNA-1273</th>
<th>BNT162b2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nab Titer (ID50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 15</td>
<td>x4.1</td>
<td>x6.2</td>
<td>x12.5</td>
</tr>
<tr>
<td>1000 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=50 N=49 N=51</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GMFR**

**GMT**

**GM IU50/mL**

**IU50/mL = ID50 x 0.242**

Lyke et al. VRBPAC Oct 14-15, 2021
Pfizer/BioNTech Booster Vaccination with 30 mcg
IgG Serum Binding Antibody Response to S-2P-Wa-1 Antigen by 4-plex ECLIA V.2, by Group, Age Group and Timepoint: BNT162b2 Booster Vaccination – Day 15

Lyke et al. VRBPAC Oct 14-15, 2021
Pseudovirus Neutralization Antibody Titers to Spike D614G through 14 days post BNT162b2 Boost by Group (top) and Age (bottom), and Timepoint

**EUA Primary Vaccination(s)**

<table>
<thead>
<tr>
<th>Age Group: EUA Primary Vaccination(s)</th>
<th>Study Day</th>
<th>Nab Titer (ID50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26.COV2.S</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>15</td>
<td>341</td>
</tr>
<tr>
<td>BNT162b2</td>
<td>1</td>
<td>238</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>678</td>
</tr>
</tbody>
</table>

**ID50**

<table>
<thead>
<tr>
<th>Group 7E: By Age Group</th>
<th>Group 8E: By Age Group</th>
<th>Group 9E: By Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=53</td>
<td>N=51</td>
<td>N=50</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Nab Titer (ID50)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>100000</td>
<td>100000</td>
<td>100000</td>
</tr>
<tr>
<td>10000</td>
<td>10000</td>
<td>10000</td>
</tr>
<tr>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

IU50/mL = ID50 x 0.242

Lyke et al. VRBPAC Oct 14-15, 2021
All Three Booster Vaccines
Pseudovirus Neutralization Antibody Titers to Spike D614G through 14 days post- mRNA-1273, Ad26.COV2.S and BNT162b2 Booster Vaccination by Group and Timepoint

EUA Primary Vaccination(s)

- **Ad26.COV2.S**
  - Group 3E: Overall
  - Group 2E: Overall
  - Group 1E: Overall

- **mRNA-1273**
  - Group 9E: Overall
  - Group 8E: Overall
  - Group 7E: Overall

- **BNT162b2**
  - Group 6E: Overall
  - Group 5E: Overall
  - Group 4E: Overall

**IU50/mL** = **ID50** x 0.242

**GMFR**
- **GMT**
- **GM IU50/mL**
Immunogenicity of all three boosters - IgG binding Antibody and Neutralizing Antibody - Day 15/29

Lyke et al. VRBPAC Oct 14-15, 2021
Immunogenicity — Variants of Concern
IgG Serum Binding Antibody Response to S-2P-Wa-1 (control), B.1.1.7 (alpha), and B.1.617.2 (delta) FFP 10-plex ECLIA, by Group and Timepoint - Results are reported as Area Under Curve (AUC) mRNA-1273 Booster Vaccination
IgG Serum Binding Antibody Response to S-2P-Wa-1 (control), B.1.1.7 (alpha), and B.1.617.2 (delta) FFP 10-plex ECLIA, by Group and Timepoint - Results are reported as Area Under Curve (AUC) Ad26.COV2.S Booster Vaccination

Antigen:
- S-2P-WT
- S2-P-B.1.1.7
- S2-P-B.1.617.2
IgG Serum Binding Antibody Response to S-2P-Wa-1 (control), B.1.1.7 (alpha), and B.1.617.2 (delta) FFP 10-plex ECLIA, by Group and Timepoint - Results are reported as Area Under Curve (AUC) BNT162b2 Booster Vaccination.

Antigen:
- S-2P-WT
- S2-P-B.1.1.7
- S2-P-B.1.617.2
All 3 vaccines

IgG Serum Binding Antibody Response to S-2P-Wa-1 (control), B.1.1.7 (alpha), and B.1.617.2 (delta)

FFP 10-plex ECLIA, by Group and Timepoint
Results are reported as Area Under Curve (AUC)
Safety
• Two SAEs
  1. Acute renal failure due to rhabdomyolysis from a fall - Unrelated
     30 days after mRNA-1273 vaccination
  2. Acute cholecystitis - Unrelated
     24 days after Ad26.COV2.S vaccination.

• No pre-specified study-halting rules were met
• No new onset chronic medical conditions occurred (through study D29)
• One related AESI
  • Severe vomiting that led to a medically attended visit the day after
    vaccination: Ad26.COV2.S boost
Unsolicited AEs (deemed related to boost) of any severity grade

- mRNA-1273: 24/154 (15.6%)
- Ad26.COV2.S: 18/150 (12.0%)
- BNT162b2: 22/154 (14.3%)

Most related AEs were Grade 1 or 2 severity

Four related Grade 3 AEs:
- Vomiting in one participant - mRNA-1273 booster group
- Vomiting in one participant - Ad26.COV2.S booster group
- Fatigue in one participant - Ad26.COV2.S booster group
- Insomnia in one participant - Ad26.COV2.S booster group
Booster Solicited AEs

Local and Systemic Reactogenicity – Day 8
Limitations -

- Non-randomized, open label design
- Study not designed to compare between boosts
  - Didn’t control for intervals between primary vaccine and boosts
- Correlates of protection are not completely elucidated.
- Correlates for severe disease and death are even less well understood.
- This is only antibody data.
  - Cellular immune responses are still being analyzed
- These data represent only early timepoints from the trial
  - Vaccines may differ in time to reach peak responses, and may have different durability of the responses
Conclusions -

1. Use of mRNA-1273, Ad26.COV2.S and BNT162b2 as booster vaccines led to anamnestic serologic responses in all 3 EUA-dose vaccine groups

2. For a given primary EUA Covid-19 vaccine, heterologous boosts elicited similar or higher serologic responses as compared to their respective homologous booster responses

3. mRNA vaccines resulted in higher antibody titers in the first 28 days after the boost

4. No safety concerns identified
The “MixNMatch” Study Team

Clinical Sites
- Kaiser Permanente
- Washington Health Research Institute
- Fred Hutch / SCHARP
- The University of Washington
- Cincinnati Children’s Hospital
- University of Pittsburgh
- University of Rochester
- New York University
- University of Maryland
- VRC
- Duke University
- Emory University

Labs
- NIH

Regulatory, Data and Statistical Centers
- Moderna, Inc., Johnson&Johnson/Janssen, Pfizer/BioNTech

University of Texas Medical Branch
Questions?