EMA/137482/2022
Committee for Medicinal Products for Human Use (CHMP)

# Type II variation assessment report

Procedure No. EMEA/H/C/005791/II/0042

Invented name: Spikevax

International non-proprietary name: elasomeran

Marketing authorisation holder (MAH): Moderna Biotech Spain, S.L.

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted and personal data anonymised.

| Status of this report and steps taken for the assessment | | | |
|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** |
| ☐ | Start of procedure | 01 Dec 2021 | 01 Dec 2021 |
| ☐ | CHMP Rapporteur Assessment Report | 06 Dec 2021 | 08 Dec 2021 |
| ☐ | CHMP members comments | 09 Dec 2021 | 09 Dec 2021 |
| ☐ | ETF discussion | 10 Dec 2021 | 09 Dec 2021 |
| ☐ | Updated CHMP Rapporteur Assessment Report | 13 Dec 2021 | 15 Dec 2021 |
| ☐ | Restart | 22 Dec 2021 | 22 Dec 2021 |
| ☐ | CHMP Rapporteur Assessment Report | 17 Jan 2022 | 17 Jan 2022 |
| | CHMP members comments | 19 Jan 2022 | 19 Jan 2022 |
| ☐ | ETF discussion | 20 Jan 2022 | 20 Jan 2022 |
| ☐ | Updated CHMP Rapporteur Assessment Report | 21 Jan 2022 | 27 Jan 2022 |
| ☐ | Request for supplementary information | 27 Jan 2022 | 27 Jan 2022 |
| ☐ | Submission of responses | 04 Feb 2022 | 03 Feb 2022 |
| ☐ | Restart | 07 Feb 2022 | 07 Feb 2022 |
| ☐ | CHMP Rapporteur AR to be circulated to all CHMP members, ETF and EMA | 14 Feb 2022 | 14 Feb 2022 |
| ☐ | CHMP members comments | 16 Feb 2022 | 16 Feb 2022 |
| ☐ | ETF meeting | 18 Feb 2022 | 18 Feb 2022 |
| ☐ | Updated CHMP Rapporteur Assessment Report | 18 Feb 2022 | 18 Feb 2022 |
| ☒ | CHMP Opinion | 24 Feb 2022 | 24 Feb 2022 |

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# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain, S.L. submitted to the European Medicines Agency on 15 November 2021 an application for a variation for Spikevax (also referred to as COVID-19 Vaccine Moderna or mRNA-1273).

The following changes were proposed:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I |

Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to include information on heterologous boosting using a 50 ug dose of Spikevax to boost subjects that have previously completed a primary vaccination series with any authorised COVID-19 vaccine, based on data from the DMID Study 21-0012, a Phase 1/2 heterologous SARS-CoV-2 vaccine dosing (mRNA-1273 booster) study of the various vaccines authorized in the US under Emergency Use Authorisation in participants ≥ 18 years old (NCT04889209). In addition, the MAH took the opportunity to make minor editorial changes/corrections throughout the product information.

The requested variation proposed amendments to the Summary of Product Characteristics.

# 2. Introduction

**DMID Study 21-0012**

DMID Study 21-0012 is a Phase 1/2 heterologous SARS-CoV-2 vaccine dosing (mRNA-1273 booster) study of the several COVID-19 vaccines with a FDA Emergency Use Authorisation (EUA):

- COVID-19 Vaccine Janssen (Ad26.COV2.S) manufactured by Janssen Pharmaceuticals/Johnson & Johnson), ChAd
- Spikevax (mRNA-1273, manufactured by Moderna), m1273
- Comirnaty (mRNA-BNT162b2) manufactured by Pfizer/BioNTech, BNT

in participants ≥ 18 years old (NCT04889209; data snapshot: 8th July 2021, report date 15th July 2021). A total of 154 participants have been enrolled and received a Spikevax boost injection (IM; 100 µg) approximately 12-20 weeks after receiving primary vaccination.

The anticipated sample size of each group is approximately 25 subjects 18 through 55 years of age and approximately 25 subjects 56 years of age and older for a total of 50 subjects per group. A summary of the groups included in this report is shown in Table I.

Table I. Summary of Groups in Cohort 1 that are included in this report

| Group | Targeted Sample Size | EUA-Dosed Vaccination | Booster Vaccination | Strategy evaluated |
|---|---|---|---|---|
| 1E | ~50 | Janssen – Ad26.COV.2.S at $5x10^{10}$ vp | 100 mcg mRNA-1273 | Evaluates a heterologous platform booster dose of mRNA-1273 among persons who previously received an Ad26.COV2.S EUA vaccination series |
| 2E | ~50 | mRNA-1273 at 100 mcg for two doses | 100 mcg mRNA-1273 | As a bridging arm evaluates a homologous platform third boosting dose of mRNA-1273 among persons who previously received a mRNA-1273 EUA vaccination series |
| 3E | ~50 | Pfizer/BioNTech - mRNA-BNT162b2 at 30 mcg for two doses | 100 mcg mRNA-1273 | Evaluates a homologous mRNA platform of mRNA-1273 booster dose among persons who previously received a mRNA-BNT162b2 EUA vaccination series |

# 3. Clinical Efficacy aspects

## *3.1. Methods – analysis of data submitted*

### 3.1.1. Disposition

As of the data snapshot date, a total of 154 participants have been enrolled into Cohort 1 and received the Spikevax booster: 53 participants in Group 1E (EUA Dosed COVID-19 Vaccine Janssen), 51 participants in Group 2E (EUA Dosed Spikevax), and 50 participants in Group 3E (EUA Dosed Comirnaty). All 154 enrolled participants received the study boost vaccination and have remained in the study.

### 3.1.2. 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.

### 3.1.3. Protocol Deviations

Table 11 below shows protocol deviations reported in this study for Groups 1E, 2E and 3E in Cohort 1. A total of 46 protocol deviations have been reported (14, 17 and 15 in Groups 1E, 2E and 3E, respectively).

**Table 11 - Protocol Deviations by Type and Group**

| | Group 1E Dosed Janssen Boost Moderna (N=53) | Group 2E Dosed Moderna Boost Moderna (N=51) | Group 3E Dosed Pfizer/BioNTech Boost Moderna (N=50) | Total (N=154) |
|---|---|---|---|---|
| Number of Protocol Deviations | 14 | 17 | 15 | 46 |
| Type of Protocol Deviations and Enrollment Violations | | | | |
| Inappropriate enrollment | 0 | 0 | 0 | 0 |
| Failure to follow randomization or blinding procedures | 0 | 0 | 0 | 0 |
| Study product management deviation | 0 | 0 | 0 | 0 |
| Study product dispensing error | 0 | 0 | 0 | 0 |
| Study product use/non-use deviation | 0 | 0 | 0 | 0 |
| Conduct of non-protocol procedure | 14 | 14 | 13 | 41 |
| Improper AE/SAE | 0 | 0 | 0 | 0 |
| Unreported AE | 0 | 0 | 0 | 0 |
| Unreported SAE/AESI | 0 | 0 | 0 | 0 |
| Breach of confidentiality | 0 | 0 | 0 | 0 |
| Physical assessment deviation | 0 | 1 | 0 | 1 |
| Lab assessment deviation | 0 | 0 | 0 | 0 |
| Mishandled lab specimen | 0 | 0 | 0 | 0 |
| Staff performing duties that they are not qualified to perform | 0 | 0 | 0 | 0 |
| Use of non-IRB/EC-approved materials | 0 | 0 | 0 | 0 |
| Use of excluded concomitant mediations, devices, or non-study products | 0 | 0 | 0 | 0 |
| Informed consent process deviation | 0 | 0 | 0 | 0 |
| Visit completed outside of window | 0 | 2 | 1 | 3 |
| Other | 0 | 0 | 1 | 1 |

**Assessment of MAH's responses**

In a study, which enrolled 154 subjects, protocol deviations were reported by 41 subjects. This protocol deviations concerning "conduct of non-protocol procedures" included either mishandled lab specimen or that the study staff did not collect the memory aid data during the Day 8 safety call. More than 20 % of enrolled subjects did not reported correctly their safety data or the blood draws were not properly handled. The MAH stated that the amount of protocol violations did not have an impact on immunogenicity data nor on the safety data base.

## 3.1.4. Endpoints

The endpoint reported here is the SARS-CoV-2-specific neutralising activity of antibodies in serum. Neutralising antibodies were assessed with Spike-pseudotyped viruses in 293T/ACE2 cells as a function of reductions in luciferase (Luc) reporter activity. Neutralisation titers are the serum dilution at which relative luminescence units (RLU) are reduced by either 50% (ID50) or 80% (ID80) compared to virus control wells after subtraction of background RLUs.

Neutralisation of SARS-CoV-2 Spike-pseudotyped viruses was assessed in 293T/ACE2 cells as described in SOP "CFAR02-A0026 Measuring Neutralizing Antibodies Against SARS-CoV-2 Using Pseudotyped Virus and 293T/ACE2 Cells." This assay has been formally validated and is part of Drug Master File # 26862 with the Federal Drug Administration. Assay validation was performed with human serum samples and monoclonal antibodies using the D614G form of the Wuhan-1 Spike. This assay is in the process of being validated for B.1.351, but has not been validated using B.1.617.2. The assay is performed in 96-well flat-bottom clear standard non-coated or Poly-L-Lysine treated culture plates for high throughput capacity. Relative luminescence units are measured in 96-well flat bottom black/white plates for enhanced luminescence with minimal bleed-over. Use of a clonal cell line provided enhanced precision and uniformity.

SARS-CoV-2 Spike-pseudotyped viruses are prepared and titrated for infectivity by using mutated forms of an expression plasmid encoding codon-optimised full-length Spike of the Wuhan-1 strain (VRC7480) provided by collaborators at the Vaccine Research Center, National Institutes of Health (USA).

**Assessment of MAH's responses**

The used assays for the determination of neutralising antibodies are the same in the DMID trial and the MAH conducted trials.

### 3.1.5. Reporting

The assay's lower limit of detection (LLOD) is 10. For descriptive analyses, values reported as below the LLOD are assigned a value of LLOD/2 = 5. Specific to Pseudovirus D614G, the lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) are as follows:

| ID50 | ID80 |
|---|---|
| LLOQ = 18.5 | LLOQ = 14.3 |
| ULOQ = 45118 | ULOQ = 10232 |

Levels that are reported as above the LLOD but below the Lower Limit of Quantification (LLOQ) are kept as reported. Values that are greater than the upper limit of quantification (ULOQ) are when actual values are provided. If actual values above the ULOQ are not provided, observations are replaced with a value equivalent to the ULOQ.

Selected summaries of neutralising titers calibrated to the WHO standard International Units (IU50 and IU80), are presented. Conversion was done using calibration factors specifically for the SARS-CoV-2 D614G Pseudovirus: a factor of 0.242 for ID50 and a factor of 1.502 for ID80.

### 3.1.6. Participants cohort

The study enrolled a total of 154 participants in Groups 1E, 2E and 3E of Cohort 1 (53, 51 and 50 participants, respectively). From these participants, 152 serum samples from Day 1 and from day 15 visits (52, 50 and 50 in each of the groups) were assayed for the Spike-pseudotyped virus SARS-CoV-2 D614G. Up to the writing of this report, 134 samples from Day 29 visit (43, 48 and 43 in each of the groups) have been assayed for the Spike-pseudotyped virus SARS-CoV-2 D614G.

For a subset of 60 participants (20 per Group, with 10 in each Age group), samples were selected to be tested with the Spike-pseudotyped virus SARS-CoV-2 B.1.617.2 (Delta variant) and the Spike-pseudotyped virus SARS-CoV-2 B.1.351 (Beta variant). This subset of 60 participants is a random subsample of the original 3-Group cohort, stratified by Group and Age Group, while allowing for replacements to ensure representation from sites with low enrolment and adequate availability of PBMC samples of the participants selected.

## *3.2. Immunogenicity Results*

Tables 1a-1d show descriptive summaries of the ID50 and ID80 neutralisation titers against Pseudovirus D614G, including the Geometric Mean Titer (GMT) with 95% CIs, by visit day and boost group. For timepoints after Day 15, the proportion of participants with a 2-fold or a 4-fold increase in ID50 and ID80 neutralisation titers, relative to baseline, is presented along with the Geometric Mean Fold Ratio (with 95% CIs). The distribution of ID50 and ID80 neutralisation titers against Pseudovirus D614G, is presented in Figures 1a and 1b.

Table 1a:

**DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1**
**Immunogenicity Endpoint Report - September 16, 2021**
**SARS-CoV-2 Pseudovirion Neutralization Assay**
**Table 1a - Neutralization Antibodies Titer (ID50) to Pseudovirus D614G[1], by Group and Timepoint - Groups 1E - 3E**

| | Group 1E [Dosed Janssen, Boost Moderna] (N=53) | Group 2E [Dosed Moderna, Boost Moderna] (N=51) | Group 3E [Dosed Pfizer, Boost Moderna] (N=50) |
|---|---|---|---|
| **Day 1 Visit (Pre-boost)** | | | |
| N (non-missing) | 52 | 50 | 50 |
| Median ($P_{25}$, $P_{75}$) | 34.30 (15.89-66.83) | 341.31 (176.25-746.61) | 118.50 (60.11-161.87) |
| Minimum - Maximum | 5.00-6566.30 | 40.88-4851.22 | 5.00-2794.06 |
| Geometric Mean (95% CI) | 36.81 (25.58-52.96) | 366.31 (280.09-479.06) | 102.44 (74.23-141.38) |
| **Day 15 Visit (14 days post-boost)** | | | |
| N (non-missing) | 52 | 50 | 50 |
| Median ($P_{25}$, $P_{75}$) | 3268.82 (1094.40-5018.44) | 3582.81 (2620.92-4437.34) | 3550.70 (1817.21-4840.33) |
| Minimum - Maximum | 563.83-29781.84 | 686.48-27221.54 | 489.42-22439.32 |
| Geometric Mean (95% CI) | 2793.90 (2138.57-3650.03) | 3726.50 (3006.38-4619.12) | 3246.95 (2464.58-4277.67) |
| N* (non-missing pre- and post-boost) | 52 | 50 | 50 |
| Participants with ≥ 2-fold rise[2], 95% CI | 100.0% (93.2%-100.0%) | 96.0% (86.3%-99.5%) | 100.0% (92.9%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 100.0% (93.2%-100.0%) | 86.0% (73.3%-94.2%) | 100.0% (92.9%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 75.91 (54.99-104.78) | 10.17 (8.05-12.85) | 31.69 (23.80-42.21) |
| **Day 29 Visit (28 days post-boost)** | | | |
| N (non-missing) | 43 | 48 | 43 |
| Median ($P_{25}$, $P_{75}$) | 2073.19 (826.88-3293.42) | 2999.98 (1725.22-4305.19) | 2173.20 (833.78-4713.91) |
| Minimum - Maximum | 203.86-13181.15 | 492.07-15673.64 | 354.88-10763.42 |
| Geometric Mean (95% CI) | 1783.68 (1333.00-2386.74) | 2892.62 (2349.52-3561.26) | 2048.44 (1530.54-2741.59) |
| N* (non-missing pre- and post-boost) | 42 | 47 | 43 |
| Participants with ≥ 2-fold rise[2], 95% CI | 97.6% (87.4%-99.9%) | 95.7% (85.5%-99.5%) | 100.0% (91.8%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 92.9% (80.5%-98.5%) | 80.9% (66.7%-90.9%) | 100.0% (91.8%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 45.06 (29.36-69.14) | 7.46 (5.92-9.39) | 20.94 (15.36-28.55) |

Table 1b

**DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1**
**Immunogenicity Endpoint Report - September 16, 2021**
**SARS-CoV-2 Pseudovirion Neutralization Assay**
**Table 1b - Neutralization Antibodies Titer (ID50) to Pseudovirus D614G[1], by Group, Age Group, and Timepoint - Groups 1E - 3E**

| | Group 1E [Dosed Janssen, Boost Moderna] Age 18-55 yo (N=21) | Group 1E [Dosed Janssen, Boost Moderna] Age ≥56 yo (N=32) | Group 2E [Dosed Moderna, Boost Moderna] Age 18-55 yo (N=26) | Group 2E [Dosed Moderna, Boost Moderna] Age ≥56 yo (N=25) | Group 3E [Dosed Pfizer, Boost Moderna] Age 18-55 yo (N=25) | Group 3E [Dosed Pfizer, Boost Moderna] Age ≥56 yo (N=25) |
|---|---|---|---|---|---|---|
| **Day 1 Visit (Pre-boost)** | | | | | | |
| N (non-missing) | 21 | 31 | 26 | 24 | 25 | 25 |
| Median ($P_{25}$, $P_{75}$) | 34.21 (14.01-70.53) | 34.94 (16.44-65.31) | 357.54 (176.25-758.00) | 333.39 (159.29-705.12) | 131.25 (84.72-175.40) | 80.34 (42.99-156.61) |
| Minimum - Maximum | 5.00-6566.30 | 5.00-548.18 | 104.33-4851.22 | 40.88-1614.17 | 5.00-2794.06 | 5.00-1091.12 |
| Geometric Mean (95% CI) | 38.55 (17.92-82.94) | 35.67 (24.66-51.60) | 381.82 (265.23-549.68) | 350.21 (229.06-535.43) | 129.82 (81.33-207.21) | 80.84 (51.22-127.60) |
| **Day 15 Visit (14 days post-boost)** | | | | | | |
| N (non-missing) | 21 | 31 | 26 | 24 | 25 | 25 |
| Median ($P_{25}$, $P_{75}$) | 3277.00 (1553.04-5285.23) | 2939.81 (1031.32-4954.53) | 3582.81 (2992.16-4835.23) | 3549.89 (2398.81-4368.78) | 3860.59 (3532.00-4998.14) | 2386.42 (1044.76-3956.27) |
| Minimum - Maximum | 563.83-29781.84 | 801.02-17623.19 | 1094.25-19433.45 | 686.48-27221.54 | 725.53-22439.32 | 489.42-15506.86 |
| Geometric Mean (95% CI) | 3126.46 (1966.74-4970.03) | 2588.95 (1842.09-3638.61) | 3941.63 (3072.98-5055.83) | 3506.68 (2405.95-5111.00) | 4451.43 (3140.94-6308.68) | 2368.38 (1567.32-3578.86) |
| N* (non-missing pre- and post-boost) | 21 | 31 | 26 | 24 | 25 | 25 |
| Participants with ≥ 2-fold rise[2], 95% CI | 100.0% (83.9%-100.0%) | 100.0% (88.8%-100.0%) | 100.0% (86.8%-100.0%) | 91.7% (73.0%-99.0%) | 100.0% (86.3%-100.0%) | 100.0% (86.3%-100.0%) |
| Participants with ≥4-fold rise[2], 95% CI | 100.0% (83.9%-100.0%) | 100.0% (88.8%-100.0%) | 92.3% (74.9%-99.1%) | 79.2% (57.8%-92.9%) | 100.0% (86.3%-100.0%) | 100.0% (86.3%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 81.11 (42.41-155.14) | 72.57 (51.04-103.19) | 10.32 (7.79-13.68) | 10.01 (6.69-14.99) | 34.29 (22.57-52.11) | 29.30 (19.25-44.58) |
| **Day 29 Visit (28 days post-boost)** | | | | | | |
| N (non-missing) | 18 | 25 | 25 | 23 | 21 | 22 |
| Median ($P_{25}$, $P_{75}$) | 2476.73 (899.00-3246.43) | 1844.80 (768.80-3293.42) | 3168.81 (1887.40-4374.95) | 2998.95 (1569.76-4034.49) | 3274.25 (1167.93-4753.28) | 1750.48 (669.79-3611.48) |
| Minimum - Maximum | 630.45-13181.15 | 203.86-11880.17 | 492.07-15673.64 | 979.32-14150.83 | 477.62-9245.19 | 354.88-10763.42 |
| Geometric Mean (95% CI) | 2104.38 (1347.53-3286.31) | 1583.49 (1056.09-2374.28) | 2858.71 (2113.84-3866.06) | 2929.94 (2150.22-3992.40) | 2539.37 (1735.52-3715.57) | 1668.64 (1062.20-2621.30) |
| N* (non-missing pre- and post-boost) | 18 | 24 | 25 | 22 | 21 | 22 |
| Participants with ≥ 2-fold rise[2], 95% CI | 100.0% (81.5%-100.0%) | 95.8% (78.9%-99.9%) | 96.0% (79.6%-99.9%) | 95.5% (77.2%-99.9%) | 100.0% (83.9%-100.0%) | 100.0% (84.6%-100.0%) |
| Participants with ≥4-fold rise[2], 95% CI | 88.9% (65.3%-98.6%) | 95.8% (78.9%-99.9%) | 80.0% (59.3%-93.2%) | 81.8% (59.7%-94.8%) | 100.0% (83.9%-100.0%) | 100.0% (84.6%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 48.04 (22.35-103.23) | 42.94 (25.12-73.40) | 7.16 (5.30-9.67) | 7.81 (5.35-11.42) | 21.74 (12.80-36.92) | 20.21 (13.82-29.55) |

Table 1c

**DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1**
**Immunogenicity Endpoint Report - September 16, 2021**
**SARS-CoV-2 Pseudovirion Neutralization Assay**
**Table 1c - Neutralization Antibodies Titer (ID80) to Pseudovirus D614G[1], by Group and Timepoint - Groups 1E - 3E**

| | Group 1E [Dosed Janssen, Boost Moderna] (N=53) | Group 2E [Dosed Moderna, Boost Moderna] (N=51) | Group 3E [Dosed Pfizer, Boost Moderna] (N=50) |
|---|---|---|---|
| **Day 1 Visit (Pre-boost)** | | | |
| N (non-missing) | 52 | 50 | 50 |
| Median ($P_{25}$, $P_{75}$) | 13.50 (5.00-19.84) | 107.09 (65.93-278.25) | 48.26 (17.60-67.56) |
| Minimum - Maximum | 5.00-1149.69 | 17.33-1495.67 | 5.00-645.11 |
| Geometric Mean (95% CI) | 13.32 (9.78-18.15) | 121.44 (93.26-158.14) | 36.10 (26.39-49.38) |
| **Day 15 Visit (14 days post-boost)** | | | |
| N (non-missing) | 52 | 50 | 50 |
| Median ($P_{25}$, $P_{75}$) | 1438.22 (426.60-1856.37) | 1597.61 (903.40-1878.56) | 1414.67 (519.06-2063.64) |
| Minimum - Maximum | 239.89-7164.69 | 332.46-9392.10 | 163.29-9360.99 |
| Geometric Mean (95% CI) | 1026.18 (795.82-1323.24) | 1419.65 (1148.93-1754.16) | 1194.90 (903.92-1579.56) |
| N* (non-missing pre- and post-boost) | 52 | 50 | 50 |
| Participants with ≥ 2-fold rise[2], 95% CI | 100.0% (93.2%-100.0%) | 98.0% (89.4%-99.9%) | 100.0% (92.9%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 100.0% (93.2%-100.0%) | 94.0% (83.5%-98.7%) | 100.0% (92.9%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 77.02 (57.05-104.00) | 11.69 (9.31-14.67) | 33.10 (25.50-42.96) |
| **Day 29 Visit (28 days post-boost)** | | | |
| N (non-missing) | 43 | 48 | 43 |
| Median ($P_{25}$, $P_{75}$) | 571.48 (351.13-1004.77) | 1012.49 (542.49-1633.83) | 590.80 (364.43-1634.37) |
| Minimum - Maximum | 85.07-3061.70 | 262.33-3818.29 | 109.95-3479.10 |
| Geometric Mean (95% CI) | 580.67 (447.70-753.13) | 961.10 (786.51-1174.44) | 730.79 (544.36-981.07) |
| N* (non-missing pre- and post-boost) | 42 | 47 | 43 |
| Participants with ≥ 2-fold rise[2], 95% CI | 97.6% (87.4%-99.9%) | 95.7% (85.5%-99.5%) | 100.0% (91.8%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 95.2% (83.8%-99.4%) | 80.9% (66.7%-90.9%) | 100.0% (91.8%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 41.27 (28.81-59.12) | 7.58 (6.08-9.44) | 21.29 (15.90-28.49) |

Table 1d

**DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1**
**Immunogenicity Endpoint Report - September 16, 2021**
**SARS-CoV-2 Pseudovirion Neutralization Assay**
**Table 1d - Neutralization Antibodies Titer (ID80) to Pseudovirus D614G[1], by Group, Age Group, and Timepoint - Groups 1E - 3E**

| | Group 1E [Dosed Janssen, Boost Moderna] Age 18-55 yo (N=21) | Group 1E [Dosed Janssen, Boost Moderna] Age ≥56 yo (N=32) | Group 2E [Dosed Moderna, Boost Moderna] Age 18-55 yo (N=26) | Group 2E [Dosed Moderna, Boost Moderna] Age ≥56 yo (N=25) | Group 3E [Dosed Pfizer, Boost Moderna] Age 18-55 yo (N=25) | Group 3E [Dosed Pfizer, Boost Moderna] Age ≥56 yo (N=25) |
|---|---|---|---|---|---|---|
| **Day 1 Visit (Pre-boost)** | | | | | | |
| N (non-missing) | 21 | 31 | 26 | 24 | 25 | 25 |
| Median ($P_{25}$, $P_{75}$) | 13.99 (5.00-20.59) | 13.15 (5.00-19.08) | 104.25 (74.78-278.25) | 109.05 (59.10-253.48) | 53.05 (26.55-64.68) | 24.51 (14.53-67.56) |
| Minimum - Maximum | 5.00-1149.69 | 5.00-127.95 | 40.32-1495.67 | 17.33-457.89 | 5.00-645.11 | 5.00-349.07 |
| Geometric Mean (95% CI) | 15.99 (8.81-29.01) | 11.77 (8.29-16.72) | 130.58 (91.58-186.18) | 112.26 (73.77-170.82) | 48.79 (32.34-73.61) | 26.72 (16.69-42.76) |
| **Day 15 Visit (14 days post-boost)** | | | | | | |
| N (non-missing) | 21 | 31 | 26 | 24 | 25 | 25 |
| Median ($P_{25}$, $P_{75}$) | 1512.93 (477.40-1840.07) | 939.09 (403.75-1872.68) | 1638.81 (1128.53-1963.05) | 1461.35 (726.85-1763.28) | 1710.19 (1293.70-2144.71) | 655.93 (404.12-1677.17) |
| Minimum - Maximum | 239.89-7010.62 | 253.42-7164.69 | 389.23-5131.04 | 332.46-9392.10 | 305.89-9360.99 | 163.29-7404.92 |
| Geometric Mean (95% CI) | 1144.01 (749.60-1745.96) | 953.34 (682.70-1331.27) | 1488.97 (1179.49-1879.64) | 1348.20 (921.14-1973.25) | 1703.50 (1192.56-2433.34) | 838.15 (559.27-1256.09) |
| N* (non-missing pre- and post-boost) | 21 | 31 | 26 | 24 | 25 | 25 |
| Participants with ≥ 2-fold rise[2], 95% CI | 100.0% (83.9%-100.0%) | 100.0% (88.8%-100.0%) | 100.0% (86.8%-100.0%) | 95.8% (78.9%-99.9%) | 100.0% (86.3%-100.0%) | 100.0% (86.3%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 100.0% (83.9%-100.0%) | 100.0% (88.8%-100.0%) | 96.2% (80.4%-99.9%) | 91.7% (73.0%-99.0%) | 100.0% (86.3%-100.0%) | 100.0% (86.3%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 71.56 (42.03-121.83) | 80.96 (55.50-118.11) | 11.40 (8.57-15.17) | 12.01 (8.20-17.59) | 34.92 (24.40-49.96) | 31.37 (20.93-47.02) |
| **Day 29 Visit (28 days post-boost)** | | | | | | |
| N (non-missing) | 18 | 25 | 25 | 23 | 21 | 22 |
| Median ($P_{25}$, $P_{75}$) | 686.96 (376.94-876.81) | 542.17 (265.09-1037.43) | 993.25 (606.16-1744.46) | 1041.60 (473.88-1383.11) | 1326.03 (455.78-1786.17) | 503.64 (254.27-1396.40) |
| Minimum - Maximum | 145.95-3061.70 | 85.07-2556.80 | 262.33-3818.29 | 324.37-3687.32 | 155.07-3389.74 | 109.95-3479.10 |
| Geometric Mean (95% CI) | 666.74 (453.00-981.35) | 525.66 (363.64-759.88) | 989.89 (749.10-1308.08) | 930.74 (681.63-1270.89) | 949.45 (649.76-1387.37) | 569.22 (362.44-893.98) |
| N* (non-missing pre- and post-boost) | 18 | 24 | 25 | 22 | 21 | 22 |
| Participants with ≥ 2-fold rise[2], 95% CI | 100.0% (81.5%-100.0%) | 95.8% (78.9%-99.9%) | 96.0% (79.6%-99.9%) | 95.5% (77.2%-99.9%) | 100.0% (83.9%-100.0%) | 100.0% (84.6%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 94.4% (72.7%-99.9%) | 95.8% (78.9%-99.9%) | 84.0% (63.9%-95.5%) | 77.3% (54.6%-92.2%) | 100.0% (83.9%-100.0%) | 100.0% (84.6%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 38.37 (21.15-69.60) | 43.59 (26.91-70.61) | 7.32 (5.47-9.78) | 7.88 (5.49-11.31) | 21.21 (13.27-33.90) | 21.36 (14.43-31.61) |

**Assessment of MAH's responses**

The pre-boost GMTs differ between the three primary vaccination regimens. Although a boost as reflected in the GMTR can be observed a difference depending on the primary regimens is notable at day 15 with highest value for the COVID-19 Vaccine Janssen group, followed by the Comirnaty group and lowest in the homologous Spikevax group. At day 29 post-booster with 100 µg with Spikevax lower GMTs were observed in all 3 groups compared to the GMTs at day 15 post-booster. At all time-points lower GMTs were observed in the older age stratum compared to the younger age stratum. Regardless of the initial vaccine regimen, boosting with 100 µg dose of Spikevax resulted in a significant increase in nAb titer (Tables 1a-1d).

Figure 1a

*DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1*
*Immunogenicity Endpoint Report - September 16, 2021*
*SARS-CoV-2 Pseudovirion Neutralization Assay*
*Figure 1a - Neutralization Antibodies Titer (ID50) to Pseudovirus D614G [1], by Group, Age Group, and Timepoint - Groups 1E - 3E*

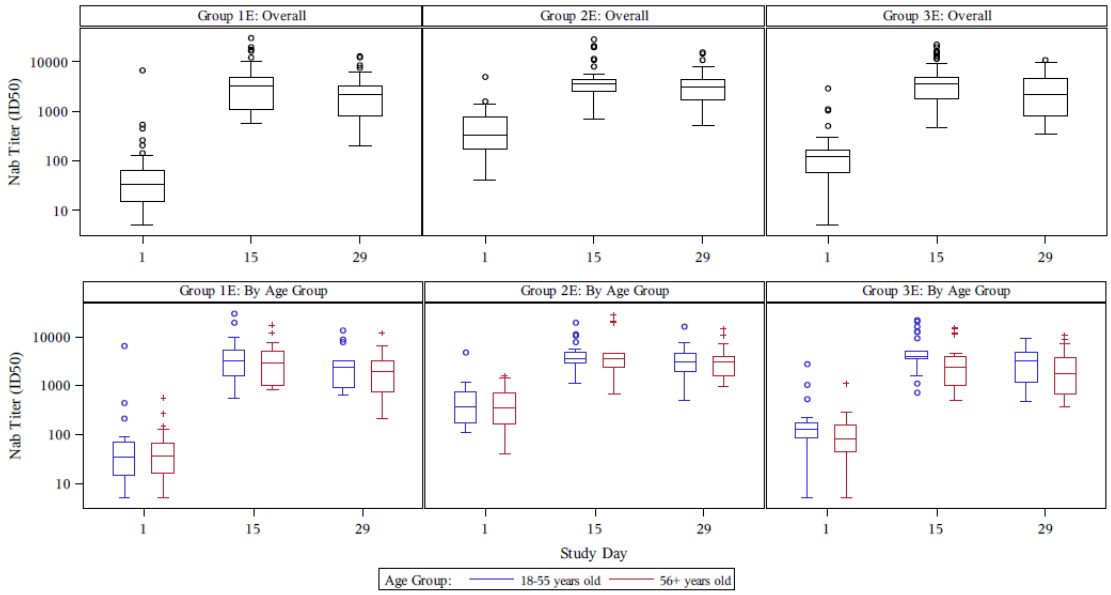
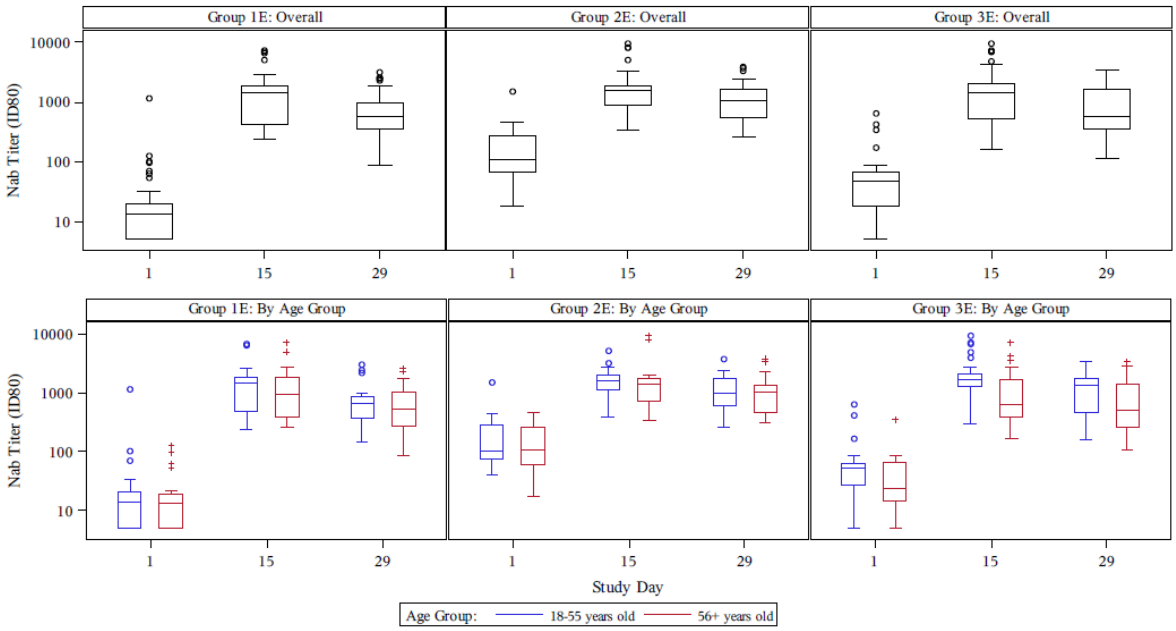



Figure 1b

*DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1*
*Immunogenicity Endpoint Report - September 16, 2021*
*SARS-CoV-2 Pseudovirion Neutralization Assay*
*Figure 1b - Neutralization Antibodies Titer (ID80) to Pseudovirus D614G [1], by Group, Age Group, and Timepoint - Groups 1E - 3E*



**Assessment of MAH's responses**

Figures 1a and 1b show that different baseline-titres in groups 1E,2E, and 3E were boosterable after administration of 100 µg dose of Spikevax and resulted in a significant increase in nAb titers on day 15 after booster and lowered at day 29 after booster. Neutralising antibodies were lower at all time points in the older age stratum (above 55 years of age) compared to the younger age stratum (18-55 years of age).

Similar information for the Spike-pseudotyped virus SARS-CoV-2 B.1.617.2 (Delta variant) is presented in Tables 2a and Figures 2a, and for the Spike-pseudotyped virus SARS-CoV-2 B.1.351 (Beta variant) in Tables 3a and Figures 3a.

Table 2a

**DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1**
**Immunogenicity Endpoint Report - September 16, 2021**
**SARS-CoV-2 Pseudovirion Neutralization Assay**
**Table 2a - Neutralization Antibodies Titer (ID50) to Pseudovirus B.1.617.2, by Group and Timepoint - Groups 1E - 3E**

| | Group 1E [Dosed Janssen, Boost Moderna] (N=53) | Group 2E [Dosed Moderna, Boost Moderna] (N=51) | Group 3E [Dosed Pfizer, Boost Moderna] (N=50) |
|---|---|---|---|
| **Day 1 Visit (Pre-boost)** | | | |
| N (non-missing) | 20 | 20 | 20 |
| Median ($P_{25}$, $P_{75}$) | 10.31 (5.00-14.94) | 119.57 (44.00-179.43) | 32.34 (15.79-44.09) |
| Minimum - Maximum | 5.00-5475.92 | 12.18-671.41 | 5.00-375.35 |
| Geometric Mean (95% CI) | 13.80 (6.20-30.71) | 98.26 (59.15-163.22) | 27.34 (16.31-45.85) |
| **Day 15 Visit (14 days post-boost)** | | | |
| N (non-missing) | 20 | 20 | 20 |
| Median ($P_{25}$, $P_{75}$) | 846.27 (533.97-1363.28) | 1057.97 (564.98-1923.82) | 920.70 (425.96-2519.23) |
| Minimum - Maximum | 113.44-10563.34 | 292.72-4890.59 | 151.45-5081.50 |
| Geometric Mean (95% CI) | 789.54 (477.99-1304.15) | 1085.42 (768.10-1533.83) | 946.29 (567.17-1578.84) |
| N* (non-missing pre- and post-boost) | 20 | 20 | 20 |
| Participants with ≥ 2-fold rise[2], 95% CI | 90.0% (68.3%-98.8%) | 90.0% (68.3%-98.8%) | 100.0% (83.2%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 90.0% (68.3%-98.8%) | 80.0% (56.3%-94.3%) | 100.0% (83.2%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 57.23 (27.27-120.10) | 11.05 (6.70-18.21) | 34.61 (23.05-51.96) |
| **Day 29 Visit (28 days post-boost)** | | | |
| N (non-missing) | 18 | 20 | 19 |
| Median ($P_{25}$, $P_{75}$) | 587.90 (382.48-793.70) | 691.54 (463.35-1177.51) | 600.90 (240.87-1696.30) |
| Minimum - Maximum | 79.99-3723.96 | 163.11-3296.81 | 101.33-8113.99 |
| Geometric Mean (95% CI) | 542.79 (326.62-902.04) | 735.02 (507.00-1065.60) | 654.46 (370.54-1155.94) |
| N* (non-missing pre- and post-boost) | 18 | 20 | 19 |
| Participants with ≥ 2-fold rise[2], 95% CI | 88.9% (65.3%-98.6%) | 95.0% (75.1%-99.9%) | 100.0% (82.4%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 88.9% (65.3%-98.6%) | 70.0% (45.7%-88.1%) | 100.0% (82.4%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 35.15 (14.69-84.06) | 7.48 (4.90-11.43) | 24.40 (15.29-38.94) |

Figure 2a

*DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1*
*Immunogenicity Endpoint Report - September 16, 2021*
*SARS-CoV-2 Pseudovirion Neutralization Assay*
*Figure 2a - Neutralization Antibodies Titer (ID50) to Pseudovirus B.1.617.2 [1], by Group, Age Group, and Timepoint - Groups 1E - 3E*

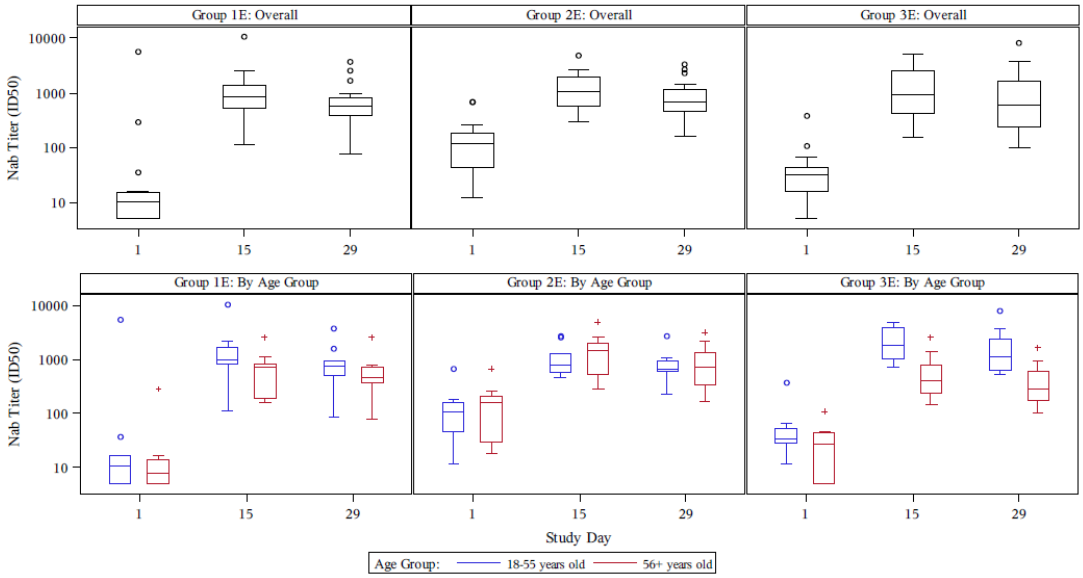
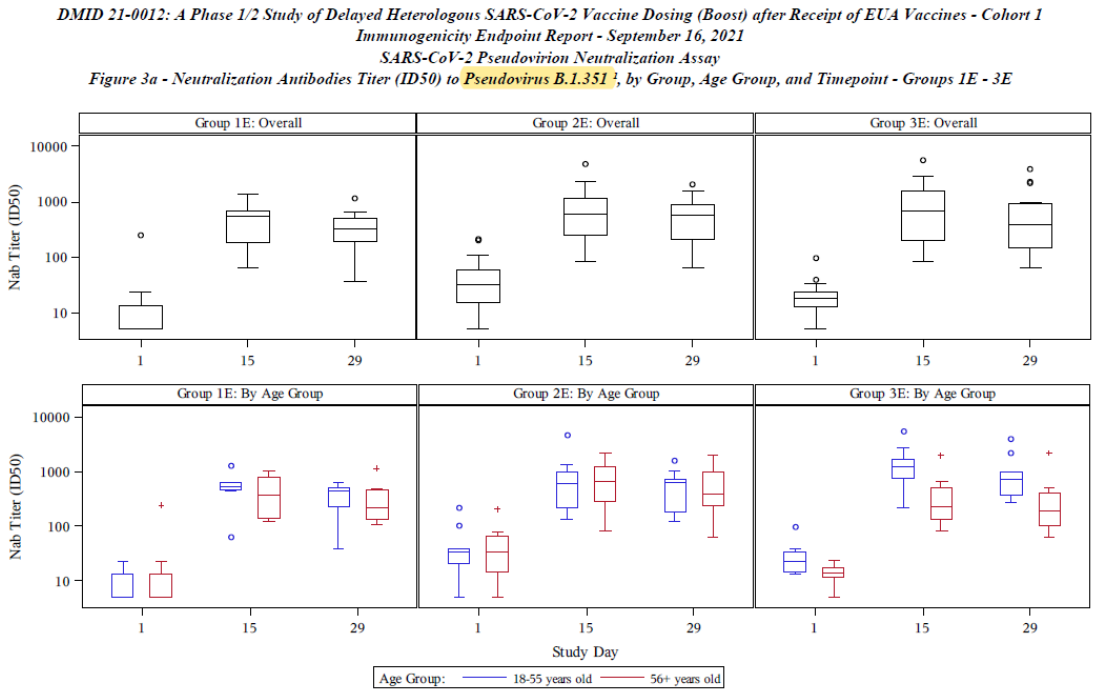



Table 3a

**DMID 21-0012: A Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines - Cohort 1**
**Immunogenicity Endpoint Report - September 16, 2021**
**SARS-CoV-2 Pseudovirion Neutralization Assay**
**Table 3a - Neutralization Antibodies Titer (ID50) to Pseudovirus B.1.351, by Group and Timepoint - Groups 1E - 3E**

| | Group 1E [Dosed Janssen, Boost Moderna] (N=53) | Group 2E [Dosed Moderna, Boost Moderna] (N=51) | Group 3E [Dosed Pfizer, Boost Moderna] (N=50) |
|---|---|---|---|
| **Day 1 Visit (Pre-boost)** | | | |
| N (non-missing) | 20 | 20 | 20 |
| Median ($P_{25}$, $P_{75}$) | 5.00 (5.00-13.33) | 32.44 (14.81-58.54) | 17.35 (13.16-23.07) |
| Minimum - Maximum | 5.00-246.66 | 5.00-213.06 | 5.00-96.78 |
| Geometric Mean (95% CI) | 8.66 (5.50-13.63) | 29.74 (17.80-49.69) | 17.81 (13.14-24.15) |
| **Day 15 Visit (14 days post-boost)** | | | |
| N (non-missing) | 20 | 20 | 20 |
| Median ($P_{25}$, $P_{75}$) | 541.64 (181.66-683.88) | 611.76 (249.00-1127.14) | 661.71 (198.58-1600.13) |
| Minimum - Maximum | 63.72-1311.06 | 82.36-4665.41 | 81.52-5627.48 |
| Geometric Mean (95% CI) | 407.53 (276.66-600.31) | 572.08 (358.19-913.69) | 582.60 (336.76-1007.90) |
| N* (non-missing pre- and post-boost) | 20 | 20 | 20 |
| Participants with ≥ 2-fold rise[2], 95% CI | 95.0% (75.1%-99.9%) | 100.0% (83.2%-100.0%) | 100.0% (83.2%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 95.0% (75.1%-99.9%) | 95.0% (75.1%-99.9%) | 100.0% (83.2%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 47.06 (25.86-85.64) | 19.23 (12.38-29.87) | 32.70 (22.42-47.71) |
| **Day 29 Visit (28 days post-boost)** | | | |
| N (non-missing) | 18 | 20 | 19 |
| Median ($P_{25}$, $P_{75}$) | 331.99 (191.06-484.13) | 569.92 (212.59-860.34) | 374.93 (146.23-906.55) |
| Minimum - Maximum | 38.12-1137.58 | 63.14-2009.86 | 61.96-3908.71 |
| Geometric Mean (95% CI) | 281.66 (188.71-420.39) | 439.79 (283.81-681.50) | 405.60 (233.58-704.32) |
| N* (non-missing pre- and post-boost) | 18 | 20 | 19 |
| Participants with ≥ 2-fold rise[2], 95% CI | 94.4% (72.7%-99.9%) | 100.0% (83.2%-100.0%) | 100.0% (82.4%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 94.4% (72.7%-99.9%) | 95.0% (75.1%-99.9%) | 100.0% (82.4%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 32.34 (16.71-62.60) | 14.79 (10.41-20.99) | 23.26 (15.69-34.47) |

Figure 3a




**Assessment of MAH's responses**

Same pattern was seen of neutralising antibody titers for the Spike-pseudotyped virus SARS-CoV-2 B.1.617.2 (Delta variant) and for the Spike-pseudotyped virus SARS-CoV-2 B.1.351 (Beta variant) compared to Pseudovirus D614G.

## Comparison of Neutralisation Titers Between 100 µg Booster Dose and 50 µg Booster Dose

### Neutralising antibody response against the prototype variant (Wuhan-Hu-1) over the course of study mRNA-1273-P201

Table 4 summarises serum nAb (PsVNA ID50, D614G) titers following the primary vaccination series (Part A of mRNA-1273-P201) and the booster vaccination (Part B of mRNA-1273-P201).

In the 100 µg Spikevax group, the 50 µg booster led to an increase in geometric mean fold rise (GMFR) of 12.99 (95% CI: 11.04, 15.29) from pre-booster to 28 days after the 50 µg booster dose. In the 50 µg Spikevax group a GMFR of 17.53 (95% CI: 14.94, 20.56) was determined from pre-booster to post-booster.

Comparing the nAb response following 28 days after the second dose (peak levels) given in the primary series with the nAb response 28 days after the third booster dose a GMFR of 1.53 (95% CI: 1.32, 1.77) was reported in the 100 µg primary series group and a GMFR of 2.93 (95% CI: 2.55, 3.35) in the 50 µg primary series group.

*Table 4: Pseudovirus Neutralising Antibody (ID50) Titers in Study mRNA-1273-P201 Part A (Primary series) and in Part B*

| | mRNA-1273 | | |
|---|---|---|---|
| | **50 µg Primary Series (+50 µg booster) N=146 n (%)** | **100 µg Primary Series (+50 µg booster) N=149 n (%)** | **Overall N=295 n (%)** |
| **Baseline (Day 1; pre-dose 1), n** | 146 | 148 | 294 |
| **GMT** | 9.35 | 9.25 | 9.30 |
| **95% CI** | 9.16, 9.54 | NE, NE | 9.20, 9.39 |
| **28 days after 2nd dose of primary series, n** | 143 | 146 | 289 |
| **GMT** | 629.23 | 1267.95 | 896.47 |
| **95% CI** | 549.33, 720.75 | 1087.90, 1477.80 | 803.35, 1000.38 |
| **Participants achieving Seroresponse, n (Seroresponse Rate %)** | | | |
| **N1** | 143 | 146 | 289 |
| **n (%)** | 141 (98.6) | 143 (97.9) | 284 (98.3) |
| **95% CI** | 95.0, 99.8 | 94.1, 99.6 | 96.0, 99.4 |
| **Baseline (Day 1; pre-booster), n** | 145 | 149 | 294 |
| **GMT** | 104.658 | 150.224 | 125.696 |
| **95% CI** | 88.282, 124.070 | 125.726, 179.495 | 111.011, 142.325 |
| **Day 29 (28 days after booster dose, n** | 146 | 149 | 295 |
| **GMT** | 1834.309 | 1951.735 | 1892.708 |
| **95% CI** | 1600.233, 2102.623 | 1729.606, 2202.392 | 1728.800, 2072.157 |
| **Participants achieving Seroresponse, n (Seroresponse Rate %)** | | | |
| **N2** | 145 | 149 | 294 |
| **n (%)** | 141 (98.6) | 143 (97.9) | 284 (98.3) |
| **95% CI** | 86.8, 96.2 | 81.6, 92.7 | 86.1, 93.3 |
| **Comparison of 28 days after booster dose vs pre-booster** | | | |
| **N2** | 145 | 149 | 294 |
| **GMFR** | 17.53 | 12.99 | 15.06 |
| **95% CI** | 14.94, 20.56 | 11.04, 15.29 | 13.43, 16.89 |
| **Comparison of 28 days after booster dose vs 28 days after the primary series** | | | |
| **N3** | 143 | 146 | 289 |
| **GMFR** | 2.93 | 1.53 | 2.11 |
| **95% CI** | 2.55, 3.35 | 1.32, 1.77 | 1.90, 2.34 |

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 mRNA-1273-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 mRNA-1273-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.

*Table 5:ID50 neutralisation titers against Pseudovirus D614G of 154 participants in Groups 1E, 2E, and 3E of Cohort 1 in Study DMID*

| | Group 1E [Dosed Janssen, Boost Moderna] (N=53) | Group 2E [Dosed Moderna, Boost Moderna] (N=51) | Group 3E [Dosed Pfizer, Boost Moderna] (N=50) |
|---|---|---|---|
| **Day 1 Visit (Pre-boost)** | | | |
| N (non-missing) | 52 | 50 | 50 |
| Median ($P_{25}$, $P_{75}$) | 34.30 (15.89-66.83) | 341.31 (176.25-746.61) | 118.50 (60.11-161.87) |
| Minimum - Maximum | 5.00-6566.30 | 40.88-4851.22 | 5.00-2794.06 |
| Geometric Mean (95% CI) | 36.81 (25.58-52.96) | 366.31 (280.09-479.06) | 102.44 (74.23-141.38) |
| **Day 15 Visit (14 days post-boost)** | | | |
| N (non-missing) | 52 | 50 | 50 |
| Median ($P_{25}$, $P_{75}$) | 3268.82 (1094.40-5018.44) | 3582.81 (2620.92-4437.34) | 3550.70 (1817.21-4840.33) |
| Minimum - Maximum | 563.83-29781.84 | 686.48-27221.54 | 489.42-22439.32 |
| Geometric Mean (95% CI) | 2793.90 (2138.57-3650.03) | 3726.50 (3006.38-4619.12) | 3246.95 (2464.58-4277.67) |
| N* (non-missing pre- and post-boost) | 52 | 50 | 50 |
| Participants with ≥ 2-fold rise[2], 95% CI | 100.0% (93.2%-100.0%) | 96.0% (86.3%-99.5%) | 100.0% (92.9%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 100.0% (93.2%-100.0%) | 86.0% (73.3%-94.2%) | 100.0% (92.9%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 75.91 (54.99-104.78) | 10.17 (8.05-12.85) | 31.69 (23.80-42.21) |
| **Day 29 Visit (28 days post-boost)** | | | |
| N (non-missing) | 43 | 48 | 43 |
| Median ($P_{25}$, $P_{75}$) | 2073.19 (826.88-3293.42) | 2999.98 (1725.22-4305.19) | 2173.20 (833.78-4713.91) |
| Minimum - Maximum | 203.86-13181.15 | 492.07-15673.64 | 354.88-10763.42 |
| Geometric Mean (95% CI) | 1783.68 (1333.00-2386.74) | 2892.62 (2349.52-3561.26) | 2048.44 (1530.54-2741.59) |
| N* (non-missing pre- and post-boost) | 42 | 47 | 43 |
| Participants with ≥ 2-fold rise[2], 95% CI | 97.6% (87.4%-99.9%) | 95.7% (85.5%-99.5%) | 100.0% (91.8%-100.0%) |
| Participants with ≥ 4-fold rise[2], 95% CI | 92.9% (80.5%-98.5%) | 80.9% (66.7%-90.9%) | 100.0% (91.8%-100.0%) |
| Geometric Mean Fold Rise[2], 95% CI | 45.06 (29.36-69.14) | 7.46 (5.92-9.39) | 20.94 (15.36-28.55) |

**Assessment of MAH's responses**

It should be noted that only the results of the neutralising antibody responses are considered for the assessment of the third booster dose as these antibodies are considered crucial for the prevention of COVID-19. The apparently higher immunogenicity in the DMID study might be related to a higher dose or a shorter interval between the second dose of the primary series and the booster dose. The shorter timeframe of booster resulted in higher baseline GMTs in Study DMID before booster compared to study mRNA-1273-P201. In addition, no GMT data are available for the comparison of the proposed booster doses of 50 µg for primary series of COVID-19 Vaccine Janssen and Comirnaty vaccines.

## *3.3. Com-COV2*

Com-COV2[1] is a single-blind, randomised, non-inferiority trial in which adults aged 50 years and older, previously immunised with a single dose of ChAd or BNT in the community, were randomly assigned (in random blocks of three and six) within these cohorts in a 1:1:1 ratio to receive a second dose intramuscularly (8–12 weeks after the first dose) with the homologous vaccine, Spikevax, or Nuvaxovid (NVX-CoV2373, manufactured by Novavax, NVX). The primary endpoint was the geometric mean ratio

[1] Stuart ASV, Shaw RH, Liu X, Greenland M, Aley PK, Andrews NJ, Cameron JC, Charlton S, Clutterbuck EA, Collins AM, Darton T, Dinesh T, Duncan CJA, England A, Faust SN, Ferreira DM, Finn A, Goodman AL, Green CA, Hallis B, Heath PT, Hill H, Horsington BM, Lambe T, Lazarus R, Libri V, Lillie PJ, Mujadidi YF, Payne R, Plested EL, Provstgaard-Morys S, Ramasamy MN, Ramsay M, Read RC, Robinson H, Screaton GR, Singh N, Turner DPJ, Turner PJ, Vichos I, White R, Nguyen-Van-Tam JS, Snape MD; Com-COV2 Study Group. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. Lancet. 2022 Jan 1;399(10319):36-49. doi: 10.1016/S0140-6736(21)02718-5. Epub 2021 Dec 6. Erratum in: Lancet. 2022 Feb 26;399(10327):802. PMID: 34883053; PMCID: PMC8648333.

(GMR) of serum SARS-CoV-2 anti-spike IgG concentrations measured by ELISA in heterologous versus homologous schedules at 28 days after the second dose, with a non-inferiority criterion of the GMR above 0·63 for the one-sided 98·75% CI. The primary analysis was on the per-protocol population, who were seronegative at baseline. Safety analyses were done for all participants who received a dose of study vaccine.

Participants who received a community prime with ChAd had a SARS-CoV-2 anti-spike IgG GMC at 28 days of 20 114 ELU/mL (95% CI 18 160 to 22 279) in the Spikevax group, 5597 ELU/mL (4756 to 6586) in the Nuvaxovid (NVX) group, and 1971 ELU/mL (1718 to 2262) in the ChAd homologous group (per-protocol analysis; table 2). The SARS-CoV-2 anti-spike IgG response to ChAd/Spikevax and ChAd/NVX were both statistically superior to that of homologous ChAd/ChAd (table 2).

Findings from this trial demonstrate that the immunogenicity of heterologous boost with Spikevax following community prime with ChAd or BNT was non-inferior to the homologous-boost schedule. When heterologous boost was with NVX, only those primed with ChAd had titres of SARS-CoV-2 anti-spike IgG that were non-inferior to the homologous schedule, whereas BNT/NVX did not meet the non-inferiority threshold against homologous BNT.

This research confirms previous evidence of mixed adenoviral and mRNA schedules as being safe, tolerable, and immunogenic alternatives to homologous schedules when given at an 8–12 weeks interval. It also provides new evidence on the response to mixed mRNA vaccinations in a randomised trial, and novel data for the incorporation of protein-based COVID-19 vaccines into heterologous schedules. These results provide reassurance that there are multiple appropriate options to complete primary immunisation in individuals primed with BNT or ChAd, which will facilitate rapid vaccine deployment globally.

**Assessment of MAH's responses**

The data provided in the published paper do not describe a booster dose, but a second dose after the Oxford/Astra Zeneca vaccine Vaxzevria or Comirnaty as first dose. Spikevax was given as 100 µg second dose and not as 50 µg booster dose, but not clearly mentioned in the paper. As second dose the homologous vaccine was given and in the two other groups the heterologous vaccines Spikevax and Nuvaxovid 8 to 12 weeks after the primary vaccination. The immune-responses were high in all groups beside the combination Comirnaty/Nuvaxovid after the second dose, but very high after a second dose with Spikevax compared to the other combinations. The reactogenicity profile showed higher frequencies of reported side effects in the groups, where Spikevax was given as second dose compared to all other combinations regarding solicited local and systemic reactions.

## *3.4. Interval between primary series and booster dose*

New booster data

The MAH proposes to the change the booster dosing interval from 'at least 6 months' to 'at least 3 months' based on

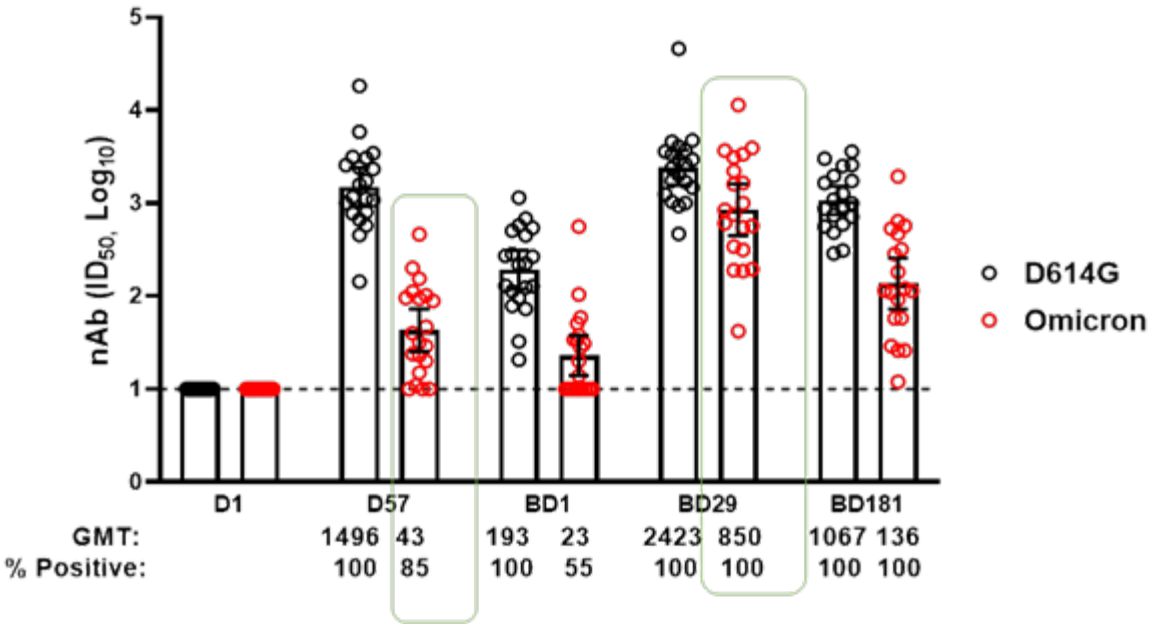
1) the demonstrated safety in study DMID 21-0012, which boosted subjects at least 12 weeks after the primary series and where no safety issues were identified (submitted 03 September 2021, EUA 27073 SN0251), and

2) neutralising antibody (nAb) responses against Omicron after a 2-dose primary series and a booster dose of Spikevax (mRNA-1273-P201B). These new data show very low levels of nAb against Omicron one month after the second dose, becoming undetectable in more than half of the subjects at month 6, and significantly increased after the booster dose in all subjects (Figure 4). A 3-month interval will allow people to receive a booster to increase nAb titers against the Omicron variant sooner after the completion of their primary series and will align programmatically with other COVID-19 mRNA vaccines.

Omicron neutralising titers.

At 1 month post-dose 2 (Day 57, Primary Series), the GMT for nAb against Omicron (N=20) after two 100 µg doses of Spikevax is 43, compared to a GMT of 1496 observed against the prototype virus (Figure 4). When participants were boosted 6 months after the primary series, GMTs increased from 23 to 850 (37-fold), demonstrating that the prototype booster generates a robust immune response against Omicron. The post-dose 2 nAb GMT (43) are likely insufficient to neutralise the Omicron variant, and therefore, the MAH believes boosting individuals promptly, rather than waiting the 6 month interval, is of importance.

**Figure 4 - Pseudovirus Neutralising Antibody ID50 Titers against Omicron**




Safety Data for 3 Month Dosing Interval

The MAH proposes to extrapolate data from DMID Study 21-0012, previously submitted to EMA on 03 September 2021 (sequence 0146),which demonstrates the safety of administration of a higher dose booster (100 µg) at a 12-week interval, to support dosing our currently authorised 50 µg booster dose 'at least 3-months post-primary series'. No new safety signals were observed in this study, with similar reactogenicity profiles to that observed after Dose 2 (DMID 21-0012 Study Safety Report Aug 31, 2021). We believe it is reasonable to extrapolate the safety data to a lower dose (50 µg) at a shorter dosing interval (as early as 12 weeks). Of note, these data include both homologous and heterologous boost.

In conclusion, the MAH believes the safety and immunogenicity data described support an amendment to the boosting dosing interval to 'at least 3 months' post-primary series.

**Assessment of MAH's responses**

The MAH argumentation that the post-dose 2 nAb GMT are likely insufficient to neutralise the Omicron variant is agreed, and therefore a booster dose should be given earlier than the previously proposed distance of 6 month. The 3 month first booster interval is justified by the DMID study data.

## *3.5. Discussion*

The application is intended to enable a heterologous booster injection using Spikevax after any authorised COVID-19 vaccine. Basis for this application is the NIH sponsored DMID 21-0012 trial that was conducted

in the USA and has recently been published. The trial demonstrates that the titres of neutralising antibodies increase considerably after a booster injection compared to the pre-booster titres. Interpretation of the data and bridging to available efficacy data is hampered by the following issues:

- The used dose was 100 µg which is double the authorised dose for a booster injection in Europe. There are no data available on the use of a 100 µg dose in comparison to a 50 µg booster dose. Data from the mRNA-1273-P201 trial assessed in a previous variation show that there is a dose response relationship observed with respect to neutralising antibody titres when using either 50 µg or 100 µg for the primary series. Based on this observation one could assume that the response to a 100 µg booster is higher than the response to a 50 µg booster. However, it is agreed that the boosting of immune response is more dependent on the baseline titers after primary vaccination series compared to the dose given as a booster dose.

- The interval between primary series and booster injection was shorter in the DMID trial compared to the mRNA-1273-P201 trial which provided the pivotal data for boosting. The role of the interval between primary immunisation and booster injection has not been systematically assessed and it is unknown whether the difference observed between trials is relevant for the interpretation of results. As titres generally decline after the primary immunisation longer intervals will be associated with lower pre-boost titres. If similar post-boost titres are obtained the GMTR may be higher with longer intervals creating the incorrect impression that a better boost is obtained. It is agreed with the argumentation of the MAH that the post-dose 2 nAb GMT are likely insufficient to neutralise the Omicron variant, and therefore a booster dose should be given earlier than the previously proposed interval of 6 month. Although not systematically used in this trial the proposal of a 3 month interval is acceptable based on the DMID trial data. The subsequently submitted safety data from the post-marketing surveillance did not reveal any new safety signals with regard to administration of a 3rd dose given *at least 3 months* after the primary series. The interval for giving the booster dose was 3 to 5 months depending on local recommendations. The data confirmed what is known about the risk of myocarditis/pericarditis, which of note appears not to be higher after dose 3 compared to after dose 2. Stratification of cases with known dose and time to onset that occur within the 7 days following vaccination, considering observed versus expected analyses, showed an increased risk following dose 2 in young males, but no similar increase has yet been observed following a third dose. A differentiation between a 100 µg 3rd dose and a 50 µg booster dose is not possible within the submitted post-marketing safety data. Uncertainties remain with regard to the methodology of recording the dose numbers. No clinical information is given for the fatal cases. The MAH was asked by PRAC to submit these data. The submitted data do not raise new safety signals with regard to a 3$^{rd}$ dose or booster dose given at least 3 months after primary series. The data do not extent the safety data base for the heterologous booster. The submitted safety data were previously submitted to PRAC within MEA 11.10 (11$^{th}$ Safety Summary Report, SSR). PRAC concluded that the benefit-risk balance of Spikevax in the approved indication remains unchanged.

- Peak titres achieved after the primary series are not available therefore comparisons on the increases in neutralising antibody titres can only made based on titres prior to and 4 weeks after the booster injection.

- Under the assumption that pre-boost titres obtained for the different vaccines are associated with remaining protection from symptomatic infection the obtained increase in titres as reflected in the GMTR pre/post-boost are regarded as meaningful and could justify the use of a heterologous boosting in the absence of suitable and better documented alternatives.

- No immunogenicity data are submitted for subjects below 18 years of age. Based on the requested SmPC wording where only boosting in adults is requested, this is an acceptable limitation for the time being.

- Data for a second dose with Spikevax after a first dose with a vector based vaccine were shown in the Com-COV2 study which investigated different "mix and match" strategies for the primary series. These data support that an immune-response to an adeno vector based COVID-19 vaccine can substantially be increased by a second dose of Spikevax. Although this trial investigated only the primary series it is accepted that it lends some support to the assumption that Spikevax could also be used for the boosting in the heterologous setting when the same antigen is used. A heterologous booster with Spikevax is also supported by immunogenicity data from the COV-BOOST study, a multicentre, randomised Phase 2 study evaluating a heterologous booster vaccination against COVID-19. Participants were adults aged 30 years or older who had received two doses of either another mRNA-vaccine or an adenoviral vector vaccine, and were at least 84 days post-second dose by the time of enrolment.

In summary, taking the safety and immunogenicity results from the DMID study, the CoV-BOOST study, Com-CoV-2 study, and from the post-marketing safety surveillance into account, the use of Spikevax given as a heterologous booster to adults who were primed with either another mRNA-or with an adeno-vector vaccine at least 3 months after priming is approvable.

In addition, the MAH requested to update the INN within the procedure, which is acceptable. A corresponding proposal for the SmPC has been submitted.

# 4. Clinical Safety aspects

## *4.1. Methods – analysis of data submitted*

This is a phase 1/2, open-label clinical trial in individuals, 18 years of age and older, who are in good health, have no known history of COVID-19 or SARS-CoV-2 infection, and meet all other eligibility criteria.

This clinical trial is designed to assess the safety, reactogenicity and immunogenicity of a delayed (>12 weeks) vaccine boost on the EUA-dosed COVID-19 vaccines Spikevax, Comirnaty or COVID-19 Vaccine Janssen. This is an adaptive design and may add arms (and increase sample size) as vaccines are awarded EUA and/or variant lineage Spike vaccines are manufactured or become available. Enrolment will occur at approximately twelve domestic clinical research sites.

**Assessment of MAH's responses**

Based on DMID 21-0012 study design some limitations have been identified:

1. No safety data from heterologous boosting are available for subjects below 18 years of age.
2. No safety data have been submitted for subjects with COVID-19 or SARS-CoV-2 infection prior to heterologous boosting. The only data available derive form the mRNA-1273-P301 trial were SARS-CoV-2 individuals have been included. These data do not raise any concerns. The evaluation of a heterologous booster is subject to the PSUR. Within the PSUR covering the time period 18/12/2020 to 30/06/2021 the MAH was requested to present data, including literature, and discuss the safety profile of Spikevax in relation to heterologous COVID-19 vaccines schedule.
3. No safety data are available for boosting after Vaxzevria. After request the MAH submitted a publication (Stuart et al) not assessing a heterologous booster after full primary series, but evaluating the "mixed-match use" within a primary series, i.e. after one dose of either Vaxzevria, or after Comirnaty, or Nuvaxovid. The data indicate a higher reactogenicity after Vaxzevria dosing, but did not raise safety concerns. The same applies to the Novavax COVID-19 vaccine. The data derive from a limited sample size, not sufficient to detect rare events like myocarditis or pericarditis, or pIMDs.

This study includes two cohorts.

Cohort 1 will provide rapid information about the safety, reactogenicity, and immunogenicity of delayed boost in a previously EUA-dosed group. This cohort can inform near term public health decisions if the variant virus becomes more widespread. Cohort 1 will include subjects greater than 18 years of age and older, stratified into two age strata (18-55 years and > 56 years) who previously received COVID-19 vaccine at EUA dosing (two doses of Spikevax at the 100 mcg dose, two doses of Comirnaty at the 30 mcg dose, or one vaccination of Ad26.COV2.S at the 5x1010 vp dose)(Table 1). Those subjects will be offered enrolment into this study 12-20 weeks after they received the last dose of their EUA vaccine. Subjects will receive an open-label delayed boost that is assigned to each of the approximately twelve domestic trial sites.

1. Previously EUA-dosed vaccination with COVID-19 Vaccine Janssen at 5x1010 vp followed by:

   Group 1E – A 100-mcg dose of Spikevax

2. Previously EUA-dosed vaccination with Spikevax at 100 mcg for two doses followed by:

   Group 2E – A 100-mcg dose of Spikevax

3. Previously EUA-dosed vaccination with Comirnaty at 30 mcg for two doses followed by:

   Group 3E – A 100-mcg dose of Spikevax

**Assessment of MAH's responses**

Additional limitation has been identified for Cohort 1.

Only 100 mcg booster dose has been studied in this study. From safety perspective this is however not an issue as it is considered "conservative" to use the more reactogenic, higher dose.

Safety data from DMID Study 21-0012 demonstrated a profile consistent with the previously described safety profile of a booster dose of 50 µg of Spikevax in the phase 2 study mRNA-1273-P201 Part B that was used as the basis of the type II variation to include the 50 µg booster dose indication in the SmPC.

The anticipated sample size of each group is approximately 25 subjects 18 through 55 years of age and approximately 25 subjects 56 years of age and older for a total of 50 subjects per group.

Subjects in Cohort 1 received a single intramuscular (IM) injection of the designated delayed booster vaccine and are followed through 12 months after vaccination. A telephone visit will occur at Day 8 and in-person follow-up visits will occur on Days 15 and 29, as well as 3, 6, and 12 months after the vaccination. Reactogenicity will be assessed at the above-mentioned visits and blood will be drawn for immunogenicity assays. A schedule of activities (SOA) for groups in Cohort 1, as defined in the protocol, is shown in following Table.

**Table II: SOA for EUA-dosed Cohort 1**

| Study Day | D-28 to D-1 | 1 | 8[b] | 15 | 29 | 91 | 169 | 366 | Illness/ Unscheduled Visit | Early Termination Visit |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number | 00[a] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | | |
| Window (+/-) | | 0 | 1 | 2 | 2 | 7 | 7 | 14 | | |
| Informed Consent[a] | X | | | | | | | | | |
| Eligibility Criteria | X | X | | | | | | | | |
| Medical History | X | X | | | | | | | | |
| Vaccination[c] | | X | | | | | | | | |
| Concomitant Meds | | X | X | X | X | | | | | |
| Interim History | | X | X | X | X | X | X | X | X | X |
| Physician Exam - Targeted | X | X | | X | X | X | X | X | X | X |
| Vital Signs[d] | X | X | | X | X | | | | X | X |
| Height/Weight (BMI)[a] | X | | | | | | | | | |
| Urine β-HCG[e] | | X | | | | | | | | |
| Memory Aid, Solicited AEs | | X | X | X[f] | | | | | | |
| Unsolicited AEs | | X | X | X | X | | | | | |
| SAEs, Protocol specified AESIs, MAAEs, and NOCMCs | | | X | X | X | X | X | X | X | X |
| Nasal swab for PCR & Sequencing | | | | | | | | | X[g] | |
| **Immunoassays** | | | | | | | | | | |
| Serum- Humoral Assays | | 32 | | 32 | 32 | 32 | 32 | 32 | | 32 |
| PBMC Cellular Assays & plasma | | 64 | | 64 | | | 64 | 64 | | 64 |
| Daily Volume (mL) | | 96 | | 96 | 32 | 32 | 96 | 96 | | 96 |
| Cumulative Volume (mL) | | 96 | | 192 | 224 | 256 | 352 | 448 | | |

[a] Optional screening visit – informed consent and height/weight only performed at screening or Day 1
[b] Telephone visit

**Assessment of MAH's responses**

In study report Table 8a – 8c (See safety report), local solicited AEs are listed on all study days from day 1 to day 8. According to SoA there is only one telephone visit on day 8. A memory aid form that assists the participant with recalling information of each study day for the telephone interviews has been provided to the subjects in the trial. This method is deemed acceptable.

A total of 154 participants have been enrolled and received a Spikevax boost injection (IM; 100 µg) approximately 12-20 weeks after receiving primary vaccination under EUA.

Cohort 2 is an adaptive cohort that will evaluate, in a prospective fashion, the safety, reactogenicity and immunogenicity of EUA-dosed vaccine followed by delayed boost. Pools of subjects will be recruited to receive EUA-dosed vaccine and will be assigned, at a later date, to a delayed booster vaccine based on availability of vaccine product, to enable rapid implementation based on situational assessment of need. This cohort will take longer to provide information on the immunogenicity of delayed boost, but it may assume priority in enrolment as it is important to inform future public health strategies and as access to COVID-19 vaccine becomes more widespread.

**Assessment of MAH's responses**

DMID 21-0012 includes also Cohort 2 with so called delayed boost. Here however, no data has been submitted within the dossier.

As Cohorts 1 and 2 are in different populations, they can be enrolled in parallel or prioritised as determined by DMID/IDCRC needs.

## *4.2. Results*

This submission includes a Day 7 safety report corresponding to data entered on or before 08 July 2021 (Safety report date 15 July 2021). As of 08 July 2021, all 154 participants were expected to have completed the Day 8 visit and **152 out of 154 (98.7%) had completed their Day 8 visit.**

No new safety signals were observed in the supportive DMID Study 21-0012 which affirms that Spikevax booster may be safely provided to previously vaccinated individuals regardless of platform (mRNA-based or adenovirus-based).

**Assessment of MAH's responses**

The follow up safety period is rather short, comparable to what has been submitted during licensure. The report of safety data covers a period of 29 days as described in the CTP. No further data have been submitted. The follow-up of heterologous booster data is subject to the PSUR. Within the PSUR covering the time period 18/12/2020 to 30/06/2021 the MAH was requested to present data, including literature, and discuss the safety profile of Spikevax in relation to heterologous COVID-19 vaccines schedule. The data and discussion should be presented in relevant sections e.g. off-label use, or in addition to the already presented PSUR headline "Interaction with other vaccines (Heterologous Vaccine Schedule)". (see also comment above). The MAH claims not to have observed any new safety signals.

### 4.2.1. Participant flow

**Table 1: Clinical Studies Supporting the Development of mRNA-1273 50 µg Heterologous Booster**

| Study | 2-Dose Primary Series | Booster Dose (Dose 3) | Interval Between Dose 2 and 3 | N | Status |
|---|---|---|---|---|---|
| DMID 21-0012 | Group 1E: Janssen (1 dose only) | 100 µg – mRNA-1273 | 12-20 weeks | 53 | Safety data available through Day 7; Immunogenicity data available through Day 15 |
| | Group 2E: 100 µg – mRNA-1273 | 100 µg – mRNA-1273 | 12-20 weeks | 51 | Safety data available through Day 7; Immunogenicity data available through Day 15 |
| | Group 3E: Pfizer 30 µg | 100 µg – mRNA-1273 | 12-20 weeks | 50 | Safety data available through Day 7; Immunogenicity data available through Day 15 |

DMID = Division of Microbiology and Infectious Diseases.

**Assessment of MAH's responses**

It is unclear why group 1E and group 2E recruited more subjects than planned. This can however happen in multicentric trials.

**Protocol deviations**

**Visit Cutoff Date: August 16, 2021**
**Table 11 - Protocol Deviations by Type and Group**

| | Group 1E Dosed Janssen Boost Moderna (N=53) | Group 2E Dosed Moderna Boost Moderna (N=51) | Group 3E Dosed Pfizer/BioNTech Boost Moderna (N=50) | Total (N=154) |
|---|---|---|---|---|
| Number of Protocol Deviations | 24 | 31 | 26 | 81 |
| Type of Protocol Deviations and Enrollment Violations | | | | |
| Inappropriate enrollment | 0 | 0 | 0 | 0 |
| Failure to follow randomization or blinding procedures | 0 | 1 | 0 | 1 |
| Study product management deviation | 0 | 0 | 0 | 0 |
| Study product dispensing error | 0 | 0 | 0 | 0 |
| Study product use/non-use deviation | 0 | 0 | 0 | 0 |
| Conduct of non-protocol procedure | 16 | 14 | 13 | 43 |
| Improper AE/SAE | 0 | 0 | 0 | 0 |
| Unreported AE | 0 | 0 | 0 | 0 |
| Unreported SAE/AESI | 0 | 0 | 0 | 0 |
| Breach of confidentiality | 0 | 0 | 0 | 0 |
| Physical assessment deviation | 0 | 1 | 0 | 1 |
| Lab assessment deviation | 0 | 0 | 0 | 0 |
| Mishandled lab specimen | 0 | 0 | 0 | 0 |
| Staff performing duties that they are not qualified to perform | 0 | 0 | 0 | 0 |
| Use of non-IRB/EC-approved materials | 0 | 0 | 0 | 0 |
| Use of excluded concomitant mediations, devices, or non-study products | 0 | 0 | 0 | 0 |
| Informed consent process deviation | 4 | 8 | 9 | 21 |
| Visit completed outside of window | 0 | 3 | 2 | 5 |
| Other | 4 | 4 | 2 | 10 |

**Assessment of MAH's responses**

With regard to protocol deviations please refer to section 7.1.3

## 4.2.2. Solicited Adverse Reactions

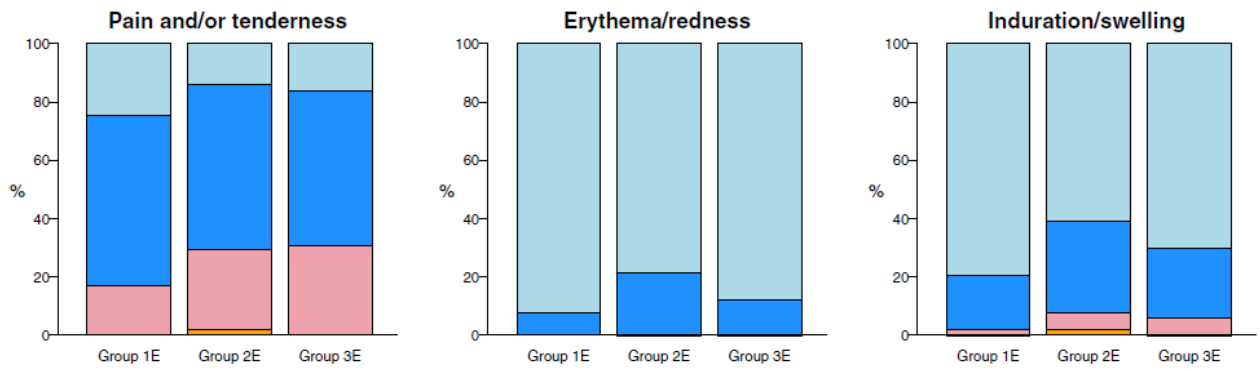
### Solicited Local Adverse Reactions

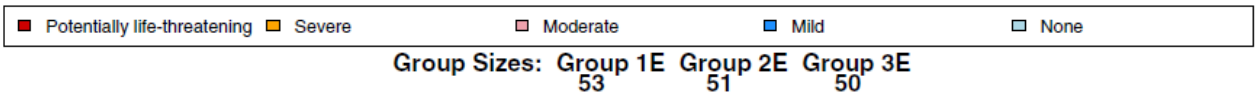
From the data available up to the data snapshot, the number and proportion of participants reporting severe local solicited events/symptoms (out of the total 154 enrolled in all 3 groups) is as follows: 0 (0%) reported severe erythema/redness, 1 (0.6%) severe induration/swelling and 1 (0.6%) severe pain and/or tenderness. The majority of the events were mild or moderate (Table 21). There were no notable clinical differences between groups.

*Table 1 Participants Experiencing Local Solicited Events by Symptom, Maximum Severity, and Group*

| | Group 1E Dosed Janssen Boost Moderna (N=53) n (%) | Group 2E Dosed Moderna Boost Moderna (N=51) n (%) | Group 3E Dosed Pfizer/BioNTech Boost Moderna (N=50) n (%) | Total (N=154) n (%) |
|---|---|---|---|---|
| **Erythema/redness**[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None/not gradable | 50 (94.3) | 40 (78.4) | 43 (86.0) | 133 (86.4) |
| Mild | 3 (5.7) | 11 (21.6) | 7 (14.0) | 21 (13.6) |
| Moderate | 0 | 0 | 0 | 0 |
| Severe | 0 | 0 | 0 | 0 |
| Potentially life-threatening | 0 | 0 | 0 | 0 |
| **Erythema/redness largest diameter**[b] **(cm)** | | | | |
| N | 5 | 13 | 8 | 26 |
| Mean (SD) | 1.0 (0.9) | 3.6 (4.2) | 0.4 (0.3) | 2.1 (3.3) |
| Median | 1.0 | 2.0 | 0.3 | 0.8 |
| 25th, 75th %tile | 0.3, 1.0 | 0.5, 5.0 | 0.1, 0.6 | 0.2,. 2.5 |
| Min, max | 0.2, 2.5 | 0.2, 14.0 | 0.1, 1.0 | 0.1, 14.0 |
| **Induration/swelling**[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None/not gradable | 42 (79.2) | 31 (60.8) | 34 (68.0) | 107 (69.5) |
| Mild | 10 (18.9) | 16 (31.4) | 13 (26.0) | 39 (25.3) |
| Moderate | 1 (1.9) | 3 (5.9) | 3 (6.0) | 7 (4.5) |
| Severe | 0 | 1 (2.0) | 0 | 1 (0.6) |
| Potentially life-threatening | 0 | 0 | 0 | 0 |
| **Induration/swelling largest diameter**[b] | | | | |
| N | 11 | 20 | 13 | 44 |
| Mean (SD) | 3.7 (2.3) | 4.3 (3.9) | 2.0 (1.8) | 3.5 (3.1) |
| Median | 4.0 | 3.0 | 1.0 | 3.0 |
| 25th, 75th %tile | 2.0, 6.0 | 1.6, 7.0 | 0.6, 4.0 | 0.8, 5.0 |
| Min, max | 0.1, 7.0 | 0.3, 15.0 | 0.1, 5.0 | 0.1, 15.0 |
| **Pain and/or tenderness**[a] | | | | |
| Missing | 0 | 0 | 1 (2.0) | 1 (0.6) |
| None | 13 (24.5) | 7 (13.7) | 8 (16.0) | 28 (18.2) |
| Mild | 31 (58.5) | 29 (56.9) | 26 (52.0) | 86 (55.8) |
| Moderate | 9 (17.0) | 14 (27.5) | 15 (30.0) | 38 (24.7) |
| Severe | 0 | 1 (2.0) | 0 | 1 (0.6) |
| Potentially life-threatening | 0 | 0 | 0 | 0 |

Figure 3: Maximum Local Solicited Events by Symptom, Severity, and Group






**Assessment of MAH's responses**

Subjects reported with a comparable frequency of solicited local ARs.

**Solicited Systemic Adverse Reactions**

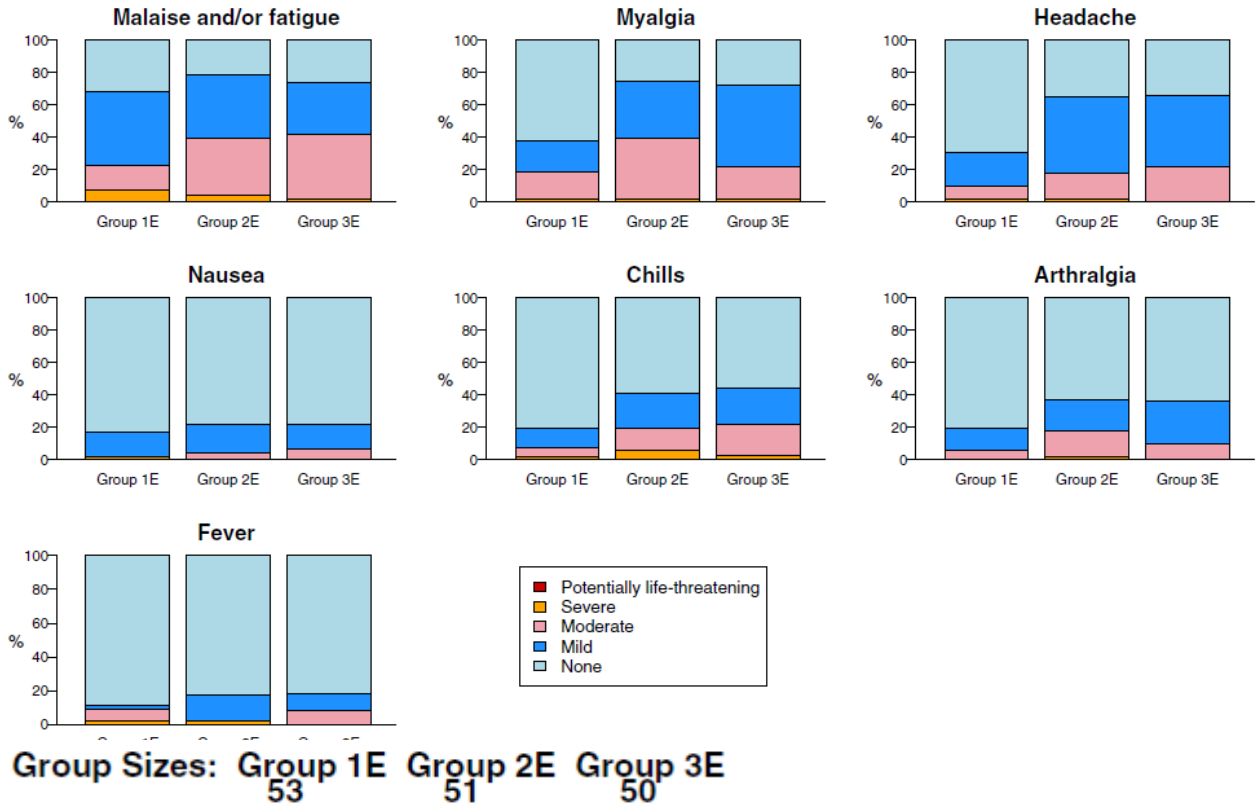
From the data available up to the data snapshot, the number and proportion of participants reporting severe systemic solicited events/symptoms (out of the total 154 enrolled in all 3 groups) are as follows: 5 (3.2%) reported chills, 7 (4.5%) malaise and/or fatigue, 3 (1.9%) myalgia, 2 (1.3%) headache, 1 (0.6%) nausea, 1 (0.6%) arthralgia, and 2 (1.3%) fever (Table 28).

No potentially life-threatening systemic solicited events/symptoms have been reported (DMID Study 21-0012 Day 7 Safety Report). Other than fever, participants in the mRNA priming series groups (Dosed Spikevax, Boost Spikevax and Dosed Comirnaty, Boost Spikevax) tended to report more solicited systemic AEs post-vaccination compared with participants in the Dosed COVID-19 Vaccine Janssen, Boost Spikevax group.

*Table 2 Participants Experiencing Systemic Solicited Events by Symptom, Maximum Severity, and Group*

| | Group 1E Dosed Janssen Boost Moderna (N=53) n (%) | Group 2E Dosed Moderna Boost Moderna (N=51) n (%) | Group 3E Dosed Pfizer/BioNTech Boost Moderna (N=50) n (%) | Total (N=154) n (%) |
|---|---|---|---|---|
| Malaise and/or fatigue[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None | 17 (32.1) | 11 (21.6) | 13 (26.0) | 41 (26.6) |
| Mild | 24 (45.3) | 20 (39.2) | 15 (30.0) | 59 (38.3) |
| Moderate | 8 (15.1) | 18 (35.3) | 21 (42.0) | 47 (30.5) |
| Severe | 4 (7.5) | 2 (3.9) | 1 (2.0) | 7 (4.5) |
| Myalgia[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None | 33 (62.3) | 13 (25.5) | 14 (28.0) | 60 (39.0) |
| Mild | 10 (18.9) | 18 (35.3) | 25 (5.0) | 53 (34.4) |
| Moderate | 9 (17.0) | 19 (37.3) | 10 (20.0) | 38 (24.7) |
| Severe | 1 (1.9) | 1 (2.0) | 1 (2.0) | 3 (1.9) |
| Headache[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None | 37 (69.8) | 18 (35.3) | 17 (34.0) | 72 (46.8) |
| Mild | 11 (20.8) | 24 (47.1) | 22 (44.0) | 57 (37.0) |
| Moderate | 4 (7.5) | 8 (15.7) | 11 (22.0) | 23 (14.9) |
| Severe | 1 (1.9) | 1 (2.0) | 0 | 2 (1.3) |
| Nausea[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None | 44 (83.0) | 40 (78.4) | 39 (78.0) | 123 (79.9) |
| Mild | 8 (15.1) | 9 (17.6) | 8 (16.0) | 25 (16.2) |
| Moderate | 0 | 2 (3.9) | 3 (6.0) | 5 (3.2) |
| Severe | 1 (1.9) | 0 | 0 | 1 (0.6) |
| Chills[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None | 43 (81.1) | 30 (58.8) | 28 (56.0) | 101 (65.6) |
| Mild | 6 (11.3) | 11 (21.6) | 11 (22.0) | 28 (18.2) |
| Moderate | 3 (5.7) | 7 (13.7) | 10 (20.0) | 20 (13.0) |
| Severe | 1 (1.9) | 3 (5.9) | 1 (2.0) | 5 (3.2) |
| Arthralgia[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None | 44 (83.0) | 32 (62.7) | 32 (64.0) | 108 (70.1) |
| Mild | 6 (11.3) | 10 (19.6) | 13 (26.0) | 29 (18.8) |
| Moderate | 3 (5.7) | 8 (15.7) | 5 (10.0) | 16 (10.4) |
| Severe | 0 | 1 (2.0) | 0 | 1 (0.6) |
| Fever[a] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| None | 46 (86.8) | 43 (84.3) | 41 (82.0) | 130 (84.4) |
| Mild | 3 (5.7) | 7 (13.7) | 5 (10.0) | 15 (9.7) |
| Moderate | 3 (5.7) | 0 | 4 (8.0) | 7 (4.5) |
| Severe | 1 (1.9) | 1 (2.0) | 0 | 2 (1.3) |

Figure 4: Maximum Systemic Solicited Events by Symptom, Severity, and Group




**Assessment of MAH's responses**

No clear pattern of differences can be recognised. Based on graphical interpretations systemic solicited AEs have in general a lower frequency and severity if booster has been administered after COVID-19 Vaccine Janssen primary vaccination.

## 4.2.3. Unsolicited Adverse Reactions

| Spalte1 | From clinical overview in Module 2 submitted in eCTD 0198 and eCTD 0146: | From body text in the safety report dated August 31st 2021 submitted in Module 5 in eCTD 0146: | From Tables 4a - 4c in the study report | From Table 5 in safety study report | From Table 6 in safety study report | From Figures 1a - 2c |
|---|---|---|---|---|---|---|
| **Unsolicited** | | | | | | |
| **1E (53 subjects)** | 13 (24.5%) participants reported 15 unsolicited AEs | 18 participants reported 21 unsolicited AEs | 18 participants reported 21 unsolicited AEs | | | 18 |
| **2E (51 subjects)** | 15 (29.4%) participants reported 19 unsolicited Aes | 16 participants reported 22 unsolicited AEs | 16 participants reported 22 unsolicited AEs | | | 16 |
| **3E (50 subjects)** | 18 (36.0%) participants reported 33 AEs | 20 participants reported 42 AEs | 20 participants reported 42 AEs | | | 20 |
| | | | | | | |
| **Unsolicited related** | | | | | | |
| **1E (53 subjects)** | 7 participants (13.2%) | 7 participants (13.2%) | 8 unsolicited AEs | 7 participants (13.2%) | | |
| **2E (51 subjects)** | 6 participants (11.8%) | 6 participants (11.8%) | 8 unsolicited AEs | 6 participants (11.8%) | | |
| **3E (50 subjects)** | 11 participants (22.0%) | 11 participants (22.0%) | 18 unsolicited AEs | 11 participants (22.0%) | | |
| | | | | | | |
| **Unsolicited unrelated** | | | | | | |
| **1E (53 subjects)** | 7 participants (13.2%) | 11 participants (20.8%) | 13 unsolicited AEs | | 11 participants (20.8%) | |
| **2E (51 subjects)** | 9 participants (17.6%) | 10 participants (19.6%) | 14 unsolicited AEs | | 10 participants (19.6%) | |
| **3E (50 subjects)** | 12 participants (24.0%) | 16 participants (32.0%) | 24 unsolicited AEs | | 16 participants (32.0%) | |

**Assessment of MAH's responses**

From the 53 participants in group 1E (EUA dosed COVID-19 Vaccine Janssen, boost Spikevax) 18 participants reported 21 unsolicited AEs. From the 51 participants in group 2E (EUA dosed Spikevax, boost Spikevax) 16 participants reported 22 unsolicited AEs. From the 50 participants in Group 3E (EUA dosed Comirnaty, boost Spikevax) 20 participants reported 42 AEs. The number (and percentage) of participants reporting unsolicited AEs, of any severity grade, that were deemed related to the study

product was 7/53 (13.2%) in Group 1E, 6/51 (11.8%) in Group 2E and 11/50 (22.0%) in Group 3E. Most participants reported related AEs of at most Grade 2 severity, with only one participant (Group 1E) reporting at least one AE of Grade 3.

The number (and percentage) of participants reporting unsolicited not related AEs, of any severity grade, was 11/53 (20.8%) in Group 1E, 10/51 (19.6%) in Group 2E and 16/50 (32.0%) in Group 3E. Most participants reported not related AEs of at most Grade 2 severity, with one participant (Group 2E) reporting at least one AE of Grade 3, and one participant (Group 1E) reporting at least one AE of Grade 4 severity.

Severity of unsolicited AEs

**Visit Cutoff Date: August 16, 2021**
**Table 4a - Total Number of Unsolicited AEs by Severity and Relationship to Study Vaccination[1] , Group 1E (Dosed Janssen)**
**Number of Participants Enrolled to Group 1E (Dosed Janssen) = 53**
**Number of Group 1E Participants with AE = 18**

| | Not Related | Related | Total |
|---|---|---|---|
| **Severity Grade** | | | |
| Grade 1 - Mild | 9 ( 60.0%) | 6 ( 40.0%) | 15 ( 71.4%) |
| Grade 2 - Moderate | 3 ( 75.0%) | 1 ( 25.0%) | 4 ( 19.0%) |
| Grade 3 - Severe | 0 ( 0.0%) | 1 (100.0%) | 1 ( 4.8%) |
| Grade 4 - Potentially life-threatening | 1 (100.0%) | 0 ( 0.0%) | 1 ( 4.8%) |
| Grade 5 - Death | 0 (-%) | 0 (-%) | 0 ( 0.0%) |
| Total | 13 ( 61.9%) | 8 ( 38.1%) | 21 (100.0%) |

**Visit Cutoff Date: August 16, 2021**
**Table 4b - Total Number of Unsolicited AEs by Severity and Relationship to Study Vaccination[1] , Group 2E (Dosed Moderna)**
**Number of Participants Enrolled to Group 2E (Dosed Moderna) = 51**
**Number of Group 2E Participants with AE = 16**

| | Not Related | Related | Total |
|---|---|---|---|
| **Severity Grade** | | | |
| Grade 1 - Mild | 8 ( 57.1%) | 6 ( 42.9%) | 14 ( 63.6%) |
| Grade 2 - Moderate | 5 ( 71.4%) | 2 ( 28.6%) | 7 ( 31.8%) |
| Grade 3 - Severe | 1 (100.0%) | 0 ( 0.0%) | 1 ( 4.5%) |
| Grade 4 - Potentially life-threatening | 0 (-%) | 0 (-%) | 0 ( 0.0%) |
| Grade 5 - Death | 0 (-%) | 0 (-%) | 0 ( 0.0%) |
| Total | 14 ( 63.6%) | 8 ( 36.4%) | 22 (100.0%) |

**Visit Cutoff Date: August 16, 2021**
**Table 4c - Total Number of Unsolicited AEs by Severity and Relationship to Study Vaccination[1] , Group 3E (Dosed Pfizer/BioNTech)**
**Number of Participants Enrolled to Group 3E (Dosed Pfizer/BioNTech) = 50**
**Number of Group 3E Participants with AE = 20**

| | Not Related | Related | Total |
|---|---|---|---|
| Severity Grade | | | |
| Grade 1 - Mild | 15 ( 60.0%) | 10 ( 40.0%) | 25 ( 59.5%) |
| Grade 2 - Moderate | 9 ( 52.9%) | 8 ( 47.1%) | 17 ( 40.5%) |
| Grade 3 - Severe | 0 (-%) | 0 (-%) | 0 ( 0.0%) |
| Grade 4 - Potentially life-threatening | 0 (-%) | 0 (-%) | 0 ( 0.0%) |
| Grade 5 - Death | 0 (-%) | 0 (-%) | 0 ( 0.0%) |
| Total | 24 ( 57.1%) | 18 ( 42.9%) | 42 (100.0%) |

**Assessment of MAH's responses**

Based on safety report from 16th August 2021, most participants experienced mild or moderate unsolicited AEs without recognisable difference between groups.

**Figure 1a - All Unsolicited Adverse Events by MedDRA System Organ Class and Severity, Group 1E (Dosed Janssen)**
**Number of Enrolled Participants = 53**
**Total Number of Participants with one or more AE = 18**

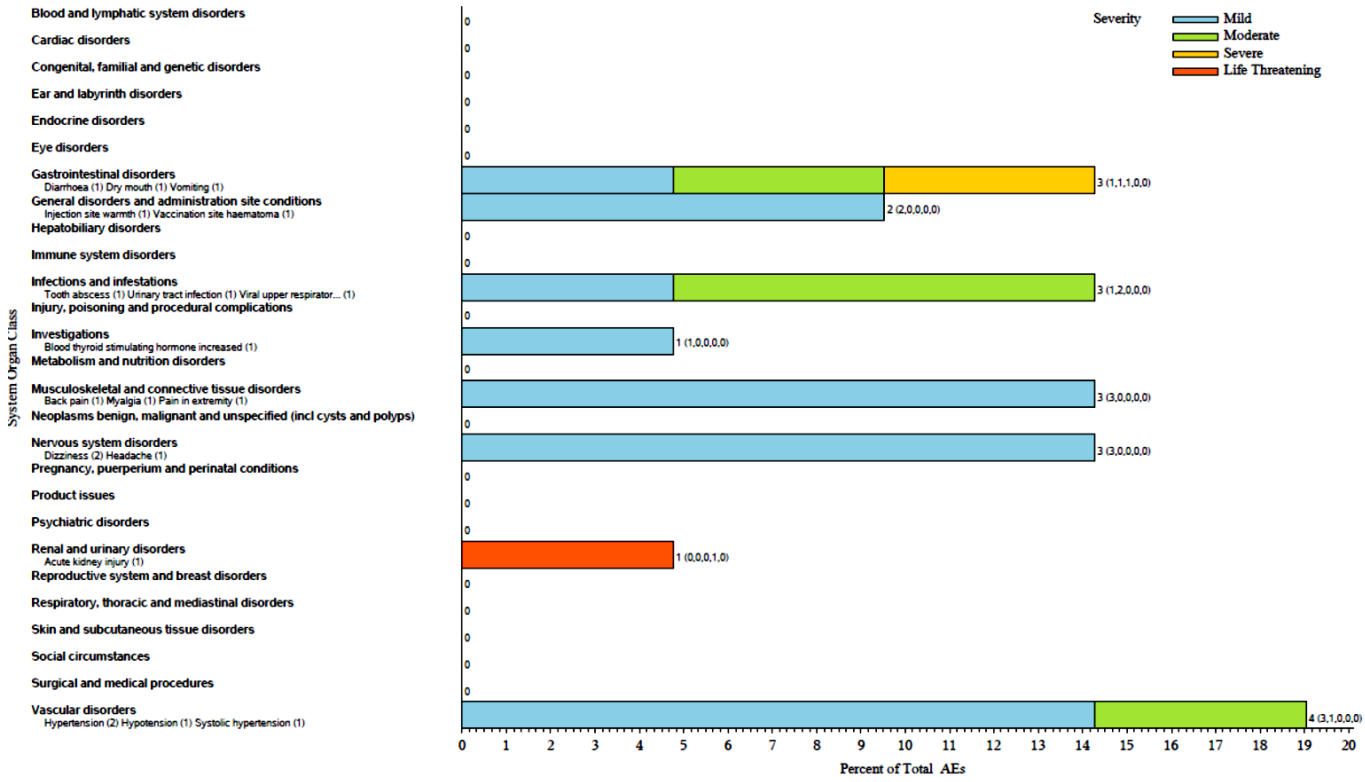


**Figure 1b - All Unsolicited Adverse Events by MedDRA System Organ Class and Severity, Group 2E (Dosed Moderna)**
**Number of Enrolled Participants = 51**
**Total Number of Participants with one or more AE = 16**

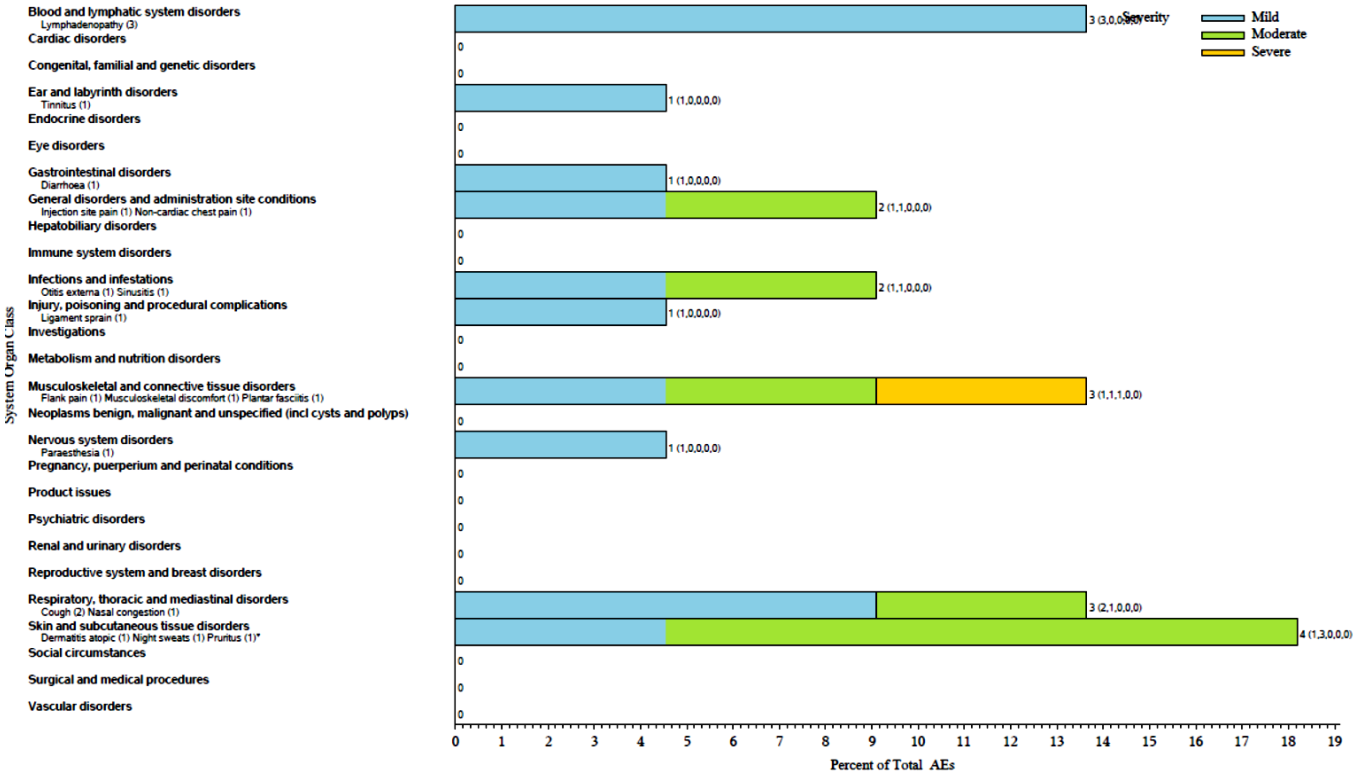



**Figure 1c - All Unsolicited Adverse Events by MedDRA System Organ Class and Severity, Group 3E (Dosed Pfizer/BioNTech)**
**Number of Enrolled Participants = 50**
**Total Number of Participants with one or more AE = 20**

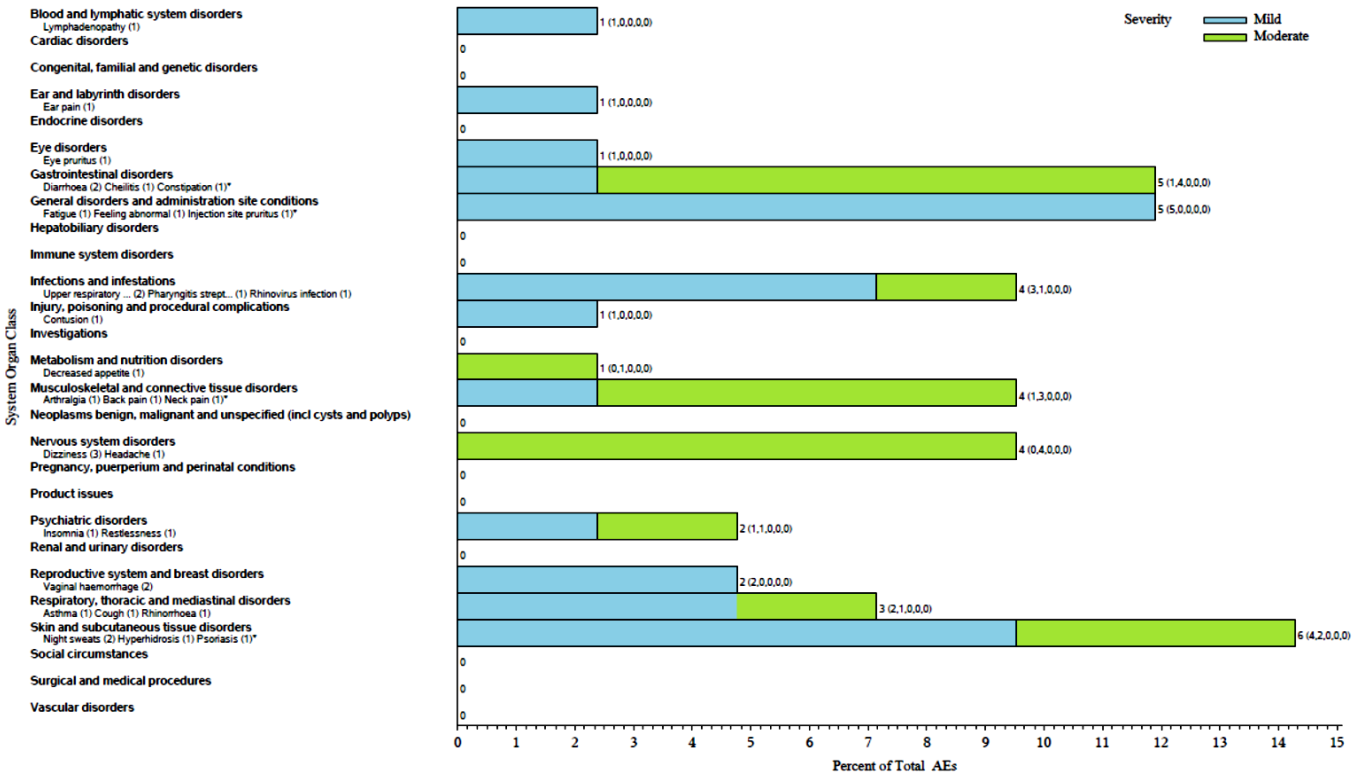


**Figure 2a - All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 1E (Dosed Janssen)**
**Number of Enrolled Participants = 53**
**Total Number of Participants with one or more AE = 18**

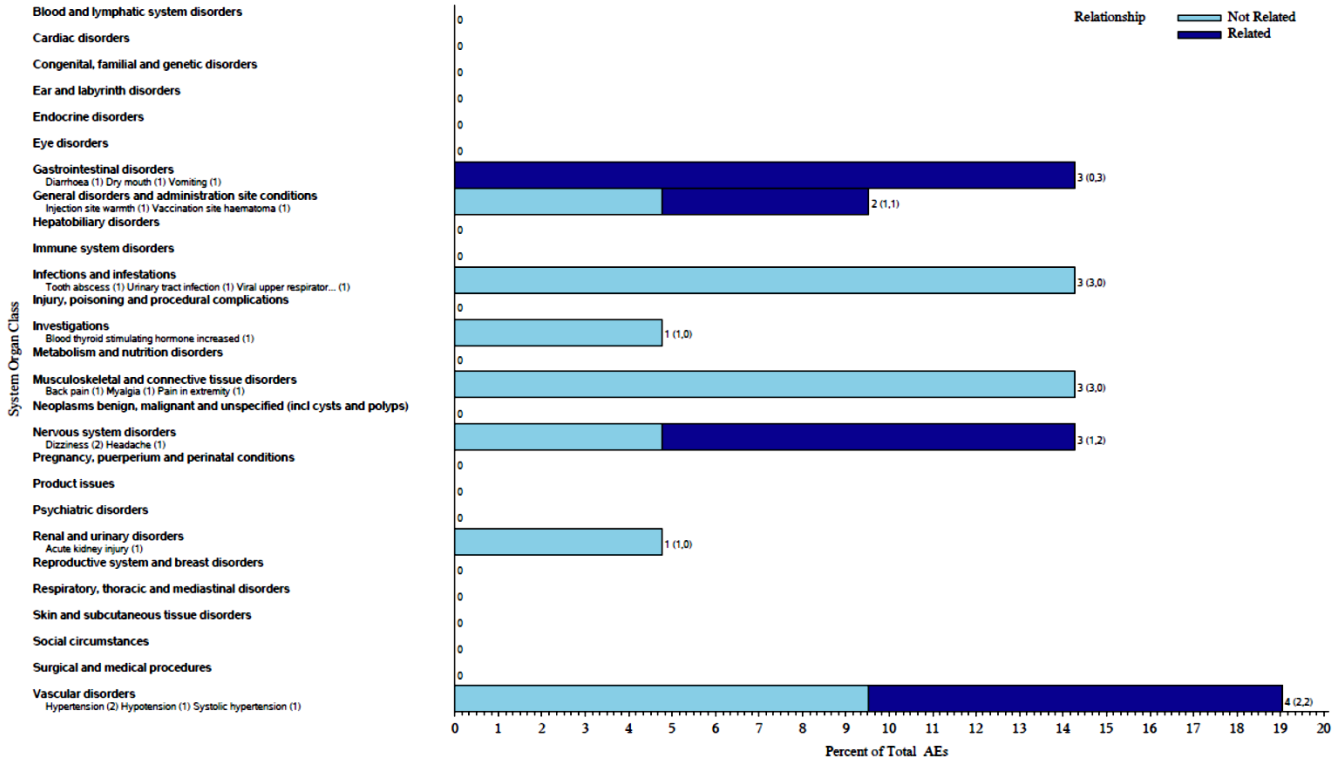



**Figure 2b - All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 2E (Dosed Moderna)**
**Number of Enrolled Participants = 51**
**Total Number of Participants with one or more AE = 16**

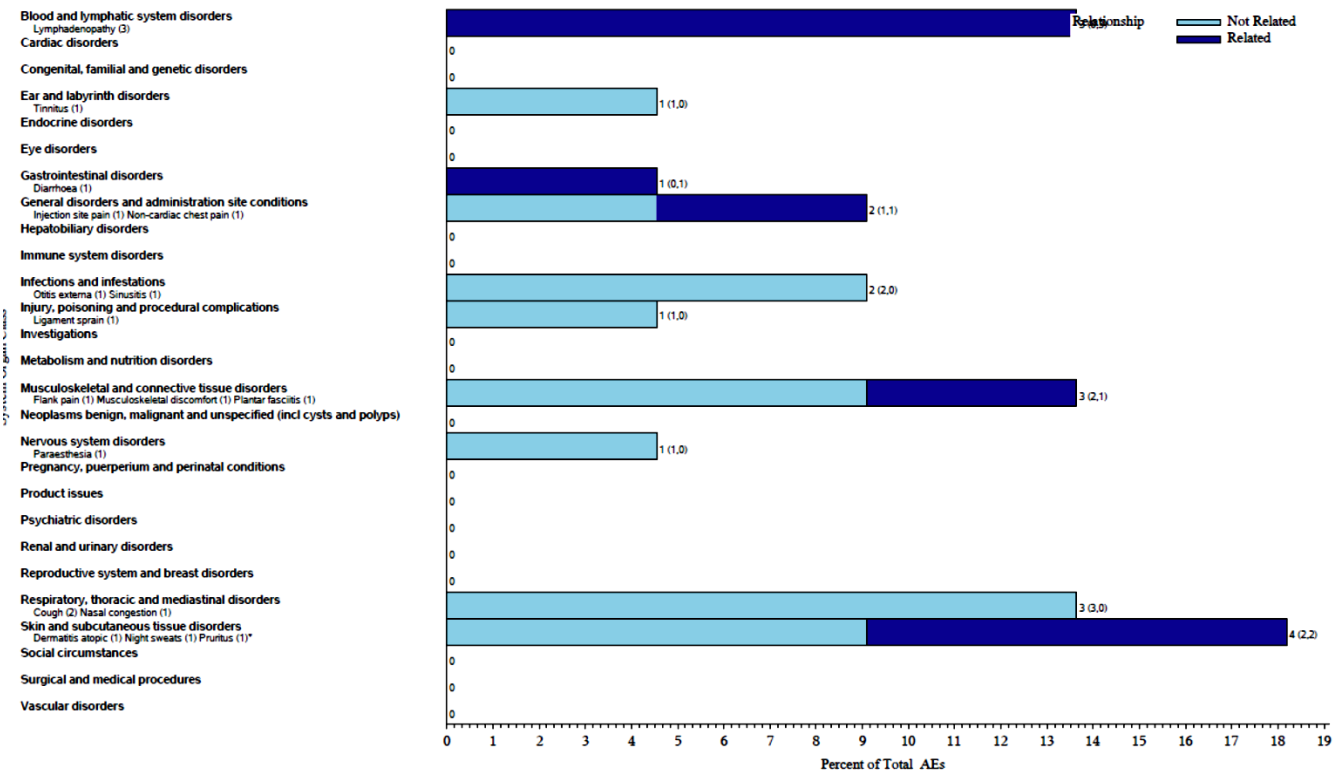
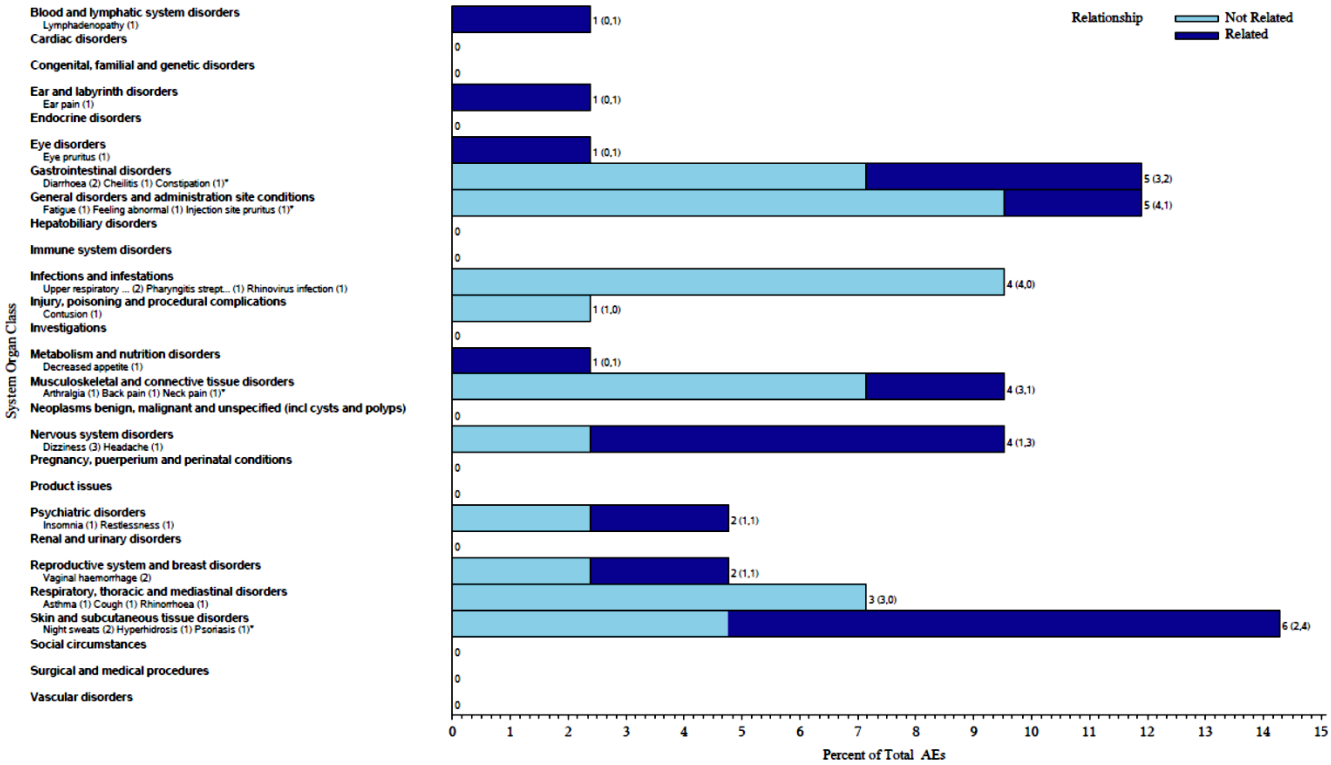


Figure 2c - All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 3E (Dosed Pfizer/BioNTech)
Number of Enrolled Participants = 50
Total Number of Participants with one or more AE = 20




### *4.2.3.1. Related unsolicited*

The most common AE related to study vaccine was lymphadenopathy. There was 1 grade 3 AE of vomiting and no grade 4 or grade 5 AEs.

Unsolicited AEs (of any severity grade) were deemed related to study vaccination

- in 7/53 (13.2%) participants in Group 1E,
- 6/52 (11.8%) in Group 2E and
- 11/50 (22.0%) in Group 3E.

Most participants reported related AEs of at most grade 2 severity, with only 1 participant (Group 1E) reporting at least 1 AE of grade 3 (vomiting).

**Visit Cutoff Date: August 16, 2021**
**Table 5 - Participants Experiencing Unsolicited Adverse Events Related to Study Vaccination, by MedDRA System Organ Class, Preferred Term, Severity, and Group**

| MedDRA System Organ Class and Preferred Term[1]/ Maximum Severity | Group 1E Dosed Janssen Boost Moderna (N=53) n (%) | Group 2E Dosed Moderna Boost Moderna (N=51) n (%) | Group 3E Dosed Pfizer/BioNTech Boost Moderna (N=50) n (%) | Total (N=154) n (%) |
|---|---|---|---|---|
| Participants with one or more AEs | | | | |
| Grade 1 - Mild | 6 ( 11.3%) | 4 ( 7.8%) | 4 ( 8.0%) | 14 ( 9.1%) |
| Grade 2 - Moderate | 0 ( 0.0%) | 2 ( 3.9%) | 7 ( 14.0%) | 9 ( 5.8%) |
| Grade 3 - Severe | 1 ( 1.9%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.6%) |
| Grade 4 - Potentially life-threatening | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Grade 5 - Death | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Total | 7 ( 13.2%) | 6 ( 11.8%) | 11 ( 22.0%) | 24 ( 15.6%) |

**Assessment of MAH's responses**

No real numerical difference in related unsolicited AEs can be seen. However, it seems that more AE of higher severity occur more often after mRNA primary series than after COVID-19 Vaccine Janssen vector primary vaccination. Of note most moderate AE are observed with the heterologous Comirnaty/Spikevax regime.

#### *4.2.3.2. Unrelated unsolicited:*

| **From clinical overview in Module 2 submitted in eCTD 0198 and eCTD 0146:** | **From safety report dated 31st August 2021 submitted in Module 5 in eCTD 0146 on page 7:** |
|---|---|
| The number (and percentage) of participants reporting **unsolicited not related** AEs, of any severity grade, was<br>- **7/53 (13.2%)** in Group 1E,<br>- **9/51 (17.6%)** in Group 2E and<br>- **12/50 (24.0%)** in Group 3E.<br>Most participants reported not related AEs of at most grade 2 severity, with only 1 participant (Group 2E) reporting at least 1 AE of grade 3 (flank pain). | The number (and percentage) of participants reporting **unsolicited not related** AEs, of any severity grade, was<br>- **11/53 (20.8%)** in Group 1E,<br>- **10/51 (19.6%)** in Group 2E and<br>- **16/50 (32.0%)** in Group 3E.<br>Most participants reported not related AEs of at most Grade 2 severity, with one participant (Group 2E) reporting at least one AE of Grade 3, and one participant (Group 1E) reporting at least one AE of Grade 4 severity (Table 6). |

See also graphical comparison at the beginning of section 7.2.1.3.

**Assessment of MAH's responses**

There is a slight numerical difference in reported unrelated unsolicited AEs as mentioned in overview and in CSR.

#### *4.2.3.3. Severe unsolicited AEs*

For severe **related** unsolicited AEs, there was 1 grade 3 AE of vomiting and no grade 4 or grade 5 AEs (DMID Study 21-0012 Day 7 Safety Report, Table 5).

For severe **unrelated** unsolicited AEs, there was 1 AKI event categorised Grade 4 and 1 unrelated grade 3 flank pain.

**Assessment of MAH's responses**

Unsolicited AEs (of any severity grade) were deemed related to study vaccination in 7/53 (13.2%) participants in Group 1E, 6/52 (11.8%) in Group 2E and 11/50 (22.0%) in Group 3E (DMID Study 21-0012 Day 7 Safety Report). Most participants reported related AEs of at most grade 2 severity, with only 1 participant (Group 1E) reporting at least 1 AE of grade 3 (vomiting).

The number (and percentage) of participants reporting unsolicited not related AEs, of any severity grade, was 7/53 (13.2%) in Group 1E, 9/51 (17.6%) in Group 2E and 12/50 (24.0%) in Group 3E (DMID Study 21-0012 Day 7 Safety Report). Most participants reported not related AEs of at most grade 2 severity, with only 1 participant (Group 2E) reporting at least 1 AE of grade 3 (flank pain).

**Deaths**

In DMID Study 21-0012, no deaths had occurred at the time of the data snapshot (DMID Study 21-0012 Day 7 Safety Report).

**Serious Adverse Events**

No SAEs have been reported in DMID Study 21-0012 (DMID Study 21-0012 Day 7 Safety Report).

**Discontinuation from Investigational Product or Study Participation**

No participants have withdrawn early for any reason from Study 21-0012 (DMID Study 21-0012 Day 7 Safety Report).

**Pregnancies**

No pregnancies were reported in DMID Study 21-0012 (DMID Study 21-0012 Day 7 Safety Report).

## *4.3. Discussion*

### 4.3.1. Study design

The safety profile of solicited and unsolicited ARs was evaluated in the supportive DMID Study 21-0012 with heterologous/homologous (Spikevax) SARS-CoV-2 vaccine dosing (Spikevax booster) study of the various EUA vaccines (COVID-19 Vaccine Janssen, Spikevax, Comirnaty) in participants' ≥ 18 years old. A total of 154 participants have been enrolled and received a Spikevax boost injection (IM; 100 µg) approximately 12-20 weeks after receiving primary vaccination under EUA. DMID 21-0012 is the only study submitted by the MAH to support heterologous booster variation.

It must be noted, that the homologous Spikevax arm in DMID Study 21-0012 is not comparable to the proposed booster dose of 50 µg of Spikevax (100 µg was administered as booster in DMID Study 21-0012 and it was administered within a shorter timeframe of 12-20 weeks after primary vaccination).

There are some limitations of the study design. One of them is the age of subjects which is above 18 years of age. No safety data are therefore submitted for subjects below 18 years of age. Based on the requested SmPC wording where only boosting in adults is requested, this is an acceptable limitation for the time being.

Another limitation is lack of data for heterologous boosting with Spikevax in subjects with a compromised state of health. A high reactogenicity might prove detrimental to these individuals. It is expected that this type of data will be collected as part of the ongoing PASS efforts. The missing information of the safety of Spikevax in patients with unstable health conditions and comorbidities is addressed in the PASS mRNA-1273-P904. Of note this study only evaluates the use of Spikevax, but not given after priming with other COVID-19 vaccines. The frail population is additionally monitored within the post-approval pharmacovigilance system within established signal detection, validation and evaluation of spontaneous reports.

The proposed shortening of the booster time interval to 3 months after the primary series is based on a rather limited safety data base, insufficient to robustly conclude on rare events like myocarditis or pericarditis, a safety concern particularly for the younger population. It is not expected to get safety data to estimate the risk for myocarditis/pericarditis in a controlled clinical trial. The assessment is therefore subject to pharmacovigilance in a larger population. Of note, widespread use of Spikevax as a booster doses is reported. The subsequently submitted safety data from the post-marketing surveillance did not reveal any new safety signals with regard to administration of a third dose given at least 3 months after

the primary series. The interval for giving the booster dose was 3 to 5 months depending on local recommendations. The data confirmed what is known about the risk of myocarditis/pericarditis, which of note appears not to be higher after the third dose compared to after the second dose A differentiation between a 100 µg third dose and a 50 µg booster dose is not possible within the submitted post-marketing safety data. Uncertainties remain with regard to the methodology of recording the dose numbers. No clinical information is given for the fatal cases and only the top 3 SAEs are presented for the post-marketing safety data base. The submitted data do not raise new safety signals with regard to a third dose or booster dose given at least 3 months after primary series. The data do not extent the safety data base for the heterologous booster. The submitted safety data were previously submitted to PRAC within MEA 11.10 (11$^{th}$ SSR). Within this procedure the MAH was asked to submit clinical information about the fatal cases and on methodological uncertainties with regard to the recording of the dose number. Additional information is expected from PASS mRNA-1273-P904 and from routine pharmacovigilance.

Based on eligibility criteria, subjects in the DMID 21-0012 study should not have had COVID-19 or SARS-CoV-2 infection prior to boosting. No safety data for a heterologous booster regime in individuals with previous COVID-19 or SARS-CoV-2 seropositive individuals are available from the trail or have been subsequently submitted by the MAH. Safety data are only available from mRNA-1273-P301 for a primary series. The safety data do not raise any concerns for the use of Spikevax in SARS-CoV-2 positive individuals compared to SARS-CoV-2 negative individuals.

A limitation seems to be the lack of data for a heterologous booster after a Vaxzevria primary series. Literature (Stewart et al) is available only for a "mixed-matched" use of Spikevax together with Vaxzevria (i.e. one dose of Spikevax after a dose of Vaxzevria). The safety data in this limited sample size indicate a higher reactogenicity after heterologous primary series with Spikevax compared with a homologous primary series. More safety and immunogenicity data for a heterologous booster after primary vaccination with an adenovector COVID-19 vaccine is available from the COV-BOOST study, a multicentre, randomised Phase 2 study of a heterologous booster vaccination. Participants were adults aged 30 years or older, who had received two doses of either Comirnaty or Vaxzevria, and were at least 84 days post-second dose by the time of enrolment. Spikevax boosted neutralising antibody response and no safety concerns were raised.

The sample size of the submitted study is too low to detect rare events or to fil the gap of missing information. Moreover, the follow-up period of 29 days is rather short. The monitoring of a heterologous booster of Spikevax in a larger population without restrictions (i.e. also including frail or SARS-CoV-2 positive individuals or individuals with previous infection is subject to the pharmacovigilance. In the PSUR covering the time period 18/12/2020 to 30/06/2021 the MAH was requested to present data, including literature, and discuss the safety profile of Spikevax in relation to heterologous COVID-19 vaccines schedule. The data and discussion should be presented in relevant sections e.g. off-label use, or in addition to the already presented PSUR headline "Interaction with other vaccines (Heterologous Vaccine Schedule)".

Additional limitation is that only 100 mcg booster dose has been studied in the submitted study. From safety perspective this is however not an issue. Please refer to the discussion on efficacy.

DMID 21-0012 includes also Cohort 2 with so called delayed boost. Here however, no data has been submitted within the dossier.

## 4.3.2. Study conduct

It is unclear why group 1E and group 2E recruited more subjects than planned. This can however happen in multicentric trials.

Protocol deviations were mostly related to appropriate consenting, but also to mishandled lab specimens.

### 4.3.3. Study results

Safety data from DMID Study 21-0012 are limited as they are based on 154 subjects. They could be considered somehow similar to what has been observed previously described in the safety profile of a booster dose of 50 µg of Spikevax in the phase 2 study mRNA-1273-P201 Part B that was used as the basis of the type II variation to include the 50 µg homologous booster in the SmPC. These data are however not considered informative to be listed in the SmPC in detail.

Solicited local and systemic reaction were followed-up up to seven days after the booster dosage of 100 µg of Spikevax. Safety data after Day 29 were not collected in the trial.

Solicited local reactions

Subjects reported with a comparable frequency of solicited local ARs.

Solicited systemic reactions

No clear pattern of differences between groups can be recognised. Based on graphical interpretations systemic solicited AEs have in general a lower frequency and severity if booster has been administered after COVID-19 Vaccine Janssen primary vaccination.

Unsolicited

Based on safety report from 16th August 2021, most participants experienced mild or moderate unsolicited AEs without recognisable difference between groups.

Unsolicited AEs (of any severity grade) were deemed related to study vaccination in 7/53 (13.2%) participants in Group 1E, 6/52 (11.8%) in Group 2E and 11/50 (22.0%) in Group 3E (DMID Study 21-0012 Day 7 Safety Report). Most participants reported related AEs of at most grade 2 severity, with only 1 participant (Group 1E) reporting at least 1 AE of grade 3 (vomiting).

The number (and percentage) of participants reporting unsolicited not related AEs, of any severity grade, was 7/53 (13.2%) in Group 1E, 9/51 (17.6%) in Group 2E and 12/50 (24.0%) in Group 3E (DMID Study 21-0012 Day 7 Safety Report). Most participants reported not related AEs of at most grade 2 severity, with only 1 participant (Group 2E) reporting at least 1 AE of grade 3 (flank pain).

No real numerical difference in related unsolicited AEs can be seen. However, it seems that higher severity could be expected more often after a mRNA primary series than after COVID-19 Vaccine Janssen vector primary vaccination.

On request the MAH submitted the CIOMS for the case of grade 4 kidney injury. The submitted clinical information do not suggest causality to the vaccination. No deaths, no SAEs, no discontinuations have been reported.

No pregnancies have been noted.

### 4.3.4. Conclusion on safety

Additional results from the ongoing Phase 1 DMID 21-0012 study, which has enrolled 154 participants who received heterologous prime series and a subsequent booster dose of 100 µg of Spikevax further seem to support a similar reactogenicity and safety profile within the 7 days following the administration of the booster dose. The sample size of the submitted study is too low to detect rare events after heterologous booster with Spikevax (e.g. myocarditis, pericarditis or potentially immune mediated

diseases), or to fill the gap of missing information (e.g. use in the frail population). Moreover, the follow-up period of 29 days is rather short. The monitoring of a heterologous booster of Spikevax in a larger population without restrictions (i.e. also including frail or SARS-CoV-2 positive individuals or individuals with previous Covid-19) is subject to the pharmacovigilance. The subsequently submitted safety data from the post-marketing surveillance did not reveal any new safety signals with regard to administration of a 3rd dose given *at least 3 months* after the primary series. The interval for giving the booster dose was 3 to 5 months depending on local recommendations. The data confirmed what is known about the risk of myocarditis/pericarditis, which of note appears not to be higher after dose 3 compared to after dose 2. Stratification of cases of myocarditis with known dose and time to onset that occur within the 7 days following vaccination, considering observed versus expected analyses, showed an increased risk following dose 2 in young males, but no similar increase has yet been observed following a third dose. A differentiation between a 100 µg 3rd dose and a 50 µg booster dose is not possible within the submitted post-marketing safety data. Uncertainties remain with regard to the methodology of recording the dose numbers. No clinical information is given for the fatal cases and only the top 3 SAEs are presented for the post-marketing safety data base. The submitted data do not raise new safety signals with regard to a 3rd dose or booster dose given at least 3 months after primary series. The data do not extent the safety data base for the heterologous booster. Supportive studies for the heterologous booster remain the DIMID and the COV-BOOST study. The interval of 3 months however could be supported by the summary of all submitted safety data (post-marketing surveillance, CoV-BOOST, Com-CoV-2, and DIMID). The submitted safety data were previously submitted to PRAC within MEA 11.10 (11$^{th}$ SSR). Within this procedure the MAH was asked to submit clinical information about the fatal cases and on methodological uncertainties with regard to the recording of the dose number. PRAC concluded, that the benefit-risk balance of Spikevax in the approved indication remains unchanged. Additional information is expected from PASS mRNA-1273-P904 and from routine pharmacovigilance.

# 5. Changes to the Product Information

As a result of this variation, sections 4.2 and 5.1 of the SmPC are being updated to introduce the heterologous booster with Spikevax. The Package Leaflet is updated accordingly.

In addition, the MAH took the opportunity to implement the WHO-approved INN 'elasomeran' in the Spikevax product information, which is acceptable. The MAH also took the opportunity to make minor editorial changes/corrections throughout the product information, which is also accepted.

Amendments to Annexes A, I, IIIA and IIIB are recommended. See Attachment 1 which includes all agreed changes to the Product Information.

# 6. Request for supplementary information

## *Clinical aspects*

## *6.1. Other concerns*

## *Clinical aspects*

Efficacy / Immunogenicity

1. In the DMID trial which enrolled 154 subjects protocol deviations were reported for 41 subjects. This protocol deviations concerning "conduct of non-protocol procedures" included either

mishandled lab specimen or that the study staff did not collect the memory aid data during Day 8 safety call. More than around 20 % of enrolled subjects did not reported correctly their safety data or the blood draws were not properly handled. The MAH is requested to analyse the impact of this high number of protocol violations on safety and immunogenicity data.

2. No data of boosting for Vaxzevria after primary vaccination are filed by the MAH for the Spikevax booster. The MAH should discuss and provide evidence to justify a broad statement as regards authorised vaccines for the primary series.
3. The MAH is requested to discuss the results in the light of the higher dose used for boosting.
4. The MAH is requested to discuss the characteristics of the used assays for determining neutralising antibodies in the DMID trial and the mRNA-1273-P201 trial and possible approaches to enable bridging e.g. by analysing identical samples or using a common standard.
5. The MAH should comment on the impact of the time intervals between primary series and booster injection. The MAH is asked to systematically assess the timeframe between the primary immunisation and the booster injection as 6 months in case of heterologous and homologous boosting may not be the appropriate timeframe. The studied interval in the DMID trial and other available evidence should be taken into consideration. Such time span based on any relevant evidence should be mentioned in section 4.2 of the SmPC with corresponding information in the PL.

Safety

6. Based on eligibility criteria, subjects in the DMID 21-0012 study should not have had COVID-19 or SARS-CoV-2 infection prior to boosting. The MAH is requested to outline the available data and comment on experience of vaccination of previously infected persons.
7. A limitation seems to be lack of any data on boosting after Vaxzevria primary series. As Vaxzevria is an approved SARS-CoV-2 vaccine in the EU, the MAH should discuss and provide supportive data on boosting after Vaxzevria.
8. From a practical point of view, it is questioned whether Tables 8a – 8c in the study report adequately reflect the occurrence of AEs from day 1 to day 8. Particularly, it is not understood, how "memory aid" has been constructed. Did the subjects have to remember each day or did they have a diary (memory aid?)? Please clarify the so called "memory aid". Please also clarify if missing of collection (protocol deviation) of "memory aid" on day 8 was only a technical issue and if quality of data was not compromised.
9. There is no new safety data submitted in the dossier compared to what has been submitted in the initial eCTD 0146 sequence. Safety report is dated 31st August 2021. Although the MAH claims not to have observed any new safety signals, this report is outdated and updated study report would be expected.
10. There is a slight incidence and frequency difference in unsolicited AEs and unsolicited unrelated AEs between submitted overview (eCTD 0146 and eCTD 0198) vs. safety report (eCTD 0146, dated 31st August 2021) to which the overview references. Please clarify the correct numbers.
11. No additional information on grade 4 acute kidney injury appears to be included in the study report. Please provide additional information.

12. There is emerging data that heterologous regimen in the primary regimen are cause for an increased risk of myocarditis/pericarditis. The MAH is requested to discuss how this possible risk of heterologous regimen using Spikevax will be followed-up.
13. The MAH is requested to outline plans to follow-up safety of booster injections in individuals with compromised state of health/multimorbid conditions.

# 7. Assessment of the responses to the request for supplementary information

## *7.1. Other concerns*

## *Clinical aspects*

Efficacy / Immunogenicity

**1. In the DMID trial which enrolled 154 subjects protocol deviations were reported for 41 subjects. This protocol deviations concerning "conduct of non-protocol procedures" included either mishandled lab specimen or that the study staff did not collect the memory aid data during Day 8 safety call. More than around 20 % of enrolled subjects did not reported correctly their safety data or the blood draws were not properly handled. The MAH is requested to analyse the impact of this high number of protocol violations on safety and immunogenicity data.**

**Summary of the MAH's response**

When reviewing the listing of protocol deviations there were multiple deviations described as "Study staff did not collect memory aid data during Day 8 Safety Call." These events were related to the memory aid data not being collected during a day 8 visit made by phone. The information from these memory aids were collected during the in-person visit on day 15. Further, the data were captured by the study participants on a memory aid, and this memory aid was reviewed during the day 15 visit to verify the data, including that documented on the day 8 phone call. As the information was collected, just 1 week later than per protocol, we do not believe this impacts the quality of the safety /reactogenicity data.

Regarding the deviations related to samples, many of these were "Mishandled lab specimen – lab specimen was stored with liquid nitrogen" does describe events in which a serum sample was stored in liquid nitrogen, rather than the protocol-specified -80C freezer. Storing samples colder than needed is not thought to affect antibody stability, so we don't believe this affects the immunogenicity results. Other Mishandled lab specimen are related to plasma and PBMC aliquots or PBS used in processing. None of these affect the immunogenicity results. The remaining events generally were isolated events. In summary, the study sponsor does not believe the protocol violations noted significantly affect safety and immunogenicity data.

**Assessment of the MAH's response**

Regarding protocol deviations of safety data in memory aid, the MAH justified that these data were collected a week later at day 15 correctly. No issues regarding missing safety data. For sampling of lab specimen, the MAH stated that no misuse of plasma and PBMC aliquots for determination of immunogenicity results had any influence on the data.

**Conclusion**

Issue solved.

**2. No data of boosting for Vaxzevria after primary vaccination are filed by the MAH for the Spikevax booster. The MAH should discuss and provide evidence to justify a broad statement as regards authorised vaccines for the primary series.**

**Summary of the MAH's response**

The data of boosting after is provided in the published paper by Stuart et al, 2022: *Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com- COV2): a single-blind, randomised, phase 2, non-inferiority trial*[2] and is provided in this submission.

**Assessment of the MAH's response**

Com-COV2 is a single-blind, randomised, non-inferiority trial in which adults aged 50 years and older, previously immunised with a single dose of ChAd or BNT in the community, were randomly assigned (in random blocks of three and six) within these cohorts in a 1:1:1 ratio to receive a second dose intramuscularly (8–12 weeks after the first dose) with the homologous vaccine, Spikevax, or Nuvaxovid. The primary endpoint was the geometric mean ratio (GMR) of serum SARS-CoV-2 anti-spike IgG concentrations measured by ELISA in heterologous versus homologous schedules at 28 days after the second dose, with a non-inferiority criterion of the GMR above 0·63 for the one-sided 98·75% CI. The primary analysis was on the per-protocol population, who were seronegative at baseline. Safety analyses were done for all participants who received a dose of study vaccine.

Findings from this trial demonstrate that the immunogenicity of heterologous boost with Spikevax following community prime with ChAd or BNT was non-inferior to the homologous-boost schedule. When heterologous boost was with NVX, only those primed with ChAd had titres of SARS-CoV-2 anti-spike IgG that were non-inferior to the homologous schedule, whereas BNT/NVX did not meet the non-inferiority threshold against homologous BNT.

This research confirms previous evidence of mixed adenoviral and mRNA schedules as being safe, tolerable, and immunogenic alternatives to homologous schedules when given at an 8–12 weeks interval. It also provides new evidence on the response to mixed mRNA vaccinations in a randomised trial, and novel data for the incorporation of protein-based COVID-19 vaccines into heterologous schedules. These results provide reassurance that there are multiple appropriate options to complete primary immunisation in individuals primed with BNT or ChAd, which will facilitate rapid vaccine deployment globally.

***Assessment of MAH's responses***

The data provided in the published paper do not describe a booster dose, but a second dose after Vaxzevria or Comirnaty as first dose. Spikevax was given as 100 µg second dose and not as 50 µg booster dose, but not clearly mentioned in the paper. As second dose the homologous vaccine was given and in the two other groups the heterologous vaccines Spikevax and Nuvaxovid 8 to 12 weeks after the primary vaccination. The immune-responses were high in all groups beside the combination

[2] Stuart ASV, Shaw RH, Liu X, Greenland M, Aley PK, Andrews NJ, Cameron JC, Charlton S, Clutterbuck EA, Collins AM, Darton T, Dinesh T, Duncan CJA, England A, Faust SN, Ferreira DM, Finn A, Goodman AL, Green CA, Hallis B, Heath PT, Hill H, Horsington BM, Lambe T, Lazarus R, Libri V, Lillie PJ, Mujadidi YF, Payne R, Plested EL, Provstgaard-Morys S, Ramasamy MN, Ramsay M, Read RC, Robinson H, Screaton GR, Singh N, Turner DPJ, Turner PJ, Vichos I, White R, Nguyen-Van-Tam JS, Snape MD; Com-COV2 Study Group. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. Lancet. 2022 Jan 1;399(10319):36-49. doi: 10.1016/S0140-6736(21)02718-5. Epub 2021 Dec 6. Erratum in: Lancet. 2022 Feb 26;399(10327):802. PMID: 34883053; PMCID: PMC8648333.

Comirnaty/Nuvaxovid after the second dose, but very high after a second dose with Spikevax compared to the other combinations. The reactogenicity profile showed higher frequencies of reported side effects in the groups, where Spikevax was given as second dose compared to all other combinations regarding solicited local and systemic reactions.

**Conclusion**

Issue solved for Vaxzevria.

**3. The MAH is requested to discuss the results in the light of the higher dose used for boosting.**

**Summary of the MAH's response**

The MAH has recently received the DMID 21-0012 D15 50 µg booster dose immunogenicity report (provided in this submission). Similar to the 100 µg booster dose, Table 1a of the immunogenicity report shows that 98-100% of all participants in cohorts 12E (COVID-19 Vaccine Janssen primed), 13E (Spikevax primed), and 14E (Comirnaty primed) attained greater than four-fold rise over baseline, achieving GMTs of 1775, 2927, and 2682 respectively. Results of DMID 21-0012 using a booster dose of Spikevax both 50 µg and 100 µg, (i) reinforce findings observed after the 50 µg boosting dose (mRNA-1273-P201 Part B), and (ii) demonstrate the utility of Spikevax regardless of the COVID-19 vaccine initially administered. Comparing GMT obtained 12-20 weeks after 2 doses of 100 µg Spikevax with GMT obtained 14 days after a 100 µg booster dose, show a significant increase in nAb titers with a GMFR of 10.17 (95%: 8.05, 12.85). This GMFR is consistent with that observed in earlier sections for the 50 µg booster, (GMFR 12.99, 95% CI: 11.04, 15.29).

Data from this study also illustrate that a booster dose of Spikevax can significantly enhance nAb responses induced by alternate COVID-19 vaccines, regardless of the vaccine used for priming. Study participants had completed authorised regimens of the COVID-19 Vaccine Janssen (n=52 participants) or Comirnaty (n=50 participants) 12-20 weeks prior to obtaining a "baseline" serum sample. Of note, these "baseline" GMTs measured in these groups were lower than that following the authorised 2-dose Spikevax regimen (366.31 following Spikevax compared with 36.81 following COVID-19 Vaccine Janssen and 102.44 following Comirnaty). Regardless of the initial vaccine regimen, boosting with 100 µg dose of Spikevax resulted in a significant increase in nAb titer ((Table 3 of Clinical Overview) and [DMID Study 21-0012 Day 15 PsVNA Report]).

Consistent with the results from mRNA-1273-P201 Part B, the older adult cohort aged ≥56 years had a GMFR consistent with the younger age cohort 18-55 years of age. GMFRs comparing GMT prior to the 100 µg Spikevax booster to the GMT 14 days after Spikevax booster were 75.91 (COVID-19 Vaccine Janssen), 10.17 (Spikevax) and 31.69 (Comirnaty) (Table 4 of Clinical Overview). These results emphasise again that fold increase is influenced by baseline titers: 2 doses of Spikevax achieved relatively high "baseline" titers (366.31) compared with "baseline" titers achieved by either the COVID-19 Vaccine Janssen or Comirnaty vaccines (36.81 and 102.44, respectively). The relatively higher titers achieved after 2 doses of 100 µg of Spikevax result in a relatively lower SRR than for participants initially given COVID-19 Vaccine Janssen or Comirnaty vaccines (86% vs 100%, respectively).

**Assessment of the MAH's response**

The conclusion that the boosting of immune response is more dependent on the baseline titers after primary vaccination series compared to the dose given as a booster dose is agreed.

**Conclusion**

Issue solved.

**4. The MAH is requested to discuss the characteristics of the used assays for determining neutralising antibodies in the DMID trial and the mRNA-1273-P201 trial and possible approaches to enable bridging e.g. by analysing identical samples or using a common standard.**

**Summary of the MAH's response**

The same assay validated assay, SARS-CoV-2 Pseudotyped Virus Neutralization, conducted at Duke University Medical Center, was used for both mRNA-1273-P201 part B as well as DMID21-0012. As the same assays and same SOPs were used in both studies, the MAH does not feel bridging would be needed.

**Assessment of the MAH's response**

The same assay is validated and has been used in all studies – so the data are comparable.

**Conclusion**

Issue solved.

**5. The MAH should comment on the impact of the time intervals between primary series and booster injection. The MAH is asked to systematically assess the timeframe between the primary immunisation and the booster injection as 6 months in case of heterologous and homologous boosting may not be the appropriate timeframe. The studied interval in the DMID trial and other available evidence should be taken into consideration. Such time span based on any relevant evidence should be mentioned in section 4.2 of the SmPC with corresponding information in the PL.**

**Summary of the MAH's response**

Please find below Table 1, summarising the time interval between completion of the primary series and administration of the booster vaccination in the DMID 20-0012 study. The following groups are represented: (i) Group 1E (primary vaccination with COVID-19 Vaccine Janssen; boosted with Spikevax), (ii) Group 2E (primary vaccination with Spikevax [100 ug]; boosted with Spikevax) and (iii) Group 3E (primary vaccination with Comirnaty; boosted with Spikevax). In all cases, booster vaccination was with 100 ug of Spikevax. The safety and immune response of a third dose of Spikevax administered a mean duration of 13.7 to 16.8 weeks after priming series with either Spikevax, COVID-19 Vaccine Janssen or Comirnaty in study 21-0012 is similar to what is observed when the third dose is given at least 6 months after the priming series. The median interval (in weeks) between primary vaccination and Spikevax booster was 16.3 weeks for Group 2E (Spikevax primary and booster), shorter than the interval between primary and booster in mRNA-1273-P201 Part B.

**Table 1. Time interval between completion of the primary series and administration of the booster vaccination**

| | Janssen (Group 1E) | Moderna (Group 2E) | Pfizer (Group 3E) | Total |
|---|---|---|---|---|
| Time from Primary Vaccination to Boost (Weeks)[1] | | | | |
| N | 53 | 51 | 50 | 154 |
| Mean (SD) | 13.7 (1.0) | 16.4 (1.9) | 16.8 (2.2) | 15.6 (2.2) |
| Median | 13.9 | 16.3 | 17.0 | 15.4 |
| 25th, 75th %tile | 12.9, 14.6 | 15.1, 18.1 | 15.4, 18.4 | 14.0, 17.3 |
| Min, Max | 12.0, 15.9 | 12.4, 20.0 | 12.0, 20.9 | 12.0, 20.9 |

[1] Calculated from second vaccination dose for participants originally vaccinated with Moderna or Pfizer. Calculated from only vaccination dose for participants originally vaccinated with Janssen.

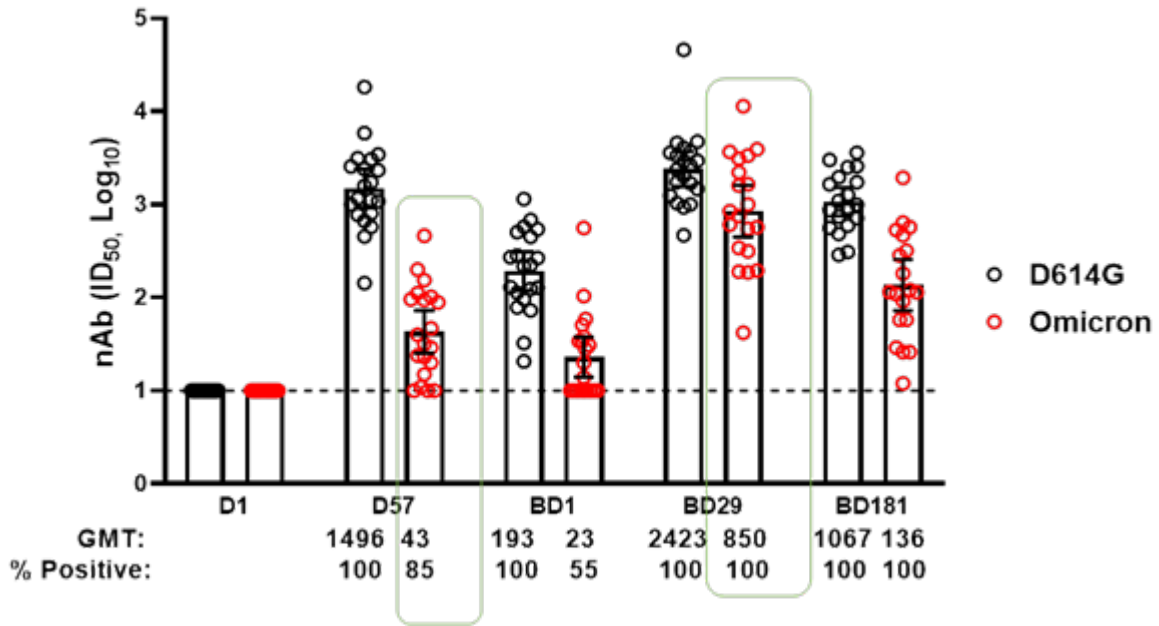
The currently available data does not suggest any differences in reactogenicity or safety based on interval since primary series for homologous or heterologous boosting. The differences in immunogenicity are likely driven by the pre-boost titers, which are both a function of time as well as the primary series (lower for non-mRNA vs. mRNA). Therefore, the MAH position is to maintain an interval of 6 months between any primary series and the Spikevax booster.

This interval may need to be adjusted based on emerging data for new variants of concern.

**Additional information provided by the MAH:**

**Omicron neutralising titers**.
At 1 month post-dose 2 (Day 57, Primary Series), the GMT for nAb against Omicron (N=20) after two 100 µg doses of Spikevax is 43, compared to a GMT of 1496 observed against the prototype virus (Figure 5). When participants were boosted 6 months after the primary series, GMTs increased from 23 to 850 537-fold), demonstrating that the prototype booster generates a robust immune response against Omicron. The post-dose 2 nAb GMT (43) are likely insufficient to neutralise the Omicron variant, and therefore, the MAH believes boosting individuals promptly, rather than waiting the 6 month interval, is of importance.

**Figure 5 - Pseudovirus Neutralising Antibody ID50 Titers against Omicron**




**Safety Data for 5 Month Dosing Interval**

The MAH proposes to extrapolate data from DMID Study 21-0012, previously submitted to EUA 27073 on 03 September 2021 (SN0251), which demonstrates the safety of administration of a higher dose booster (100 µg) at a 12-week interval, to support dosing our currently authorised 50 µg booster dose 'at least 5-months post-primary series'. No new safety signals were observed in this study, with similar reactogenicity profiles to that observed after Dose 2 (DMID 21-0012 Study Safety Report Aug 31, 2021). We believe it is reasonable to extrapolate the safety data to a lower dose (50 µg) at a shorter dosing interval (as early as 12 weeks). Of note, these data include both homologous and heterologous boost. Although we believe this data would support lowering interval down to 3 months, in the interest of facilitating the response to the current Omicron surge and minimising operational challenges, we are requesting to change the interval to 5 months at this time to harmonise with other mRNA vaccines.

In conclusion, the MAH believes the safety and immunogenicity data described support an amendment to the boosting dosing interval to 'at least 3 months' post-primary series.

**Assessment of the MAH's response**

The MAH´s claim is accepted. For the mRNA vaccines the time till booster are roughly 6 weeks, only a bit less for COVID-19 Vaccine Janssen which is likely due to the fact that only one dose of COVID-19 Vaccine Janssen is given for primary vaccination and hence the need for an somewhat earlier booster was seen as the titers were waning.

**Safety**

**6. The MAH is requested to outline plans to follow-up safety in individuals with compromised state of health/multimorbid conditions.**

**Summary of the MAH's response**

The MAH Risk Management Plan (RMP) includes as part of the safety concerns of Spikevax, under Missing information: Use in immunocompromised subjects; Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders), and Use in subjects with autoimmune or inflammatory disorders. The MAH has an established signal management process including signal detection, validation and evaluation of spontaneous reports from all sources. Safety surveillance prioritisation is for the safety concerns of the RMP, AESIs, or those AEs that may be serious or known to be often medicine related. As immunocompromised and/or immunosuppressed people were excluded from clinical trials, the MAH is monitoring the safety profile in this population through routine pharmacovigilance. Thus far, the review of post-EUA data has not identified any patterns or specific safety concerns in the immunocompromised population. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. There have been nonserious, serious and fatal cases of COVID-19 in this subpopulation, perhaps reflective of reduced immunogenicity/effectiveness of the vaccine in this population and the surge of the delta variant. Otherwise, the general pattern of commonly reported adverse events in those with a medical history of immunosuppression/immune.

**Assessment of the MAH's response**

Immunocompromised and/or immunosuppressed people were excluded from clinical trials, the efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy during licensure and is therefore implemented as missing information. The same applies to frail individuals with compromised state of health/multimorbid conditions. This is the population actually addressed in the question. Individuals with chronic disease or risk for severe Covid-19 course of disease were not excluded from the clinical trials, but had to be in stable health conditions. Therefore use in frail individuals with unstable health conditions and co-morbidities is included as missing information in the RMP. The missing information of the safety of

Spikevax in patients with unstable health conditions and comorbidities is addressed in the PASS mRNA-1273-P904. Of note this study only evaluates the use of Spikevax, not given after priming with other Covid-19 vaccines. The frail population is monitored within the post-approval pharmacovigilance system within established signal detection, validation and evaluation of spontaneous reports. As stated in the MAH response, post-approval safety surveillance did not reveal any specific safety concerns with regard to the safety of Spikevax in immunocompromised individuals yet, which is actually not the population addressed in the question. The monitoring of individuals not included in the clinical trials via routine pharmacovigilance within an established routine pharmacovigilance system is acknowledged. Of note in multimorbid individuals causality assessment could be hampered. In summary, the data base from the submitted trial is insufficient to conclude on the safety of a heterologous prime boost in the frail population. The issue is therefore up to pharmacovigilance monitoring in a larger population without restrictions. This is not only restricted to the routine pharmacovigilance, which is not acceptable as the only tool for safety assessment, but also from PASS mRNA-1273-P904. Moreover, within the PSUR covering the time period 18/12/2020 to 30/06/2021 the MAH was requested to present data, including literature, and discuss the safety profile of Spikevax in relation to heterologous COVID-19 vaccines schedule.

**Conclusion**

Issue partially solved and not further pursued here.

**7. Based on eligibility criteria, subjects in the DMID 21-0012 study should not have had COVID-19 or SARS-CoV-2 infection prior to boosting. The MAH is requested to outline the available data and comment on experience of vaccination of previously infected persons.**

**Summary of the MAH's response**

The experience with people who have been previously infected, either symptomatically or asymptomatically with SARS-CoV-2, is best extrapolated from mRNA-1273-P301. In mRNA-1273-P201B, the number of seropositives in the study are low. In mRNA-1273-P301, for seronegative populations, local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1. In the 347 participants who were seropositive for SARS-CoV-2 at baseline, systemic reactogenicity reactions were more frequently reported after Dose 1, compared to subjects who were seronegative for SARS-CoV-2 at baseline; however, reactogenicity following Dose 2 was similar between these two groups. In general, the safety profile in subjects receiving Spikevax who were seropositive for SARSCoV-2 at baseline was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

**Assessment of the MAH's response**

In fact, the MAH did not provide any heterologous booster safety data available for individuals with previous SARS-CoV-2 infection nor did comment on the availability of these data as requested.

However, safety data of SARS-CoV-2 seropositive individuals collected in mRNA-1273-P301 do not raise safety concerns for the use of Spikevax in SARS-CoV-2 seropositive subjects compared to seronegative subjects. Subjects with previous Covid-19 however have not been enrolled in mRNA-1273-P301.The safety monitoring is subject to pharmacovigilance. Within the PSUR covering the time period 18/12/2020 to 30/06/2021 the MAH was requested to present data, including literature, and discuss the safety profile of Spikevax in relation to heterologous COVID-19 vaccines schedule.

**Conclusion**

The issue is not further pursued here. The submitted data are not sufficient to conclude on the safety of Spikevax given as a heterologous booster to SARS-CoV-2 seropositive individuals or those with previous infection. This is subject to pharmacovigilance.

**8. A limitation seems to be lack of any data on boosting after Vaxzevria primary series. As Vaxzevria is an approved SARS-CoV-2 vaccine in the EU, the MAH should discuss and provide supportive data on boosting after Vaxzevria.**

**Summary of the MAH's response**

The data of boosting after Vaxzevria is provided in the following published paper: *Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial* and is provided in this submission.

**Assessment of the MAH's response**

The data provided belong to the is a UK multicentre, single-blinded, randomised, phase 2, non-inferiority study, investigating the safety, reactogenicity, and immunogenicity of heterologous boost COVID-19 vaccine schedules.

The findings from this study demonstrate that the immunogenicity of heterologous boost with Spikevax following community prime with ChAd or BNT was non-inferior to the homologous-boost schedule. When heterologous boost was with NVX, only those primed with ChAd had titres of SARS-CoV-2 anti-spike IgG that were non-inferior to the homologous schedule, whereas BNT/NVX did not meet the non-inferiority threshold against homologous BNT.

Nevertheless, within the limitations of comparing between non-randomised cohorts, SARS-CoV-2 anti-spike IgG titres induced by BNT/NVX were still above that of homologous ChAd, a schedule with demonstrated effectiveness of 65–70% against symptomatic SARS-CoV-2 infection and over 90% against hospitalisation and death.
However the study has a number of limitations related to the age range (50–78 years) and ethnicity (90·7% of participants primed with ChAd and 94·7% of those primed with BNT self-identified as White) of the study cohort limit generalisability of the reactogenicity and immunology results to younger populations and people who are not of White ethnicity. These groups might be more likely to receive heterologous COVID-19 vaccine schedules as a primary course, given age-associated safety concerns with the use of ChAd, and logistic constraints in lower income regions.

**Assessment of the MAH's response**

The study does not assess the heterologous booster, but only the mixed-match" use of Spikevax after one dose of Vaxzevria given within a primary series. The study has supported other previous findings that mixed adenoviral-vectored and mRNA COVID-19 vaccine schedules being more reactogenic than homologous schedules, consistent with other studies examining BNT/ChAd. In addition, there was evidence of increased reactogenicity for the heterologous over the homologous mRNA schedule (BNT/Spikevax *vs* BNT/BNT). By contrast, there was no evidence of increased reactogenicity for the Nuvaxovid containing schedules. No safety signals were raised in the study.

**Conclusion**

Issue solved

**9. From a practical point of view, it is questioned whether Tables 8a – 8c in the study report adequately reflect the occurrence of AEs from day 1 to day 8. Particularly, it is not understood, how "memory aid" has been constructed. Did the subjects have to remember each day or did they have a diary (memory aid?)? Please clarify the so called "memory aid". Please also clarify if missing of collection (protocol deviation) of "memory aid" on day 8 was only a technical issue and if quality of data was not compromised.**

**Summary of the MAH's response**

The memory aid is a form on which participants can record temperature, systemic symptoms, local reactogenicity, and other symptoms, and is filled out daily, from home, by the participant. The memory aid was to be used by the participant when answering questions during the telephone call on Day 8, and then brought to the clinic visit on Day 15 for review by study site. The memory aid assists the participant with recalling information. The term and use of memory aids are described in the protocol.

**Assessment of the MAH's response**

The MAH described the use of a memory aid form that assists the participant with recalling information of each day after vaccination for the telephone interviews. This method is deemed acceptable.

**Conclusion**

Issue solved.

**10. 10. There is no new safety data submitted in the dossier compared to what has been submitted in the initial eCTD 0146 sequence. Safety report is dated 31st August 2021. Although the MAH claims not to have observed any new safety signals, this report is outdated and updated study report would be expected.**

**Summary of the MAH's response**

The interim safety analyses described in the protocol (section 9.4.6.1) SMC reports with cumulative AEs through day 29. Additional safety analyses have not been performed.

**Assessment of the MAH's response**

The report of safety data covers a follow-up period of 29 days as described in the CTP. No further data have been submitted. This period is rather short, but comparable to what has been submitted during licensure. The monitoring and additional collection of safety data for the heterologous booster is subject to pharmacovigilance. In the PSUR covering the time-period 18/12/2020 to 30/06/2021 the MAH was requested to present data, including literature, and discuss the safety profile of Spikevax in relation to heterologous COVID-19 vaccines schedule.

**Conclusion**

Issue not further pursued here.

**11. There is a slight incidence and frequency difference in unsolicited AEs and unsolicited unrelated AEs between submitted overview (eCTD 0146 and eCTD 0198) vs. safety report (eCTD 0146, dated 31st August 2021) to which the overview references. Please clarify the correct numbers.**

**Summary of the MAH's response**

The Clinical Overview contains only relevant safety data related to solicited AR and unsolicited AE (up to study Day 7) for the supportive Study DMID Study 21-0012. The MAH has provided unsolicited AE data below from the D29 Safety report which the Clinical Overview references.

All unsolicited adverse events (AE) reported in the study Groups 1E to 3E, cross-classified by severity and relationship to study product, are shown in Tables 4a to 4c. Adverse events that have been assigned a MedDRA System Organ Class (SOC) classification are presented in Figures 1a to 1c (by SOC and severity**)**, and in Figures 2a to 2c (by SOC and relationship to study product). From the 53 participants in

group 1E (EUA dosed COVID-19 Vaccine Janssen, boost Spikevax) 18 participants reported 21 unsolicited AEs (Table 4a, Figures 1a and 2a). From the 51 participants in group 2E (EUA dosed Spikevax, boost Spikevax) 16 participants reported 22 unsolicited AEs (Table 4b, Figures 1b and 2b). From the 50 participants in Group 3E (EUA dosed Comirnaty, boost Spikevax) 20 participants reported 42 AEs (Table 4c, Figures 1c and 2c). Table 5 summarises the number and proportion of participants experiencing unsolicited adverse events related to the study vaccination, classified by maximum severity and by Group. For those AEs which have been assigned a MedDRA code, Table 5 also presents these summaries by MedDRA SOC and preferred term. Similarly, Table 6 summarises the number and proportion of participants experiencing unsolicited adverse events not related to study vaccination. The number (and percentage) of participants reporting unsolicited AEs, of any severity grade, that were deemed related to the study product was 7/53 (13.2%) in Group 1E, 6/51 (11.8%) in Group 2E and 11/50 (22.0%) in Group 3E. Most participants reported related AEs of at most Grade 2 severity, with only one participant (Group 1E) reporting at least one AE of Grade 3 (Table 5). The number (and percentage) of participants reporting unsolicited not related AEs, of any severity grade, was 11/53 (20.8%) in Group 1E, 10/51 (19.6%) in Group 2E and 16/50 (32.0%) in Group 3E. Most participants reported not related AEs of at most Grade 2 severity, with one participant (Group 2E) reporting at least one AE of Grade 3, and one participant (Group 1E) reporting at least one AE of Grade 4 severity (Table 6).

**Assessment of the MAH's response**

All the unsolicited adverse events (AE) have been reported for the study groups 1E to 3E. Adverse events that have been assigned a MedDRA System Organ Class (SOC) were presented accordingly in the respective figures. The findings were comparable between the groups and most participants reported unsolicited not related AEs. The numbers were clarified within a high level summary.

**Conclusion**

Issue solved.

**12. No additional information on grade 4 acute kidney injury appears to be included in the study report. Please provide additional information.**

**Summary of the MAH's response**
The updated CIOMs report on grade 4 acute injury is provided in this submission.

**Assessment of the MAH's response**

CIOMs report present the acute renal failure case as per below:
An investigator report of Acute Renal Failure in a male subject enrolled in the DMID protocol 21-0012 entitled "Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) after Receipt of EUA Vaccines." The DMID Medical Monitor has assessed the event as serious, unexpected and not related to the study product. The subject's past medical history included withdrawal polysubstance abuse, gastroesophageal reflux disease (GERD), hyperlipidaemia, hypertension and retinal tear of right eye. His family history was significant for high blood pressure with both parents.

Concomitant medications included simvastatin 20 mg orally (PO) daily (QD), lisinopril 10 mg PO QD, citalopram 40 mg PO QD, folic acid 1 mg PO QD, multivitamin 1 tablet PO QD, testosterone cypionate 200 mg intramuscularly (IM) every 7 days, hydroxyzine HCl 8 mg PO every 8 hours, omeprazole 20 mg PO before every meal, tadalafil 20 mg PO as needed (PRN), sildenafil 100 mg PO PRN.

The subject received the first and last dose of the study product, Spikevax 0.5 mL (100 mcg) IM. Per reactogenicity records, the subject experienced a local reaction of pain (Severity Level 1) on Day 1. He also experienced systemic reactions of fatigue (Severity Level 1) and myalgia (Severity Level 1) on Day 1. The study product was last administered prior to the onset of the serious adverse event (SAE) on this day. On Study day 30, the subject presented to the emergency department (ED) with emesis and head injury. The subject experienced pain on his left side after a fall on Study Day 25, hitting his head and

losing consciousness for an unclear amount of time after substance abuse. Since the fall he experienced constant nausea, vomiting approximately 10 times per day, and could not keep down any food or water, He also reported no bowel movement for 5 days, with intermittent chills, diffuse body aches, and he also complained of pain in his left arm, foot and hip.

On Study Day 32 based on the laboratory tests and examinations (X-ray, CT scan) the subject suffered acute kidney injury in the setting of polysubstance abuse and hypertension. On Study Day 59, the event acute injury was considered recovered/ resolved. The investigator has assessed the event, Acute Renal Failure, as serious and not related to the study product.

It is also agreed that the acute renal failure was not related to the administration of the study product.

**Conclusion**
Issue solved

**13. There is emerging data that heterologous regimen in the primary regimen are cause for an increased risk of myocarditis/pericarditis. The MAH is requested to discuss how this possible risk of heterologous regimen using Spikevax will be followed-up.**

**Summary of the MAH's response**

The MAH Risk Management Plan (RMP) includes as part of the safety concerns of Spikevax, under Missing information: Interaction with other vaccines. The MAH has an established signal management process including signal detection, validation and evaluation of spontaneous reports from all sources. Safety surveillance prioritisation is for the safety concerns of the RMP, AESIs, or those AEs that may be serious or known to be often medicine related.

On 20th October 2021, the USA FDA expanded the use of a booster dose for COVID-19 vaccines in eligible populations. In the case of heterologous use, the FDA has authorised Spikevax for use in eligible individuals "as a heterologous (or "mix and match") booster dose following completion of primary vaccination with a different available COVID-19 vaccine. ***For example, Pfizer-BioNTech COVID-19 Vaccine and Janssen COVID-19 vaccine recipients 18 years of age and older may receive a single booster dose of the Moderna COVID-19 Vaccine."***

Limited data are currently available on the interactions of Spikevax with other COVID-19 vaccines, drugs and/or other vaccines. As such, it is unclear whether the performance of heterologous regimens including Spikevax are complementary, synergistic, or exhibit lower effectiveness compared with the two-dose Spikevax regimen that is authorised in numerous jurisdictions.

Review of adverse event reports Spikevax that indicated vaccine interactions or other vaccines administered found no concerning patterns or notable trends. Based on patients' risk factors for concurrent and past illnesses, and concomitant medications, confounding is a significant challenge for causality assessment for this topic.

Review of adverse event reports involving Spikevax that indicated coadministration with other vaccines administered found no concerning patterns or notable trends. The MAH is monitoring the safety profile in this population through routine pharmacovigilance.

**Assessment of the MAH's response**

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Spikevax. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Spikevax has not yet been characterised.

The safety data base for the heterologous booster with regard to myocarditis and pericarditis is scarce either, and is subject to pharmacovigilance monitoring. In the PSUR covering the time period 18/12/2020 to 30/06/2021 the MAH was requested to present data, including literature, and discuss the safety profile of Spikevax in relation to heterologous COVID-19 vaccines schedule. The data and discussion should be presented in relevant sections e.g. off-label use, or in addition to the already presented PSUR headline "Interaction with other vaccines (Heterologous Vaccine Schedule)". Addition information on the safety of Spikevax is expected from PASS mRNA-1273-P904, and from routine pharmacovigilance. The safety data submitted are not considered sufficient to conclude on the safety of Spikevax when given as a (homologous or heterologous) booster within a 3 month time period after primary vaccination, particularly with regard to myocarditis /pericarditis in the younger population. Since a widespread use of booster injections is reported, more safety data are expected before approval of the shorten booster interval of 3 months. As a consequence, the interval of the (heterologous) booster dose and the corresponding wording in the SMPC require further discussion and consideration, when data are available.

**Conclusion**

The issue is not solved.

1. The safety of the administration of booster injection (heterologous and homologous) using a shortened interval is insufficiently characterised especially with regard to myo/pericarditis in the younger population. The widespread use of booster injections has been reported and the MAH is requested to provide an overview and analysis using all available data sources.
2. The MAH is in consequence asked to re-discuss the interval of the (heterologous) booster dose based on available safety data, and amend section 4.2 accordingly, as appropriate.

**Assessment of MAH's responses to unresolved RSI**

Item 1
The safety of the administration of booster injection (heterologous and homologous) using a shortened interval is insufficiently characterised especially with regard to myo/pericarditis in the younger population. The widespread use of booster injections has been reported and the MAH is requested to provide an overview and analysis using all available data sources.

Summary of MAH's response
The booster data on shortened intervals is being generated from the NIH/DMID 21-0012 study (the MAH is not the study sponsor). This study is still ongoing, and therefore the MAH currently does not have access to datasets for internal analysis or study report development. Furthermore, with respect to myocarditis/pericarditis risk, it is highly unlikely that the risk assessment can come from this Ph2 randomised controlled trial as the numbers of participants are insufficient to identify/characterise this risk.

Real-world evidence in populations of sufficient size to characterise the risk needs to be generated via large observational studies such as the ongoing MAH US and EU PASS studies, however availability of booster dose data from these analyses will not be available until a sufficient number of booster doses has accrued to support analyses. Pending sample size, such data may be described in the April 2022 (US PASS) and September 2022 (EU PASS) interim analyses.

The MAH is providing an overview and analysis of post-authorisation safety data, extrapolating from the proportion of US vaccine recipients, to estimate global use, where it is estimated that 88,621,617 individuals received a third dose. In the interpretation of these results, it should be noted that current

data do not fully distinguish between individuals who received a third 100 mcg dose, as is indicated in the context of immunocompromise in some settings, and a 50 ug booster dose. It is also important to note, that current data also do not distinguished the different dosing intervals that have been recommended for booster implementation in different countries, for example, France (3 months), Germany (3 months), UK (3 months), Canada - Ontario (3 months), Switzerland (4 months), and U.S. (5 months).

The reporting period is 01 Dec to 31 Dec 2021.

Cumulatively, as of 31 December 2021, an estimated 827,274,740 doses of Spikevax had been distributed; 559,872,937 doses are estimated to have been administered. It is estimated that 88,621,617 individuals received a third dose. Cumulatively, the MAH has received 429,187 cases (1,648,231 events, of which 288,418 events were serious). The distribution of events by dose was presented (Table 1).

**Table 1. Distribution of Events By Dose Number and Time to Onset (TTO) (Cumulative as of 31 December 2021)**

| Dose Number | TTO (days) | Events (N) | Events (%) |
|---|---|---|---|
| Dose 1 | ***Subtotal*** | ***667,794*** | ***40.5*** |
| | 0 days | 259,808 | 15.8 |
| | 01-02 | 174,329 | 10.6 |
| | 03-04 | 32,781 | 2.0 |
| | 05-06 | 31,101 | 1.9 |
| | 07-13 | 126,687 | 7.7 |
| | 14-29 | 26,452 | 1.6 |
| | 30+ | 16,636 | 1.0 |
| Dose 2 | ***Subtotal*** | ***479,310*** | ***29.1*** |
| | 0 days | 197,614 | 12.0 |
| | 01-02 | 180,509 | 11.0 |
| | 03-04 | 17,344 | 1.1 |
| | 05-06 | 8,021 | 0.5 |
| | 07-13 | 16,657 | 1.0 |
| | 14-29 | 16,368 | 1.0 |
| | 30+ | 42,797 | 2.6 |
| Dose 3 | ***Subtotal*** | ***52,312*** | ***3.2*** |
| | 0 days | 21,758 | 1.3 |
| | 01-02 | 22,312 | 1.4 |
| | 03-04 | 2,699 | 0.2 |
| | 05-06 | 1,237 | 0.1 |
| | 07-13 | 2,051 | 0.1 |
| | 14-29 | 1,031 | 0.1 |
| | 30+ | 1,224 | 0.1 |
| Dose 4 | ***Subtotal*** | ***42*** | ***0.0*** |
| | 0 days | 30 | 0.0 |
| | 01-02 | 12 | 0.0 |
| Unknown | ***Subtotal*** | ***448,773*** | ***27.2*** |
| | Missing | 448,773 | 27.2 |
| **Grand Total** | | **1,648,231** | **100.0** |

**Assessment of MAH's responses**

Absolute events by dose have been provided. It is estimated that 88,621,617 individuals received a third dose. 559,872,937 doses are estimated to have been administered overall. This means that approximately 6.3 times more first and second doses than third doses have been administered. 1.147.104 events occurred after dose 1 or dose 2, but only 52,312 after dose 3 (approximately 21.9 times more events after dose 1 and dose 2 than after dose 3). For almost 1/3 of all events (i.e. 448,773,

27.2% of grand total) the dose was unknown. Available data do not distinguish between individuals who received 100 µg as 3rd dose, as indicated for immunocompromised individuals, and a 50 ug booster dose. The dosing intervals range from 3 months to 5 months depending on the national recommendations for administration of a booster dose. The proportion of each interval on all booster administrations is unknown.

**Cumulatively**, the MAH has received 17,511 cases (52,354 events, of which 29,181 events were serious) for recipients **after a third dose or booster dose of SPIKEVAX**. Of the cumulative reported cases, 5,171 cases were medically confirmed, 8,346 cases were serious, and 142 cases had fatal outcomes. The majority of cases were reported in females (66.7%, 11,673) compared to males (28.0%, 4,896) with the mean age of 52.8 years (SD: 16.6; median: 53.0 years).

**During the reporting period (01 Dec to 31 Dec 2021)**, the MAH received 11,074 cases (31,467 events, of which 20,366 were serious) for recipients after a third dose or booster dose of SPIKEVAX. Of the total cases during this reporting period, 2,190 cases were medically confirmed. 5,995 cases were serious, and 63 cases had fatal outcomes. The majority of cases were reported in females (69.3%, 7,673) compared to males (26.0%, 2,876) with the mean age of 47.9 years (SD: 15.0; median: 48.0 years). **Cases** after the 3rd dose by reporting interval are presented in Table 2.

**Table 2. Post-authorization Cases After a Third Dose or Booster Dose of SPIKEVAX by Reporting Interval** (01 Dec to 31 Dec 2021).

| Review Period | Non-Serious | | Serious | | Total Cases (N) | Total Cases (%) |
|---|---|---|---|---|---|---|
| | Cases (N) | Cases (%) | Cases (N) | Cases (%) | | |
| Prior to Review Period | 4,086 | 44.6 | 2,351 | 28.2 | 6,437 | 36.8 |
| Review Period | 5,079 | 55.4 | 5,995 | 71.8 | 11,074 | 63.2 |
| **Grand total** | **9,165** | **100.0** | **8,346** | **100.0** | **17,511** | **100.0** |

**Assessment of MAH's responses**

More cases (serious and non-serious) were reported for the review period of one month compared with the prior to review period. This could be because of significantly more 3rd doses administered in the review period compared to the pre-review period.

The distribution of cases for recipients after a third dose or booster dose of SPIKEVAX by age group and gender is presented in Table 3 and only by age group during this reporting period in Table 4.

**Table 3 Distribution of Cases After a Third Dose or Booster Dose of SPIKEVAX by Age Group and Gender During the Reporting Period**

| Age Group | Females N (%) | Males N (%) | Unknown N (%) | Grand Total N (%) |
|---|---|---|---|---|
| <2 | 10 (0.1) | 3 (0.0) | 1 (0.0) | 14 (0.1) |
| 02-11 | 0 | 2 (0.0) | 0 | 2 (0.0) |
| 12-15 | 3 (0.0) | 0 | 0 | 3 (0.0) |
| 16-17 | 8 (0.1) | 4 (0.0) | 0 | 12 (0.1) |
| 18-29 | 810 (7.3) | 281 (2.5) | 35 (0.3) | 1,126 (10.2) |
| 30-39 | 1,401 (12.7) | 432 (3.9) | 44 (0.4) | 1,877 (16.9) |
| 40-49 | 1,641 (14.8) | 551 (5.0) | 65 (0.6) | 2,257 (20.4) |
| 50-64 | 2,263 (20.4) | 914 (8.3) | 88 (0.8) | 3,265 (29.5) |
| 65-74 | 502 (4.5) | 268 (2.4) | 41 (0.4) | 811 (7.3) |
| 75+ | 244 (2.2) | 179 (1.6) | 23 (0.2) | 446 (4.0) |
| Missing | 791 (7.1) | 242 (2.2) | 228 (2.1) | 1,261 (11.4) |
| **Grand total** | **7,673 (69.3)** | **2,876 (26.0)** | **525 (4.7)** | **11,074 (100.0)** |

**Table 4 Distribution of Cases After a Third Dose or Booster Dose of SPIKEVAX by Age Groups by Reporting Period (01 Dec to 31 Dec 2021).**

| Age Group | Prior to Reporting Period | | Reporting Period | | Total Cases (N) | Total Cases (%) |
|---|---|---|---|---|---|---|
| | Cases (N) | Cases (%) | Cases (N) | Cases (%) | | |
| <2 | 3 | 0.0 | 14 | 0.1 | 17 | 0.1 |
| 02-11 | 4 | 0.1 | 2 | 0.0 | 6 | 0.0 |
| 12-15 | 4 | 0.1 | 3 | 0.0 | 7 | 0.0 |
| 16-17 | 3 | 0.0 | 12 | 0.1 | 15 | 0.1 |
| 18-29 | 235 | 3.7 | 1,126 | 10.2 | 1,361 | 7.8 |
| 30-39 | 395 | 6.1 | 1,877 | 16.9 | 2,272 | 13.0 |
| 40-49 | 580 | 9.0 | 2,257 | 20.4 | 2,837 | 16.2 |
| 50-64 | 1,816 | 28.2 | 3,265 | 29.5 | 5,081 | 29.0 |
| 65-74 | 1,584 | 24.6 | 811 | 7.3 | 2,395 | 13.7 |
| 75+ | 1,095 | 17.0 | 446 | 4.0 | 1,541 | 8.8 |
| Missing | 718 | 11.2 | 1,261 | 11.4 | 1,979 | 11.3 |
| **Grand total** | **6,437** | **100.0** | **11,074** | **100.0** | **17,511** | **100.0** |

The majority of interval cases were derived from the UK, EEA and US. The substantially higher number of cases in the UK for the reporting period compared to other regions was attributable to bolus submission of approximately 4,000 cases by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) in December 2021.

The MAH provided the cumulative distribution of events for recipients after a third dose or booster dose of SPIKEVAX by time to onset (Table 6). The majority of events occurred < 7 days after administration of Dose 3 (95.6%).

Table 6 provides the cumulative distribution of events for recipients after a third dose or booster dose of SPIKEVAX by time to onset. The majority of events occurred < 7 days after administration of Dose 3 (95.6%).

**Table 6. Distribution of Events After a Third Dose or Booster Dose of SPIKEVAX By Dose Number and Time to Onset (TTO) (Cumulative as of 31 Dec 2021)**

| Dose Number | TTO (days) | Events (N) | Events (%) |
|---|---|---|---|
| Dose 3 | 0 days | 21,758 | 41.6 |
| | 01-02 | 22,312 | 42.6 |
| | 03-04 | 2,699 | 5.2 |
| | 05-06 | 1,237 | 2.4 |
| | 07-13 | 2,051 | 3.9 |
| | 14-29 | 1,031 | 2.0 |
| | 30+ | 1,224 | 2.3 |
| **Grand Total** | | **52,312** | **100.0** |

**Assessment of MAH's responses**

The majority of reports during the reporting period were recorded for females.

During the reporting period, a total of 31,467 events for recipients after a third dose or booster dose of SPIKEVAX were reported of which 20,366 were serious. The Top 3 SOC, HLT, and PT for all events and for serious events for recipients after a third dose or booster dose of SPIKEVAX in this reporting period are presented in Table 7 and Table 8, respectively.

**Table 7. Top 3 Events After a Third Dose or Booster Dose of SPIKEVAX by SOC, HLT, and PT During the Reporting Period (01 Dec to 31 Dec 2021)**

| Classification | Event | Events (N) | Events (%) |
|---|---|---|---|
| SOC | General disorders and administration site conditions | 9,078 | 28.8 |
| | Nervous system disorders | 4,815 | 15.3 |
| | Musculoskeletal and connective tissue disorders | 3,743 | 11.9 |
| HLT | Headaches NEC | 2,210 | 7.0 |
| | Febrile disorders | 1,868 | 5.9 |
| | Asthenic conditions | 1,867 | 5.9 |
| PT | Headache | 2,113 | 6.7 |
| | Pyrexia | 1,865 | 5.9 |
| | Fatigue | 1,427 | 4.5 |

Abbreviations: HLT = higher level term; NEC = not elsewhere classified; PT = preferred term; SOC = system organ class.

**Table 8. Top 3 Serious Events After a Third Dose or Booster Dose of SPIKEVAX by SOC, HLT, and PT During the Reporting Period (01 Dec to 31 Dec 2021)**

| Classification | Event | Events (N) | Events (%) |
|---|---|---|---|
| SOC | General disorders and administration site conditions | 6,093 | 29.9 |
| | Nervous system disorders | 3,533 | 17.3 |
| | Musculoskeletal and connective tissue disorders | 2,572 | 12.6 |
| HLT | Headaches NEC | 1,639 | 8.0 |
| | Febrile disorders | 1,435 | 7.0 |
| | Asthenic conditions | 1,394 | 6.8 |
| PT | Headache | 1,562 | 7.7 |
| | Pyrexia | 1,433 | 7.0 |
| | Fatigue | 1,097 | 5.4 |

Abbreviations: HLT = higher level term; NEC = not elsewhere classified; PT = preferred term; SOC = system organ class.

Overview of Outcomes

A total of 63 cases (275 events) with fatal outcomes were reported for recipients after a third dose or booster dose of SPIKEVAX during this interval with fatal outcomes. Remaining event outcomes are presented below in Table 9.

**Table 9. Overview of Event Outcomes After a Third Dose or Booster Dose of SPIKEVAX by Period**

| Event Outcome | Prior to Review Period | | Review Period | | Total Events (N) | Total Events (%) |
|---|---|---|---|---|---|---|
| | Events (N) | Events (%) | Events (N) | Events (%) | | |
| Fatal | 337 | 1.6 | 275 | 0.9 | 612 | 1.2 |
| Not Recovered/ Not Resolved | 5,993 | 28.7 | 12,850 | 40.8 | 18,843 | 36.0 |
| Recovered/ Resolved | 7,430 | 35.6 | 9,175 | 29.2 | 16,605 | 31.7 |
| Recovered/ Resolved with Sequelae | 137 | 0.7 | 326 | 1.0 | 463 | 0.9 |
| Recovering/ Resolving | 2,341 | 11.2 | 6,104 | 19.4 | 8,445 | 16.1 |
| Unknown | 4,649 | 22.3 | 2,737 | 8.7 | 7,386 | 14.1 |
| **Grand total** | **20,887** | **100.0** | **31,467** | **100.0** | **52,354** | **100.0** |

**Assessment of MAH's responses**

The MAH did not provide further information with regard to the 63 fatal cases. The submitted safety data were previously submitted to PRAC within MEA 11.10 (11th SSR). Within this procedure the MAH was asked to submit clinical information about the fatal cases within the next SSR.

Assessment of Myocarditis

Observed versus expected

Stratification of cases of myocarditis with known dose and time to onset that occur within the 7 days following vaccination, considering observed versus expected analyses, showed an increased risk following dose 2 in young males, but no similar increase has yet been observed following a third dose (Table 10).

**Table 10. Reporting Rate of Myocarditis within 7 Days of Vaccination by Age and Dose per 100,000 Doses Administered of SPIKEVAX, Cumulative Through 31 December 2021**

| Age (years) | All | | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|---|---|
| | Dose 1 | Dose 2 | Dose 3 | Dose 1 | Dose 2 | Dose 3 | Dose 1 | Dose 2 | Dose 3 |
| <12 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 12-17 | 0.15 | 0.71 | 0.00 | 0.26 | 1.39 | 0.00 | 0.05 | 0.09 | 0.00 |
| 18-24 | 0.44 | 2.10 | 0.07 | 0.79 | 4.03 | 0.15 | 0.12 | 0.35 | 0.00 |
| 25-39 | 0.24 | 0.69 | 0.13 | 0.38 | 1.25 | 0.14 | 0.12 | 0.18 | 0.11 |
| 40-49 | 0.08 | 0.27 | 0.06 | 0.11 | 0.41 | 0.05 | 0.05 | 0.14 | 0.06 |
| 50-64 | 0.05 | 0.07 | 0.04 | 0.04 | 0.10 | 0.02 | 0.05 | 0.04 | 0.06 |
| 65-74 | 0.01 | 0.04 | 0.06 | 0.02 | 0.05 | 0.04 | 0.00 | 0.02 | 0.07 |
| 75+ | 0.03 | 0.02 | 0.03 | 0.02 | 0.01 | 0.02 | 0.04 | 0.04 | 0.04 |

The age and sex distribution presented here is based on the observed distribution in the US with the assumption that a maximum of 3% of SPIKEVAX doses administered annually were used in individuals <18. For dose 3, this approach may underestimate the number of women (who are more often diagnosed with autoimmune conditions leading to immunocompromise, an early indication of a third dose in some countries) and older individuals receiving dose 3. This may explain why observed vs. expected ratios are at unity for young women (where dose 3 reporting rates may be overestimated) but not for young men. Rates appear to be lower following dose 3 compared with dose 2 (Table 11).

**Table 11. Observed vs. Expected Analyses of Myocarditis, Cases Occurring within 7 Days of a Known Dose, Cumulative Through 31 December 2021***

| | Observed vs Expected (95% CI) | | |
|---|---|---|---|
| | **Dose 1** | **Dose 2** | **Dose 3** |
| All | 0.35 (0.31, 0.39) | 2.52 (2.23, 2.85) | 0.5 (0.38, 0.65) |
| **By age** | | | |
| <12 years | NA | NA | NA |
| 12-17 years | 0.28 (0.14, 0.54) | 2.86 (1.59, 5.14) | NA |
| 18-24 years | 0.81 (0.63, 1.06) | 8.41 (6.23, 11.36) | 0.35 (0.15, 0.83) |
| 25-39 years | 0.59 (0.48, 0.73) | 3.59 (2.84, 4.54) | 0.8 (0.5, 1.3) |
| 40-49 years | 0.2 (0.14, 0.29) | 1.41 (1.02, 1.96) | 0.35 (0.17, 0.76) |
| 50-64 years | 0.15 (0.1, 0.21) | 0.44 (0.3, 0.64) | 0.34 (0.18, 0.65) |
| 65-74 years | 0.03 (0.01, 0.08) | 0.25 (0.13, 0.46) | 0.44 (0.2, 0.97) |
| 75+ years | 0.11 (0.05, 0.22) | 0.18 (0.07, 0.45) | 0.25 (0.07, 0.9) |
| **By gender** | | | |
| Male | 0.4 (0.34, 0.46) | 3.43 (2.96, 3.97) | 0.36 (0.25, 0.53) |
| Female | 0.27 (0.21, 0.34) | 0.98 (0.77, 1.26) | 0.75 (0.5, 1.13) |
| **By age and gender** | | | |
| **Male** | | | |
| <12 years | NA | NA | NA |
| 12-17 years | 0.36 (0.17, 0.77) | 4.2 (2.07, 8.5) | NA |
| 18-24 years | 1.09 (0.81, 1.48) | 12.12 (8.36, 17.58) | 0.56 (0.22, 1.4) |
| 25-39 years | 0.68 (0.53, 0.88) | 4.91 (3.69, 6.53) | 0.68 (0.36, 1.28) |
| 40-49 years | 0.21 (0.13, 0.33) | 1.61 (1.07, 2.4) | 0.25 (0.08, 0.74) |
| 50-64 years | 0.09 (0.05, 0.16) | 0.49 (0.3, 0.78) | 0.13 (0.04, 0.45) |
| 65-74 years | 0.04 (0.01, 0.12) | 0.26 (0.12, 0.56) | 0.23 (0.07, 0.82) |
| 75+ years | 0.06 (0.02, 0.2) | 0.06 (0.01, 0.42) | 0.13 (0.02, 1.07) |
| **Female** | | | |
| <12 years | NA | NA | NA |
| 12-17 years | 0.14 (0.03, 0.63) | 0.57 (0.14, 2.35) | NA |
| 18-24 years | 0.34 (0.19, 0.61) | 2.1 (1.17, 3.77) | NA |
| 25-39 years | 0.42 (0.29, 0.63) | 1.37 (0.87, 2.18) | 1.07 (0.5, 2.27) |
| 40-49 years | 0.2 (0.1, 0.37) | 1.12 (0.63, 2.02) | 0.56 (0.19, 1.68) |
| 50-64 years | 0.24 (0.15, 0.4) | 0.37 (0.19, 0.74) | 0.73 (0.31, 1.72) |
| 65-74 years | 0.02 (0, 0.16) | 0.23 (0.08, 0.7) | 0.84 (0.28, 2.49) |
| 75+ years | 0.19 (0.07, 0.49) | 0.4 (0.13, 1.28) | 0.48 (0.09, 2.6) |

*Reference rates from Boehmer 2021. Because age by sex stratified estimates of the reference rate were not available in the source material, estimates are obtained by multiplying the age specific rate estimate by the ratio of the sex-specific stratum-specific rate to the overall rate.

Overview of Cases

Myocarditis and Pericarditis (Cumulative to 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 3,818 cases (4075 events) of myocarditis and/or pericarditis have been reported, with 2,836 (74.3%) cases medically confirmed. In 227 cases, events of both myocarditis and pericarditis were reported. There were 39 cases with fatal outcomes.

The majority of cases reporting myocarditis and/or pericarditis involved male patients (2,651, 69.4%) and 1,108 (29%) that involved female patients; 59 reports (1.5%) did not include gender data. The mean age of the patients was 36.3 years (SD 16.8), with a median age of 31 years (min 12 /max 94); 387 cases were missing age data.

The greatest proportion of cases reporting myocarditis and pericarditis events involved males between the ages of 18 to 39-years-old (1,652, 43.3%). Overall, there were 2,137 cases that reported myocarditis and pericarditis events in patients in the 18 to 39-years-old range. This represents 56% of all cases (Table 12).

**Table 12. Number and Percentage of Cases Reporting Myocarditis and Pericarditis by Age and Gender - Cumulative to 31 Dec 2021**

| Age Group | Female | | Male | | Unknown | | Total # Cases | % Total Cases |
|---|---|---|---|---|---|---|---|---|
| | # Cases | % Cases | # Cases | % Cases | # Cases | % Cases | | |
| 12-15 | 8 | 0.2 | 34 | 0.9 | 0 | 0 | 42 | 1.1 |
| 16-17 | 5 | 0.1 | 69 | 1.8 | 0 | 0 | 74 | 1.9 |
| 18-29 | 277 | 7.3 | 1180 | 30.9 | 5 | 0.1 | 1462 | 38.3 |
| 30-39 | 196 | 5.1 | 472 | 12.4 | 7 | 0.2 | 675 | 17.7 |
| 40-49 | 173 | 4.5 | 247 | 6.5 | 1 | 0 | 421 | 11 |
| 50-64 | 205 | 5.4 | 234 | 6.1 | 5 | 0.1 | 444 | 11.6 |
| 65-74 | 106 | 2.8 | 111 | 2.9 | 1 | 0 | 218 | 5.7 |
| 75+ | 48 | 1.3 | 46 | 1.2 | 1 | 0 | 95 | 2.5 |
| Missing | 90 | 2.4 | 258 | 6.8 | 39 | 1 | 387 | 10.1 |
| **Grand total** | **1108** | **29** | **2651** | **69.4** | **59** | **1.5** | **3818** | **100** |

Myocarditis and pericarditis events occurred most frequently after the second dose (1,664; 40.8%). Regardless of dose number, almost half of the events had an onset less than 7 days from vaccination (1,821, 44.7%), inclusive of 113 events following a 3rd or booster dose, and the median time to onset from most recent dose was 3 days (min: 0; max: 290). There were 1,399 events (34.3%) reported with insufficient information to determine time to onset (Table 13).

**Table 13. Number and Percent of Events of Myocarditis and Pericarditis by Dose Number and Time to Onset (TTO) - Cumulative to 31 Dec 2021**

| Dose Number | TTO All Doses (Days) | # Events | % Events |
|---|---|---|---|
| Dose 1 | *Subtotal* | *871* | *21.4* |
| | 0 days | 67 | 1.6 |
| | 01-02 | 191 | 4.7 |
| | 03-04 | 167 | 4.1 |
| | 05-06 | 74 | 1.8 |
| | 07-13 | 135 | 3.3 |
| | 14-29 | 144 | 3.5 |
| | 30+ | 93 | 2.3 |
| Dose 2 | *Subtotal* | *1,664* | *40.8* |
| | 0 days | 119 | 2.9 |
| | 01-02 | 566 | 13.9 |
| | 03-04 | 449 | 11.0 |
| | 05-06 | 75 | 1.8 |
| | 07-13 | 95 | 2.3 |
| | 14-29 | 149 | 3.7 |
| | 30+ | 211 | 5.2 |
| Dose 3 | *Subtotal* | *141* | *3.5* |
| | 0 days | 23 | 0.6 |
| | 01-02 | 50 | 1.2 |
| | 03-04 | 27 | 0.7 |
| | 05-06 | 13 | 0.3 |
| | 07-13 | 16 | 0.4 |
| | 14-29 | 9 | 0.2 |
| | 30+ | 3 | 0.1 |
| Unknown | *Subtotal* | *1,399* | *34.3* |
| | Missing | 1,399 | 34.3 |
| **Grand total** | | **4,075** | **100** |

Myocarditis and Pericarditis in Adolescents (12 to 17 years old) – Cumulative to 31 Dec 2021

Cumulatively, there were 116 cases (122 events) of myocarditis and pericarditis in adolescents 12 to 17 years of age (3% of all cases reported), with 98 cases medically confirmed. There were 103 (88.8%) cases reported in males and 13 (11.2%) in females. The mean age of the adolescents was 15.7 years (SD: 1.3) and the median age was 16 years (min: 12/max: 17). The majority of the cases reported in adolescents were in males aged 16 to 17 years (69, 59.5%) (Table 14).

**Table 14. Number and Percentage of Myocarditis and Pericarditis Cases in Adolescents (12 to 17 years old) by Age and Gender - Cumulative to 31 Dec 2021**

| Age Group | Female | | Male | | # Total Cases | % Total Cases |
|---|---|---|---|---|---|---|
| | # Cases | % Total Cases | # Cases | % Total Cases | | |
| 12-15 | 8 | 6.9 | 34 | 29.3 | 42 | 36.2 |
| 16-17 | 5 | 4.3 | 69 | 59.5 | 74 | 63.8 |
| **Grand total** | **13** | **11.2** | **103** | **88.8** | **116** | **100** |

Cumulatively, there were 101 events of myocarditis reported in adolescents (including 1 event of myocarditis infectious), with the greatest proportion of the events (46; 45.5%) occurring after the second dose. Of the events with a known TTO, all but 9 events had an onset of less than 7 days from vaccination.

**Table 15. Number and Percentage of Events Reporting Myocarditis in Adolescents (12 to 17 years old) by Dose and Time to Onset (TTO) –Cumulative to 31 Dec 2021**

| Dose Number | TTO (Days) | # Events | % Events |
|---|---|---|---|
| Dose 1 | *Subtotal* | *18* | *17.8* |
| | 01-02 | 7 | 6.9 |
| | 03-04 | 4 | 4 |
| | 07-13 | 2 | 2 |
| | 14-29 | 2 | 2 |
| | 30+ | 3 | 3 |
| Dose 2 | *Subtotal* | *46* | *45.5* |
| | 0 days | 4 | 4 |
| | 01-02 | 18 | 17.8 |
| | 03-04 | 18 | 17.8 |
| | 05-06 | 4 | 4 |
| | 14-29 | 2 | 2 |
| Unknown | *Subtotal* | *37* | *36.6* |
| | Missing | 37 | 36.6 |
| **Grand total** | | **101** | **100** |

Myocarditis and Pericarditis in Patients Receiving a 3rd or Booster dose of SPIKEVAX

Cumulatively as of 31 December 2021, there were 134 cases (141 events) received of myocarditis and pericarditis following a 3rd or booster dose of SPIKEVAX, which included 80 events of myocarditis (including one event of hypersensitivity myocarditis) and 61 events of pericarditis. The cases involved 82 males (61.2%) and 52 females (38.8%), with a mean age of 46.7 years (SD: 18.7) and a median age of 43.5 years (min: 18/max: 86). The time to onset from vaccination was less than 7 days for 113 (80.1%) of the events. It is important to note that in most of these reports it is not known whether the 3rd dose was given due to the patient being an immunocompromised individual or as a true booster dose.

A review of the data received cumulatively showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days.

Review of the data also show no difference in the observed safety profile of SPIKEVAX in the adolescent population, or in those individuals receiving a 3rd dose of SPIKEVAX.

Implementation of a new reference rate did not change the interpretation of observed vs. expected analyses.

Based on the information provided by both literature and surveillance sources consistently describing an increase in the incidence of myocarditis, predominantly within the first 7 days following receipt of a second dose of vaccine, that appears largely isolated to younger men (<40 years of age).

Based on the analysis of all the safety data received cumulative as of 31 December 2021, the MAH considers that cases of myocarditis and pericarditis to be consistent with the known safety profile of SPIKEVAX and appropriate risk minimisation and risk communications strategies have already been implemented by the MAH. The MAH will continue to monitor the reported events of Myocarditis and

Pericarditis using routine and enhanced surveillance activities. The benefit-risk evaluation remains positive.

ITEM 2:
The MAH is in consequence asked to re-discuss the interval of the (heterologous) booster dose based on available safety data, and amend section 4.2 accordingly, as appropriate.

MAH's response:

Please refer to the data presented to Item 1 above. The MAH position is to maintain Section 4.2 as proposed below.

**Assessment of response (Item 1 and Item 2)**
The MAH informs that real-world data from the two PASS studies conducted in the US and the EU will not be available until a sufficient number of booster doses has accrued to support analyses. Pending sample size, such data may be described in the April 2022 (US PASS) and September 2022 (EU PASS) interim analyses. The MAH submitted post-authorisation safety data for a 3rd dose of Spikevax. The data and analyses in the response have previously been submitted and were assessed by the PRAC within MEA 011.10, the 11$^{th}$ SSR.

Literature to extent information on the experience after dose 3 was not submitted by the MAH.

The MAH submitted post-marketing surveillance data. The analysis is based on extrapolation of administered doses in the US.

More events were recorded for after dose 1 and 2 compared to after dose 3. It is estimated that 88,621,617 individuals received a third dose in the US. 559,872,937 doses are estimated to have been administered overall. This means that approximately 6.3 times more first and second doses than third doses have been administered. More events were reported after Dose 1 (667,794 events) compared to Dose 2 (479,310 events). Taking together, 1.147.104 events occurred after dose 1 or dose 2, but only 52,312 after dose 3 (i.e. approximately 21.9 times more events after dose 1 and dose 2 together than after dose 3). For almost 1/3 of all events (i.e. 448,773, 27.2% of grand total) the dose was unknown. Available data do not distinguish between individuals who received 100 µg as 3rd dose, as indicated for immunocompromised individuals, and a 50ug booster dose. The dosing intervals range from 3 months to 5 months depending on the national recommendations for administration of a booster dose. The proportion of each interval on all booster administrations is unknown.

More cases (serious and non-serious) were reported for the review period of one month compared with the prior to review period (6,437 cases in the prior to review period, and 11,074 in the review period). This could be due to significantly more 3$^{rd}$ doses administered in the review period.

The analysis does not distinguish between a 3$^{rd}$ dose of 100 µg as given to immunocompromised individuals and the 50 µg dose as given as booster to healthy individuals.

The analysis does do not distinguish between the different dosing intervals for booster administration. The interval of a booster dose in this analysis is 3 to 5 months. The intervals derive from the different booster recommendations in different countries.

The TTO of events is comparable to what is known from dose 1 and dose 2. The majority of events post-dose 3 occurred with the first 2 days after administration. The top three events and top 3 serious events after dose 3 by preferred term were headache, pyrexia and fatigue.

During the reporting period, a total of 31,467 events for recipients after a third dose or booster dose of Spikevax were reported of which 20,366 were serious. Only the top 3 serious AEs were provided. Those

were headache, pyrexia, and fatigue. A total of 63 fatal cases (275 events) were reported, for which the MAH did not submit any information.

Myocarditis/Pericarditis

The majority of cases reporting myocarditis and/or pericarditis involved male patients (2,651, 69.4%). 1,108 cases (29%) involved female patients; 59 reports (1.5%) did not include gender. The mean age of the patients was 36.3 years.

The greatest proportion of cases reporting myocarditis and pericarditis events involved males between the ages of 18 to 39-years-old (1,652, 43.3%). The majority of myocarditis/pericarditis cases in adolescents occurred in 16 to 17 years of age (74 cases, 63.8%, males and females together). 42 cases (36.2%) were recorded for 12-15 years old individuals (males and females together).

Stratification of cases of myocarditis with known dose and time to onset that occur within the 7 days following vaccination, considering observed versus expected analyses, showed an increased risk for myocarditis following dose 2 in young males, but no similar increase has yet been observed following a third dose (Table 10).

The data have previously been submitted to PRAC and assessed within Post-Authorisation Measure 011.10 (11$^{th}$ SSR).

With regard to the 3$^{rd}$ dose, the MAH was requested by PRAC to present more data on vaccinees exposed to third dose and with a fatal outcome in the upcoming SSRs. This should contain at least age distribution, TTO, and meaningful categories of causes of death. Moreover, with regard to the third or booster doses, retrieving information on dose administered is not straightforward in most spontaneous reporting databases, and it is not clear how the companies are handling this information and the difficulties they may be facing in this respect. The MAH was asked to comment on. It will be also of relevance to have further insight in how the estimation of 3rd doses exposure is being performed.

**Conclusion:**
The submitted safety data did not reveal any new safety signals with regard to administration of a 3$^{rd}$ dose. Stratification of myocarditis cases with known dose and time to onset that occur within the 7 days following vaccination, considering observed versus expected analyses, showed an increased risk for myocarditis following dose 2 in young males, but no similar increase has yet been observed following a third dose (Table 10). The given time interval of a 3$^{rd}$ dose or booster dose ranges between 3 months and 6 months. A differentiation between a 100 µg 3$^{rd}$ dose and a 50 µg booster dose is not possible. Uncertainties remain with regard to the methodology of recording the dose numbers. The submitted data do not raise new safety signals with regard to a 3$^{rd}$ dose or booster dose given at least 3 months after primary series. The data do not extent the safety data base for the heterologous booster. They nonetheless do not indicate a higher risk of myocarditis after third dose. The interval of 3 months however could be supported by the summary of all submitted safety data (post-marketing safety surveillance, CoV-boost study, Com-CoV-2 study and DIMID study.

**Conclusion**

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

# 8. Overall conclusion and impact on the benefit/risk balance

The variation is intended to enable a heterologous booster injection of Spikevax (also referred to as COVID-19 Vaccine Moderna or mRNA-1273) after any authorised COVID-19 vaccine. The basis for this application is the NIH sponsored DMID 21-0012 trial conducted in the USA and recently published. The trial demonstrates that the titres of neutralising antibodies increase considerably after a booster injection compared to the pre-booster titres. Interpretation of the data and bridging to available efficacy data is hampered by the following issues:

- The used dose was 100 µg which is double the authorised dose for a booster injection in Europe. There are no data available on the use of a 100 µg dose in comparison to a 50 µg booster dose. Data from the mRNA-1273-P201 trial assessed in a previous variation show that there is a dose response relationship observed with respect to neutralising antibody titres when using either 50 µg or 100 µg for the primary series. Based on this observation one could assume that the response to a 100 µg booster is higher than the response to a 50 µg booster. It can be agreed that the boosting of immune response is more dependent on the baseline titres after primary vaccination series compared to the dose given as a booster dose.

- The interval between primary series and booster injection was shorter in the DMID trial compared to the mRNA-1273-P201 trial which provided the pivotal data for boosting. The role of the interval between primary immunisation and booster injection has not been systematically assessed and it is unknown whether the difference observed between trials is relevant for the interpretation of results. As titres generally decline after the primary immunisation longer intervals will be associated with lower pre-boost titres. If similar post-boost titres are obtained the GMTR will be higher with longer intervals creating the incorrect impression that a better boost is obtained. Based on the submitted data it can be agreed, that the post-dose 2 nAb GMT are likely insufficient to neutralise the Omicron variant, and therefore a booster dose should be given earlier than the previously proposed interval of 6 month, This is moreover justified by the DMID study were a booster was given approximately 12-20 weeks after the primary series.

- Peak titres achieved after the primary series are not available therefore comparisons on the increases in neutralising antibody titres can only made based on titres prior to and 4 weeks after the booster injection.

- Under the assumption that pre-boost titres obtained for the different vaccines are associated with remaining protection from symptomatic infection the obtained increase in titres as reflected in the GMTR pre/post-boost are regarded as meaningful and justify the use of a heterologous boosting in the absence of suitable and better documented alternatives.

- Data for a second dose with Spikevax after a first dose with a vector based vaccine were shown in the Com-COV2 study which investigated different "mix and match" strategies for the primary series. These data support that an immune-response to a vector based COVID-19 vaccine can substantially be increased by a second dose of Spikevax. Although this trial investigated only the primary series it is accepted that it lends some support to the assumption that Spikevax could also be used for the boosting in the heterologous setting when the same antigen is used.

A heterologous booster with Spikevax is also supported by immunogenicity data from the COV-BOOST study, a multicentre, randomised Phase 2 study evaluating a heterologous booster vaccination against COVID-19. Participants were adults aged 30 years or older who had received two doses of either another mRNA-vaccine or an adenoviral vector vaccine, and were at least 84 days post-second dose by the time of enrolment.

The safety profile of solicited and unsolicited ARs was evaluated in the DMID Study 21-0012 with heterologous/homologous (Spikevax) SARS-CoV-2 vaccine dosing (Spikevax booster) study of the various FDA Emergency Use Authorisation (EUA) vaccines (COVID-19 Vaccine Janssen, Spikevax, Comirnaty) in participants ≥ 18 years old. A total of 154 participants have been enrolled and received a Spikevax boost injection (IM; 100 µg) approximately 12-20 weeks after receiving primary vaccination under EUA. Overall, the safety profile appears comparable.

No safety and immunogenicity data are submitted for subjects below 18 years of age. As only boosting in adults is requested by the MAH, this is an acceptable limitation for the time being.

The follow-up time-period for safety is short, with 29 days. Another limitation is the lack of data for heterologous boosting with Spikevax in subjects with a compromised state of health or prior COVID-19. A high reactogenicity might prove detrimental to these individuals. It is expected that this type of data will be collected as part of the ongoing PASS efforts. The safety of a heterologous booster is also subject to routine pharmacovigilance and the PSURs.

The subsequently submitted safety data from the MAH's post-marketing surveillance did not reveal any new safety signals with regard to administration of a third dose given *at least 3 months* after the primary series. The interval for giving the booster dose was 3 to 5 months depending on local recommendations. The data confirmed what is known about the risk of myocarditis/pericarditis, which of note appears not to be higher after dose 3 compared to after dose 2. Stratification of cases with known dose and time to onset that occur within the 7 days following vaccination, considering observed versus expected analyses, showed an increased risk following the second dose in young males, but no similar increase has yet been observed following a third dose. A differentiation between a 100 µg third dose and a 50 µg booster dose is not possible within the submitted post-marketing safety data. Uncertainties remain with regard to the methodology of recording the dose numbers. No clinical information is given for the fatal cases and only the top 3 SAEs are presented for the post-marketing safety data base. The submitted data do not raise new safety signals with regard to a third dose or booster dose given at least 3 months (i.e. from 3 to 5 month) after primary series. The submitted post-marketing safety data do not extent the safety data base for the heterologous booster. Supportive studies for the heterologous booster remain the DIMID, the COV-BOOST study, and the Com-CoV-2 study. The interval of *at least 3 months* is supported by the summary of all submitted safety data (post-marketing safety data, CoV-BOOST and DMID). The submitted post-marketing safety data were previously submitted to PRAC within MEA 11.10 (11$^{th}$ SSR). Within this procedure the MAH was asked to submit clinical information about the fatal cases and on methodological uncertainties with regard to the recording of the dose number. PRAC concluded that the benefit-risk balance of Spikevax in the approved indication remains unchanged. Additional information is expected from PASS mRNA-1273-P904 and from routine pharmacovigilance.

The submitted trials indicate the utility of Spikevax to increase the titre of neutralising antibodies regardless of the primary series with a mRNA-based or a vector based vaccine using the same antigen.

In addition, the MAH took the opportunity to implement the WHO-approved INN 'elasomeran' in the Spikevax product information, which is acceptable. The MAH also took the opportunity to make minor editorial changes/corrections throughout the product information, which is also accepted.

The benefit-risk balance of Spikevax remains favourable.

# 9. Recommendations

Based on the review of the submitted data, this application regarding the following change:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | A, I, IIIA, IIIB |

Update of sections 4.2 and 5.1 of the SmPC in order to include information on heterologous boosting using a 50 ug dose of Spikevax to boost subjects that have previously completed a primary vaccination series with any authorised COVID-19 vaccine, and to shorten the duration of the interval between the primary series and the booster dose to 3 months, based on data from the DMID Study 21-0012, a Phase 1/2 heterologous SARS-CoV-2 vaccine dosing (mRNA-1273 booster) study of the various vaccines authorized in the US under Emergency Use Authorisation in participants ≥ 18 years old (NCT04889209). In addition, the MAH took the opportunity to implement the WHO-approved INN 'elasomeran' and make minor editorial changes/corrections throughout the product information. The Annex A, the Labelling and the Package Leaflet are amended accordingly.

☒is recommended for approval.

### *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annexes A, I, IIIA and IIIB are recommended.

## 10. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

### *Scope*

Please refer to the Recommendations section above

### *Summary*

SmPC new text

A booster dose of Spikevax (0.25 mL, containing 50 micrograms mRNA, which is half of the primary dose) should be given intramuscularly to adults at least 3 months after completion of the primary series.

Spikevax may be used to boost adults who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine.

Safety and immunogenicity of a heterologous booster with Spikevax were studied in an investigator-initiated trial with 154 participants. The minimum time interval between primary series using a vector based or RNA-based COVID-19 vaccine and booster injection with Spikevax was 12 weeks (range: 12 weeks to 20.9 weeks). The dose used for boosting in this study was 100 micrograms. Neutralising antibody titres as measured by a pseudovirus neutralisation assay were assessed on Day 1 prior to administration and at Day 15 and Day 29 after the booster dose. A booster response was demonstrated regardless of primary vaccination. Only short-term immunogenicity data are available; long-term protection and immunological memory are currently unknown.

COV-BOOST is a multicentre, randomised Phase 2 investigator-initiated trial of third dose booster

vaccination against COVID-19 with a subgroup to investigate detailed immunology. Participants were adults aged 30 years or older, in good physical health (mild to moderate well-controlled co-morbidities were permitted), who had received two doses of either Pfizer–BioNTech or Oxford–AstraZeneca (first dose in December 2020, January 2021 or February 2021), and were at least 84 days post second dose by the time of enrolment. Spikevax boosted antibody and neutralising responses and was well tolerated regardless of the prime series. The dose used for boosting in this study was 100 micrograms. Neutralising antibody titres as measured by a pseudovirus neutralisation assay were assessed on Day 28 after the booster dose.