EMA/618924/2021
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/005791/II/0034

Invented name: Spikevax

Common name: COVID-19 mRNA Vaccine (nucleoside-modified)

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	25 Sep 2021	25 Sep 2021
☐	CHMP Rapporteur Assessment Report	14 Oct 2021	14 Oct 2021
☐	CHMP members comments	19 Oct 2021	19 Oct 2021
☐	Updated CHMP Rapporteur Assessment Report	22 Oct 2021	22 Oct 2021
☒	Opinion	25 Oct 2021	25 Oct 2021

Procedure resources	
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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 3 September 2021 an application for a variation.

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, IIIA and IIIB

To update sections 2, 4.2, 4.8, 5.1, 6.5 and 6.6 of the SmPC to include a booster dose for Spikevax, based on new clinical data from studies mRNA-1273-P201, a Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older (NCT04405076), mRNA-1273-P301, an ongoing Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older (NCT04470427) and DMID 21-0012, a Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines (NCT04889209). The package leaflet is updated accordingly.

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

2. Introduction

Data from the blinded part of the pivotal study P301 Part A support the persistence of efficacy of the primary series through to at least 6 months. Vaccine efficacy of the final blinded analysis (data base lock: 04 May 2021) were consistent with the results of the previous interim and primary analysis (data cut-offs: 11 November 2020, 25 November 2020), confirming the persistence of high rates of efficacy over a median of 5.3-months observation period (P301 Interim CSR, dated 05 August 2021). These efficacy results were obtained prior to the widespread circulation of the Delta variant in the USA. After unblinding, participants initially randomised to the placebo group were offered to be vaccinated within the trial from 29 December 2020 to 30 April 2021. During July and August 2021, a steep increase in the number of cases caused by the Delta variant was observed in the US indicating broad circulation and likely exposure to it. Preliminary data of an ad hoc analysis of COVID-19 incidences between July and August 2021 of the ongoing pivotal clinical trial P301 suggest a relative case reduction of 36% (1 – ratio of incidences rates) in vaccine recipients initially randomised to the placebo group and vaccinated following unblinding compared to subjects vaccinated during the blinded phase from 27 July 2020 to 16 December 2020.

In addition, the persistence of neutralising antibody titers over time shows waning of the neutralising antibody response following the primary series. Considering the emergence of SARS-CoV-2 variants of concern, further investigations with pseudoviruses representing various variants of concerns (VOCs) were conducted by Choi et al 2021 (Nature Medicine, https://doi.org/10.1038/s41591-021-01527-y): A subset of participants vaccinated in P201 Part A (n=20) were tested 6-8 months after the primary series and neutralising antibody (nAb) results (using a research grade vesicular stomatitis virus [VSV]-based pseudoviral assay [VSV-PsVNA] [D614G]) were compared with those obtained 1 month after the primary series (2 doses of 100 µg). These limited data show that 6-8 months after the primary series, nAb titers waned 6- to 7-fold compared with 1 month post-dose 2 primary series titers. Similarly, by 6-8 months after the primary series, titers against the B.1.351 (Beta) and P.1 (Gamma) strains as well as B.1.617

(Delta) strains declined ~40-fold versus peak (1 month post) titers. These data were provided also within this submission.

Although an antibody threshold inferring protection against SARS-CoV-2 infection or COVID-19 has not been established, decline in neutralisation capacity against wild-type Wuhan-Hu-1 isolate (WT) and VOCs after approximately 6 months shows waning circulating titers, which may place vulnerable populations at a greater risk of infection or disease.

Multiple strategies for a booster vaccine are currently investigated in the clinical development plan of Spikevax including a booster dose with the parental Wuhan strain or other candidate vaccines representing variants of concerns. This submission is intended to support the use of a booster of Spikevax (representing the Wuhan-Hu1 isolate) at a 50 µg dose.

3. Clinical Efficacy aspects

Table 1 displays the clinical studies evaluating the prototype vaccine, mRNA-1273 to be given as a 50 µg booster dose and for which data were submitted.

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

Study	2-Dose Primary Series	Spikevax Booster Dose (Dose 3)	Interval Between Dose 2&3	N	Status
P201 B	50 µg mRNA-1273	50 µg	≥6 mo	173	Data available through Day 29 post-boost
	100 µg mRNA-1273	50 µg	≥6 mo	171	
DMID 21-0012	Group 1E: Janssen (single dose)	100 µg	12-20 weeks	53	Safety data available through Day 7; Immunogenicity data available through Day 15
	Group 2E: 100 µg mRNA-1273	100 µg	12-20 weeks	51	Safety data available through Day 7; Immunogenicity data available through Day 15
	Group 3E: Pfizer 30 µg	100 µg	12-20 weeks	50	Safety data available through Day 7; Immunogenicity data available through Day 15

CHMP comment: Data from study DMID21-0012 was considered for safety only. In this study immunogenicity was evaluated only following a 100 µg booster dose and no comparison with a 50 µg booster was performed. In addition, the neutralising antibody response was determined with an assay not employed in study P201 or P301 therefore it does not allow any comparison of these data with the results obtained on the 50 µg booster dose in study P201.

3.1. Methods – analysis of data submitted

Study P201

In Part A of the study participants in the 2 age cohorts received either 50 µg, 100 µg of mRNA-1273, or placebo (see Table 2).

Table 2 – Part A treatment groups

Cohort	Treatment Groups	Investigational Product	Number of Participants
Cohort 1 ≥ 18 to < 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Cohort 2 ≥ 55 years old	mRNA-1273 Arm	mRNA-1273 50 µg	100
	mRNA-1273 Arm	mRNA-1273 100 µg	100
	Placebo Arm	Placebo	100
Total			**600**

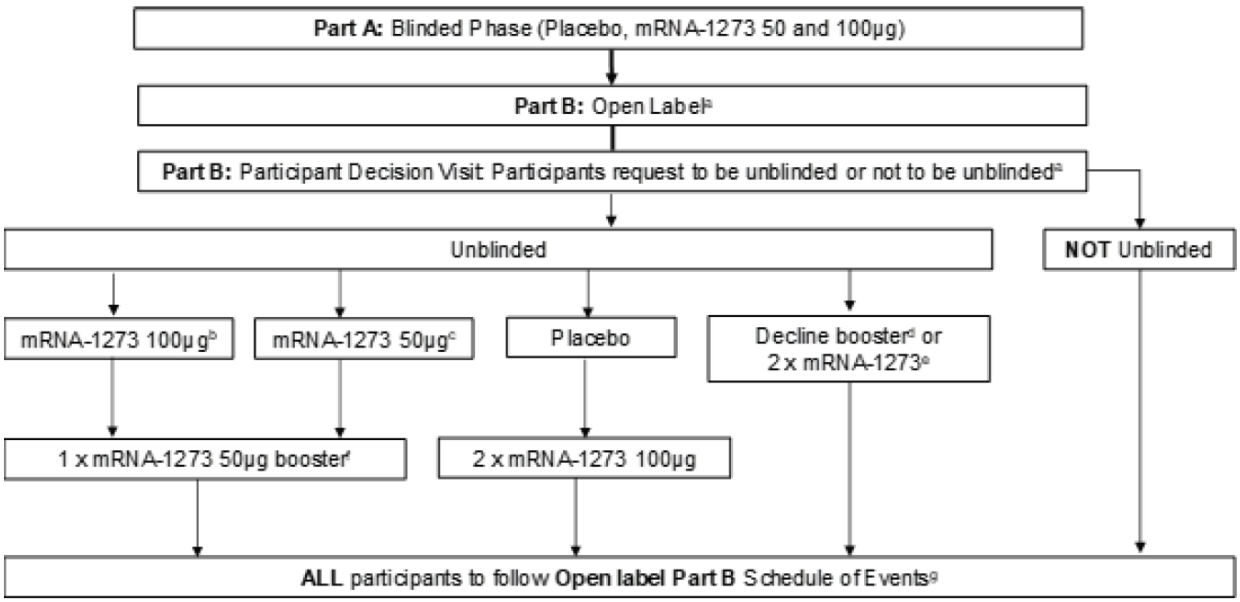
After the primary analysis for Study P201 was completed (End of Part A, blinded portion of P201 13 August 2021 per Protocol Amendment 6 dated 22 April 2021), the study was amended (Amendment 4, 15 January 2021) to include an open-label interventional phase Part B (Figure 1).

Participants having received 2 doses of Spikevax (either 50 µg or 100 µg) were invited to participate in Part B of the study. Participants in the placebo arm were invited to obtain the primary vaccination with two doses of mRNA-1273.

Part B is the open-label part of the P201 study assessing immunogenicity responses following administration of a 50 µg booster of mRNA-1273 to participants primed with 2 doses of mRNA-1273 in P201 Part A (50 µg or 100 µg of mRNA-1273) at least 6 months earlier.

Of note, study P201 is ongoing and 60 participants from P301 (the pivotal phase 3 trial) are to be enrolled in Part C of study P201, where subjects are to receive candidate vaccines representing VOCs. Part C was introduced with Amendment 5 (19 February 2021). No data were provided for Part C participants within this submission.

Figure 1: P201 Part B, Open-Label Schema



[a] All participants will proceed to Part B, Open-Label Interventional Phase; begins with the Participant Decision Visit.
[b] Participants who received 2 injections of mRNA-1273 100 µg during Blinded Part A.

[c] Participants who received 2 injections of mRNA-1273 50 µg during Blinded Part A.
[d] Participants who received 2 injections of mRNA-1273 in Part A and decline booster injection in Part B.
[e] Participants who received placebo in Part A and decline 2 injections of mRNA-1273 in Part B.
[f] Participants who received 2 injections of mRNA-1273 (50 µg or 100 µg) in Part A will receive 1 booster injection of mRNA-1273 50 µg in Part B.

Objectives (Part B)

Primary Immunogenicity Objective

The primary immunogenicity objective is to evaluate the immunogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose or 100 µg of mRNA-1273 administered as 2 doses 28 days apart, as assessed by the level of specific bAb.

Secondary Immunogenicity Objective

The secondary objective is to evaluate the immunogenicity of 50 µg of mRNA-1273 vaccine administered as a single booster dose or 100 µg of mRNA-1273 100 µg administered as 2 doses 28 days apart, as assessed by the titer of nAb.

Immunogenicity objectives per SAP V2.0 (Comparison of P201 Part B with P301)

A standalone SAP for P201 Part B (Version 1.0, dated 04 June 2021, Version 2.0, dated 06 August 2021) described new primary immunogenicity objectives to infer efficacy of the 50 µg booster by establishing noninferiority (NI) to P301 immunogenicity results.

Against the Prototype Virus Strain

The objective was to evaluate the immune response 28 days after a single booster dose of 50 µg mRNA-1273 against the prototype virus strain and the immune response 28 days after the completion of the primary series of mRNA-1273 100 µg against the prototype virus strain. Immune response 28 days after a single booster dose of 50 µg mRNA-1273 against the prototype virus strain was to be assessed by those P201 Part B participants who received a single booster dose of 50 µg mRNA-1273; and immune response 28 days after the completion of the primary series of mRNA-1273 100 µg against the prototype virus strain was to be assessed in P301 participants on mRNA-1273 100 µg, based on the same assays.

The immune response to a single booster dose of 50 µg mRNA-1273 was to be considered to be non-inferior of that to the primary series of mRNA-1273 100 µg if both of the following criteria were met:

- If the point estimate of ratio of the geometric mean titer (GMR; booster dose of 50 µg mRNA-1273 P201 Part B against the prototype virus strain vs. primary series of 100 µg mRNA-1273 P301 against the prototype virus strain) was ≥1 and the lower bound of the corresponding 95% CI was ≥ 0.67, based on the non-inferiority margin of 1.5, and
- The lower bound of the 95% CI of the difference in seroresponse rate against the prototype virus strain (P201 Part B - P301) was ≥ -10%.

Against the Variant Virus Strain (B.1.617.2)

The objective was to evaluate the immune response 28 days after a single booster dose of 50 µg mRNA-1273 against the variant virus stain (B.1.617.2) and the immune response 28 days after the completion of the primary series of mRNA-1273 100 µg against the prototype virus strain. Immune response 28 days after a single booster dose of 50 µg mRNA-1273 against the variant virus stain (B.1.617.2) was to be assessed by those P201 Part B participants who received a single booster dose of 50 µg mRNA-1273 based on the Duke assay against the variant virus stain (B.1.617.2, Delta); and immune response 28 days after the completion of the primary series of mRNA-1273 100 µg against the prototype virus strain

was to be assessed in P301 participants on mRNA-1273 100 µg, based on the Duke assay against the prototype virus strain.

Criteria for non-inferiority were defined in analogy to the criteria for the prototype virus strain.

CHMP comment:

The initial objectives in the protocol for P201 Part B remained very vague. Only with the SAP, which was drafted rather late, the objectives were properly defined.

Comparison of immune response (nAbs only) against the variant virus strain (B.1.617.2) for P201 Part B to immune response against prototype (Wuhan) virus strain for P301 was defined with SAP version 2.0 but was not provided with the submission. The comparison is, however, not considered of relevance for this procedure.

Statistical Methods used for P201 Part B and P301 Comparison

Assays

Immunogenicity endpoints were to be assessed by validated assays to measure pseudovirus neutralising antibody ID50 and ID80 (PsVNT50 and PsVNT80), anti-Spike ELISA (VAC65 Spike IgG Antibody) and anti-Spike by MSD Multiplex. Pseudovirus neutralising antibody assays (PsVNA) were to be assessed for the prototype virus as well as the virus strain B.1.617.2 (Delta).

Definition of seroresponse

For each of the antibodies of interest, participants with a change from below the LLOQ to ≥ 4×LLOQ, or at least a 4-fold rise if baseline was ≥ the LLOQ were to be considered achieving seroresponse. In the initial SAP seroresponse was defined based on assay specific criteria (Table 3).

Table 3: SAP1: Seroresponse definition against prototype strain based on SAP V1.0

Assay Name	Category	Test Name/ Description	Definition of Seroresponse
Pseudovirus (PsVNA)	nAb	PsVNT50 (ID 50)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 3.3-foldrise
		PsVNT80 (ID 80)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 2.3-foldrise
Anti-Spike ELISA	bAb	anti-Spike VAC65 Spike IgG Antibody	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 4.6-foldrise
MSD multiplex	bAb	anti-Spike	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 1.9-foldrise

Analysis methods

To assess the magnitudes of the differences in immune response 28 days after a single booster dose of 50 µg mRNA-1273 (P201 Part B participants received a booster dose of 50µg mRNA-1273) and the immune response 28 days after the completion of the primary series of mRNA-1273 100 µg (P301 participants on mRNA-1273 100 µg), an analysis of covariance (ANCOVA) model was to be used. The model included log-transformed antibody titers at D29 in P201 Part B, and D57 in P301 as the dependent variable, treatment groups (P201 Part B 50 µg mRNA-1273 booster, P301 mRNA-1273 100 µg primary series) as explanatory variable, adjusting for age groups (< 65, ≥ 65). The geometric least squares mean (GLSM) and corresponding 2-sided 95% CI for the anti- body titers for each treatment group were to be provided. The GLSM and corresponding 95% CI results on log-transformed scale were to be back-

transformed to obtain estimates on the original scale. GMR, estimated by the ratio of GLSM and the corresponding 2-sided 95% CI was to be provided to assess the treatment difference.

The seroresponse rate, the proportion of participants achieving seroresponse, was to be provided. Seroresponse rate in P201 during the Part A for the primary series, and Part B after the booster was to be assessed separately. Specifically, seroresponse rate in P201 Part A was to be calculated based on the baseline pre-Dose 1 (pre-vaccination) value on Day 1; seroresponse rate in Part B will be calculated based on the pre-booster value (Day 1 in Part B). To compare the seroresponse rates between 28 days after a single booster dose of 50 µg mRNA-1273 (P201 Part B participants received a booster dose of 50 µg mRNA-1273) and the immune response 28 days after the completion of the primary series of mRNA-1273 100 µg (P301 participants on mRNA-1273 100 µg), the Miettinen-Nurminen's method was to be used to calculate the 95% CI for the difference in seroresponse rates.

Subgroup analysis will be performed in the following age groups to assess the immune response in the age categories ≥ 18 and < 65, ≥ 65 years.

CHMP comment:

Statistical methods for the primary immunogenicity analyses in Part B were not described at all within the protocol for P201 Part B. Only with the SAP, which was drafted rather late, the statistical methods were properly defined.

Overall the statistical methods are considered acceptable. The reason to use external controls from P301 to assess non-inferiority per the primary immunogenicity objective instead of conducting an intra-subject comparison (pre vaccination to post primary vaccination *vs.* pre booster to post booster) is not fully understood as the comparison between trials might be hampered by e.g. selection bias or other sources of bias. However, given the observed results between trials and the reported results within trial P201, this is not considered of high relevance to this procedure.

The definition of seroresponse was modified with SAP version 2.0. For subjects with baseline values < LLOQ the initial criterion required a titre ≥ LLOQ. The new criterion was always more demanding as a 4-fold increase over the LLOQ was required. For subjects with measurable baseline titres the initial criteria were assay specific. The new criterion the same for all assays and was more demanding for all but anti-spike ELISA (VAC65 Spike IgG Antibody) where the change from baseline was reduced from a 4.6-fold to a 4-fold increase. Overall this is considered acceptable.

The initial trial P201 was stratified by age with age strata < 55 and ≥ 55, whereas subgroups were only specified with an age cut-off of 65. As randomisation in the original Part A no longer plays a role for the analysis of antibody titres after booster vaccination, this is considered acceptable.

Timing of the Application

This submission was triggered by the availability of data from the pre-planned analysis conducted after participants in Study P201 Part B who received a 50 µg booster dose of mRNA-1273 reached the Day 29 post-boost visit (database lock: 10 June 2021; data extraction: 11 June 2021). This analysis included the safety and immunogenicity data from a total of 344 participants who received 50 µg mRNA-1273 single booster dose in P201 Part B.

Study P301

Study P301 is an ongoing pivotal randomised, observer-blind, placebo-controlled, stratified study to evaluate efficacy, immunogenicity, and safety in adults ≥ 18 years of age. The final efficacy analysis of Part A (blinded phase) based on a database lock of 04 May 2021 demonstrated a VE of 93.2% (95% CI: 91.0%, 94.8%, p < 0.0001), which was consistent with previous results of the interim and primary analysis (data cut-offs: 11 November 2020, 25 November 2020), confirming persistent, high efficacy over

a substantially larger effective sample size (i.e., number of confirmed COVID-19 cases) and over a median 5.3-months blinded observation period from randomisation in Part A (mRNA-1273-P301 primary CSR).

In this submission, to support the use of 50 µg mRNA-1273 as a booster for the mRNA-1273, immunogenicity data from adults ≥18 years in Study P301, based on a database lock date of 04 May 2021, were used as a comparator group to infer efficacy based on the immunogenicity response of a single 50 µg booster (Study P201 Part B).

CHMP comment: Non-inferiority analysis is based on immunogenicity data derived from study P201 4 weeks post booster dose to immunogenicity results obtained from a subset of subjects enrolled in the pivotal study P301 at peek levels 28 days after they received their second dose in the primary series. Supplementary data were provided for an intra-study comparison. The approach is overall considered acceptable.

3.2. Results

Conduct of the study and baseline characteristics

Following Study P201 Part A, 344 participants received a booster dose in Part B. Of these 344, 173 received 2 doses of 50 µg and 171 received 2 doses of 100 µg in Part A. The interval between the prime series in Part A and the booster ranged from 177-269 days overall (or 5.8-8.8 months), with a mean (SD) of 216.9 (19.12) days (or approximately 7.1 months). As of the database lock date for the Day 29 planned analysis, all participants had completed the Day 29 visit.

Disposition

At the time of analysis, 15 participants had discontinued from Part B of the study, with the most frequently reported reason for discontinuation from the study of withdrawal of consent (other).

*Table 4**:** Disposition of subjects in study P201 (Part A and Part B)*

	mRNA-1273 50 µg Primary Series N=200 n (%)	**mRNA-1273 100 µg Primary Series N=200 n (%)**	**mRNA-1273 Total N=400 n (%)**
Number of subjects in Part A			
Received first injection	200 (100)	200 (100)	400 (100)
Received second injection	195 (97.5)	198 (99.0)	393 (98.3)
Discontinued Study Vaccine in Part A	5 (2.5)	2 (1.0)	7 (1.8)
Reason for Discontinuation of Study Vaccine in Part A			
Adverse Event (COVID-19 Infection)	1 (0.5)	0	1 (0.3)
Adverse Event (Other)	1 (0.5)	1 (0.5)	2 (0.5)
Death	0	0	0
Lost to Follow-Up	2 (1.0)	0	2 (0.5)
Physician Decision	0	0	0
Pregnancy	0	0	0
Protocol Deviation	0	0	0
Study Terminated by Sponsor	0	0	0

Withdrawal of Consent (COVID-19 Non-Infection Related)	1 (0.5)	0	1 (0.3)
Withdrawal of Consent (Other)	0	0	0
Other	0	1 (0.5)	1 (0.3)
Discontinued in Part A of Study	12 (6.0)	15 (7.5)	27 (6.8)
Reason for Discontinuation of Study			
Adverse Event (COVID-19 Infection)	0	0	0
Adverse Event (Other)	0	0	0
Death	0	0	0
Lost to Follow-Up	6 (3.0)	6 (3.0)	12 (3.0)
Physician Decision	1 (0.5)	2 (1.0)	3 (0.8)
Pregnancy	0	0	0
Protocol Deviation	3 (1.5)	3 (1.5)	6 (1.5)
Study Terminated by Sponsor	0	0	0
Withdrawal of Consent (COVID-19 Non-Infection Related)	1 (0.5)	0	1 (0.3)
Withdrawal of Consent (Other)	1 (0.5)	4 (2.0)	5 (1.3)
Other	0	0	0
Consented to Part B	188 (94.0)	185 (92.5)	373 (93.3)
Agreed to be Unblinded	187 (93.5)	186 (93.0)	373 (93.3)
Agreed to Receive mRNA-1273 in Part B	**174 (87.0)**	**171 (85.5)**	**345 (86.3)**
Actually Received Booster Injection	**173 (86.5)**	**171 (85.5)**	**344 (86.0)**
Discontinued Study Vaccine in Part B	0	0	0
Discontinued from Study in Part B	9 (4.5)	6 (3.0)	15 (3.8)
Completed Study [b]	0	0	0
Discontinued from Study in Part B			
Reason for Discontinuation of Study in Part B			
Adverse Event (COVID-19 Infection)	0	0	0
Adverse Event (Other)	0	0	0
Death	0	0	0
Lost to Follow-up	3 (1.5)	2 (1.0)	5 (1.3)
Physician Decision	0	0	0
Pregnancy	0	0	0
Protocol Deviation	0	0	0
Study Terminated by Sponsor	0	0	0
Withdrawal of Consent (COVID-19 Non-Infection Related)	0	0	0
Withdrawal of Consent (Other)	5 (2.5)	3 (1.5)	8 (2.0)
Other	1 (0.5)	1 (0.5)	2 (0.5)

Analysis Sets

The planned Day 29 analysis in Part B evaluated the safety, reactogenicity and immunogenicity of mRNA-1273 50 µg administered as a single booster dose given 6-8 months after completing the 2-dose mRNA-1273 50 µg or 100 µg prime series in Part A.

Relevant P201 Part B analysis populations include: Safety Set, Solicited Safety Set, Full Analysis Set and Per-Protocol (PP) Set (Table 5).

Among 306 participants in Part B of P201 who received a booster injection and had both baseline and Day 29 immunogenicity assessment (FAS), 11 were excluded from the PP Set: 10 because of SARS-CoV-2 infection at baseline, and 1 because of a major protocol deviation.

Table 5: Study P201 Part B Number of Subjects in Each Analysis Set by Prime Series Group (50 µg and 100 µg mRNA-1273)

	mRNA-1273 50 µg Primary Series + 50 µg Booster n (%)	**mRNA-1273 100 µg Primary Series + 50 µg Booster n (%)**	**P201 Part B mRNA-1273 50 µg Booster Total n (%)**
Safety Set[a]	173	171	344
Solicited Safety Set[b]	163 (94.2)	167 (97.7)	330 (95.9)
Full Analysis Set[c]	150 (66.7)	156 (91.2)	306 (89.0)
Per-Protocol Set[d]	146 (84.4)	149 (87.1)	295 (85.8)

Only subjects who received booster injection in Part B are included and are summarised under the vaccination groups which they actually received in Part A. Percentages are based on the number of safety subjects.
a All participants who are randomised in Part A and received any booster injection during Part B.
b All participants who are randomised in Part A and received any booster injection during Part B, and contribute any solicited AR data, i.e., have at least 1 post-baseline solicited safety assessment in Part B.
c All subjects who received any booster injection in Part B and had immunogenicity data available at both baseline (Part B Day 1) and at least 1 post-booster visit.
d All subjects in the Full Analysis Set who did not have SARS-CoV-2 infection (positive reverse transcription polymerase chain reaction [RT-PCR] result or positive Elecsys result) at baseline (Part B Day 1), did not have a major protocol deviation that impacted immune response, had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for booster injection).

Demographics and Baseline Characteristics

Demographic and baseline characteristics of the PP Immunogenicity Subsets for P201 Part B and P301 are displayed in Table 6. Although numerical differences between PP Immunogenicity Subsets were observed for gender, and ethnicity, these differences are not expected to influence the comparison of GMT between groups. This assessment is based on the consistency of VE estimates and nAb results observed across various subgroups (including age and ethnicity) in Study P301.

Table 6: Demographic and Baseline Characteristics in Study P201 Part B and Study P301: Per-Protocol Immunogenicity Subset

Statistic	**P201 Part B 50 µg Booster (N=295)**	**P301 100 µg Primary Series (N=1055)**
Age (Years)		
n	295	1055
Mean (SD)	52.77 (15.170)	54.51 (15.329)
Median	56	57
Min, Max	18.0, 87.0	18.0, 87.0
Age Group		
≥18 and <65 years old	219 (74.2)	700 (66.4)
≥65 years old	76 (25.8)	355 (33.6)
Gender, n (%)		
Male	103 (34.9)	560 (53.1)
Female	192 (65.1)	495 (46.9)

Race, n (%)		
White	281 (95.3)	767 (72.7)
Black or African American	7 (2.4)	188 (17.8)
Asian	3 (1.0)	26 (2.5)
American Indian or Alaska Native	2 (0.7)	17 (1.6)
Native Hawaiian or Other Pacific Islander	1 (0.3)	5 (0.5)
Multiple	1 (0.3)	15 (1.4)
Other	0	27 (2.6)
Not Reported	0	5 (0.5)
Unknown	0	5 (0.5)
Ethnicity, n (%)		
Hispanic or Latino	20 (6.8)	334 (31.7)
Not Hispanic or Latino	274 (92.9)	717 (68.0)
Not Reported	1 (0.3)	2 (0.2)
Unknown	0	2 (0.2)
Body Mass Index (kg/m^2)		
n	290	1050
Mean (SD)	25.65 (3.210)	30.96 (7.758)
Median	26.05	29.62
Min, Max	18.0, 34.9	14.0, 79.2
Positive Baseline SARS-CoV-2 Status [a]	0	0

Percentages are based on the number of Per-Protocol Immunogenicity Subset subjects.
Age in P201 is defined at P201 Part A screening.
a Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1 in P201 Part B or Day 1 in P301.

CHMP comment: In general, the study populations of study P201 and P301 are comparable as regards age and ratio of subjects above 65 years. Gender and ethnicity between study populations differ with substantially more females and white subjects included in study P201 compared to P301.

Immunogenicity results

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 crucial for the prevention of COVID-19.

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

Table 7 summarises serum nAb (PsVNA ID50, D614G) titers following the primary vaccination series (Part A of P201) and the booster vaccination (Part B of P201).

In the 100 µg mRNA-1273 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 mRNA-1273 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 7:Pseudovirus Neutralising Antibody (ID50) Titers in Study P201 Part A (Primary series) and in Part B

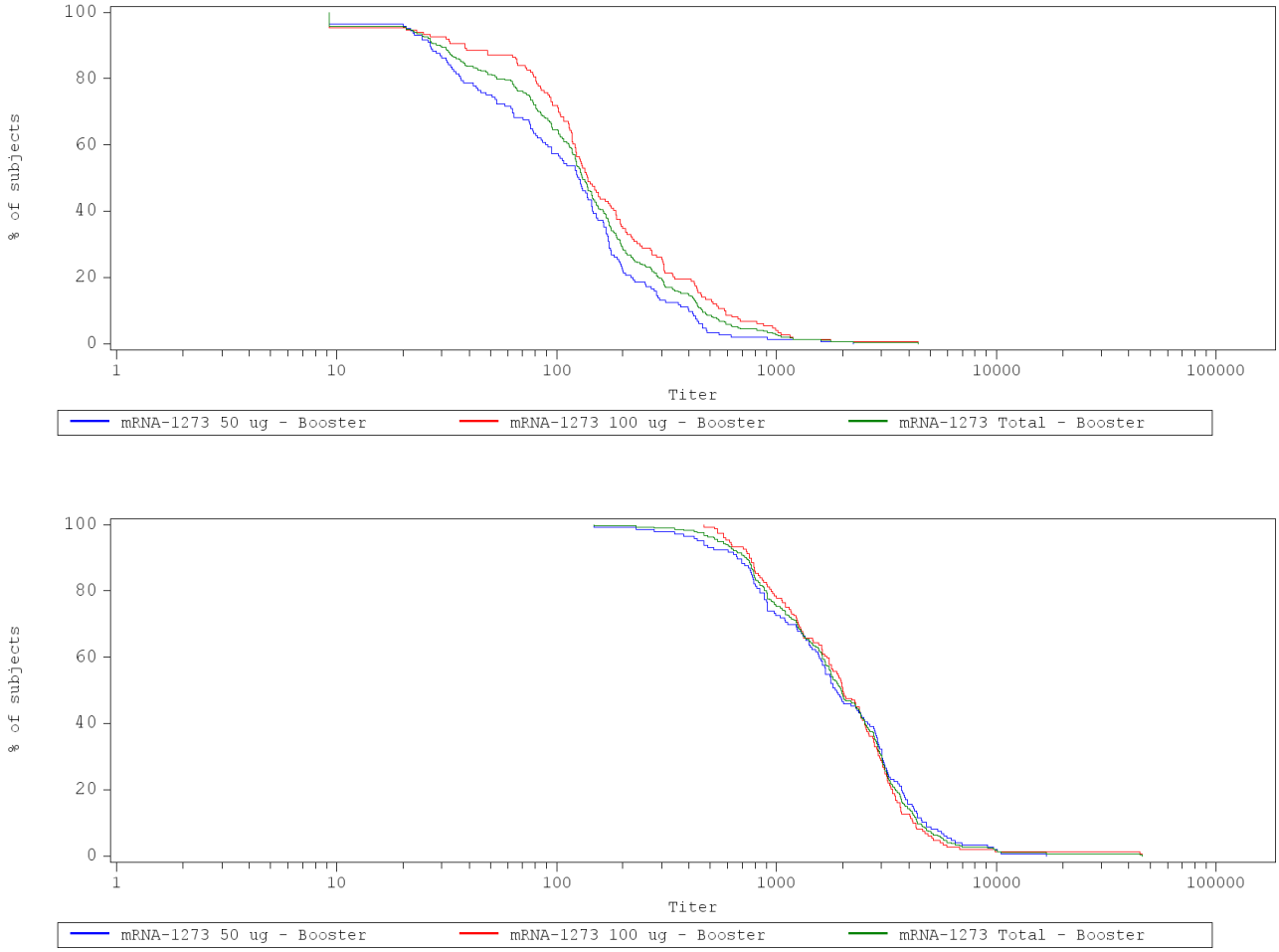
	mRNA-1273		
	50 µg Primary Series (+50 µg booster) N=146 n (%)	**100 µg Primary Series (+50 µg booster) N=149 n (%)**	**Overall N=295 n (%)**
Baseline (Day 1; pre-dose 1), n [1]	146	148	294
GMT	9.35	9.25	9.30
95% CI [2]	9.16, 9.54	NE, NE	9.20, 9.39
28 days after 2nd dose of primary series, n [3]	143	146	289
GMT	629.23	1267.95	896.47
95% CI [2]	549.33, 720.75	1087.90, 1477.80	803.35, 1000.38
Participants achieving Seroresponse, n (Seroresponse Rate %) [4]			
N1	143	146	289
n (%)	141 (98.6)	143 (97.9)	284 (98.3)
95% CI [5]	95.0, 99.8	94.1, 99.6	96.0, 99.4
Baseline (Day 1; pre-booster), n [3]	145	149	294
GMT	104.658	150.224	125.696
95% CI [2]	88.282, 124.070	125.726, 179.495	111.011, 142.325
Day 29 (28 days after booster dose, n [3]	146	149	295
GMT	1834.309	1951.735	1892.708
95% CI [2]	1600.233, 2102.623	1729.606, 2202.392	1728.800, 2072.157
Participants achieving Seroresponse, n (Seroresponse Rate %) [4]			
N2	145	149	294
n (%)	141 (98.6)	143 (97.9)	284 (98.3)
95% CI [5]	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 [2]	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]	2.55, 3.35	1.32, 1.77	1.90, 2.34

nAb = Neutralising antibody. GMT = Geometric Mean Titer. CI = Confidence intervals.
N1 = Number of subjects with non-missing data at baseline and the corresponding visit.
N2 = Number of subjects with non-missing data at pre-booster and the corresponding visit.
N3 = Number of subjects with non-missing data at 28 days after the primary series and 28 days after the booster dose.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of subjects in the Per-Protocol Set with non-missing data at baseline and the corresponding visit (N1).
[1] Number of subjects with non-missing baseline.
[2] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
[3] Number of subjects in the Per-Protocol Set with non-missing data at the corresponding visit.
[4] Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4xLLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.

[5] 95% CI is calculated using the Clopper-Pearson method.

The reverse cumulative distribution curves of nAb according to the primary vaccination series (50 µg/dose or 100 µg/dose) and for all subjects combined for the pre dose 3 (pre-booster) and post dose 3 titers are provided in Figure 2. The distribution curves indicate that subjects in the 100 µg primary dosing group generally had higher antibody titers pre-booster but no difference in nAb titer distribution between dosing groups was observed following a third 50 µg dose.

Figure 2: Reverse Cumulative Distribution Function of Pseudovirus Neutralising Antibody ID50 Immunogenicity Results after Booster Injection Per-Protocol Set (Part B, Open-Label Phase)



Pseudovirus Neutralising Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118) at Day 1 (pre-boost) and Day 29 (post-boost) (Figure 14.2.6.3.1) OL = Open-Label.
Note: Percentages are based on the number of subjects in the Per-Protocol Set with non-missing data at each visit.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available.

A subgroup analysis following stratification of the nAb response according to age groups and primary immunisation series is shown in Table 8. Generally, higher nAb responses (GMTs) are seen in the 18-55 years age group compared to the age group of the 55 years and older at pre dose 3 and 28 days post dose 3 in subjects having received 2 doses of 100 µg as primary series. However, a higher GMR is observed in subjects 55 years and older. No further subgroup analysis stratified according to other age groups (≥18-<65 yoa, ≥65 yoa) and primary series were provided with the initial submission.

Table 8: Subgroup analysis stratified according to age group and priming group (2x50 µg vs 2x100 µg)

	Age ≥ 18 to < 55 Years		Age ≥ 55 Years		Overall	
	50 µg Primary Series + 50 µg Booster N=63	100 µg Primary Series + 50 µg Booster N=68	50 µg Primary Series + 50 µg Booster N=83	100 µg Primary Series + 50 µg Booster N=81	≥18-<55 years N=131	≥55 years N=164
Baseline						
n	62	68	83	81	130	164
GMT	142.389	172.685	83.156	133.640	157.507	105.113
95% CI	110.899, 182.819	136.022, 219.231	65.582, 105.440	105.089, 169.947	132.519, 187.206	88.474, 124.882
28 Days after Booster						
n	63	68	83	81	131	164
GMT	2024.609	2001.294	1910.607	1699.914	2012.380	1803.469
95% CI	1709.910, 2397.227	1703.216, 2351.538	1629.225, 2240.586	1446.665, 1997.496	1792.123, 2259.707	1612.330, 2017.267
GMR	12.85	12.71	18.18	16.17	12.78	17.16
95% CI	10.86, 15.22	10.81, 14.93	15.50, 21.32	13.76, 19.00	11.38, 14.35	15.34, 19.19

Neutralising antibody response against the Delta variant pre and post dose 3

The neutralising antibody response of all participants in study 201 Part B was determined by a validated assay using a pseudovirus based on the B.1.617.2 (Delta) variant. Serum samples were obtained from participants in P201B (at least 6 months after receiving two primary doses of either 50 or 100 µg of mRNA-1273) pre-booster and on Day 29 post booster. Results of the Pseudovirus nAb assay against the Delta variant (B.1.617.2) are presented in Table 9.

Administration of the mRNA-1273 booster (50 µg) induced an 18-fold-rise in neutralising titers against the Delta variant compared to pre-booster levels in all participants combined (GMFR=18.97; 95% CI, 16.72, 21.53; overall group, n=295). In the overall P201B group (previously primed with 2 doses of either 50 or 100 µg mRNA-1273, n=293), the pre-booster nAb GMT (for the Delta variant) was 42.27 (95% CI, 37.19, 48.04; n=293) and 28 days post-booster the GMT was 803.51 (95% CI, 731.42, 882.70; n=295). Over 90% of booster recipients in the overall group (92.2%; 95% CI, 88.5-95.0%; n=293) met the definition of a seroresponse for the Delta variant (using a four-fold increase from pre-booster baseline).

Administration of the 50 µg mRNA-1273 prototype booster resulted in substantial increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 50 µg had a GMFR of 20.89 (95% CI, 17.54, 24.87); those primed with 100 µg had a GMFR of 17.28 (95% CI, 14.38, 20.77). Numerically slightly lower GMTs pre and post dose 3 were reported in the 50 µg priming group compared to the 100 µg priming group.

Table 9: Summary of Pseudovirus Neutralising Antibody ID50 Titers Against New Variant Strain (B.1.617.2, Delta) Per-Protocol Immunogenicity Subset

Timepoint Statistic	P201 Part B 50 µg booster after 50 µg priming N=146	P201 Part B 50 µg booster after 100 µg priming N=149	P201 Part B Overall N=295
Pre-Booster			

n[1]	144	149	293
GMT	37.14	47.89	42.27
95% CI[2]	31.25, 44.15	39.68, 57.79	37.19, 48.04
Median	35.40	38.81	36.87
Min, Max	9.3, 818.3	9.3, 2730.5	9.3, 2730.5
28 Days After Boost Dose			
n[3]	146	149	295
GMT	779.48	827.77	803.51
95% CI[2]	670.05, 906.78	738.48, 927.86	731.42, 882.70
Median	819.12	792.27	801.12
Min, Max	43.5, 9720.8	124.2, 5587.5	43.5, 9720.8
GMFR	20.89	17.28	18.97
95% CI[2]	17.54, 24.87	14.38, 20.77	16.72, 21.53
Participants Achieving Seroresponse Comparing to Pre-booster, n (Seroresponse Rate %)[4]			
N1	144	149	293
n (%)	137 (95.1)	133 (89.3)	270 (92.2)
95% CI[5]	90.2, 98.0	83.1, 93.7	88.5, 95.0

Abbreviations: CI = Confidence intervals; GMFR=Geometric Mean Fold-Rise; GMT = Geometric Mean Titer; N1 = Number of subjects with non-missing data at pre-booster and
the corresponding visit; nAb = Neutraliing antibody.
Note: Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification
(ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of subjects in the Per-Protocol Set with non-missing data at baseline
and the corresponding visit (N1).
1 Number of subjects with non-missing data at pre-booster.
2 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back
transformed to the original scale for presentation.
3 Number of subjects in the Per-Protocol Set with non-missing data at the corresponding visit.
4 Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4xLLOQ, or a 4-times or higher ratio in
participants with titers above LLOQ.
5 95% CI is calculated using the Clopper-Pearson method.

Additional analyses of Delta variant nAb GMT by age group based on all subjects included in the PP set are provided in Table 10 and 11. nAb responses in older adults, defined either as ≥65 or ≥55 or years, are numerically similar to those observed in the younger groups (749.94 vs. 822.98 and 758.68 vs. 863.39, respectively). No analyses according to primary vaccination series and age group were submitted.

Table 10: Summary of Pseudovirus Neutralising Antibody ID50 titers Against New Variant Strain (B.1.617.2) - By Age Group (≥18 and <65 years old vs ≥65 years old) Per-Protocol Immunogenicity Subset

Timepoint **Statistic**	**P201 Part B 50 µg mRNA-1273 Booster**		
	≥18 and <65 years N=219	**≥ 65 years N=76**	**Overall N=295**
Pre-Booster			
n[1]	218	75	293
GMT	47.20	30.67	42.27
95% CI[2]	40.64, 54.81	24.20, 38.88	37.19, 48.04
Median	39.57	28.39	36.87
Min, Max	9.3, 2730.5	9.3, 204.3	9.3, 2730.5
28 Days After Boost Dose			
n[3]	219	76	295
GMT	822.98	749.94	803.51
95% CI[2]	743.49, 910.97	600.87, 935.99	731.42, 882.70

Median	829.23	690.44	801.12
Min, Max	43.5, 5587.5	76.8, 9720.8	43.5, 9720.8
GMFR	17.38	24.45	18.97
95% CI[2]	14.98, 20.18	19.33, 30.92	16.72, 21.53
Participants Achieving Seroresponse Comparing to Pre-booster, n (Seroresponse Rate %)[4]			
N1	218	75	293
n (%)	197 (90.4)	73 (97.3)	270 (92.2)
95% CI[5]	85.7, 93.9	90.7, 99.7	88.5, 95.0

CI = Confidence intervals; GMFR=Geometric Mean Fold-Rise; GMT = Geometric Mean Titer; N1 = Number of subjects with non-missing data at pre-booster and the corresponding visit; nAb = Neutralising antibody.
Note: Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of subjects in the Per-Protocol Set with non-missing data at baseline and the corresponding visit (N1).
1 Number of subjects with non-missing data at pre-booster.
2 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
3 Number of subjects in the Per-Protocol Set with non-missing data at the corresponding visit.
4 Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4xLLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
5 95% CI is calculated using the Clopper-Pearson method.

Table 11: Summary of Pseudovirus Neutralising Antibody ID50 titers Against New Variant Strain (B.1.617.2) - By Age Group (≥18 and <55 years old vs ≥55 years old) Per-Protocol Immunogenicity Subset

Timepoint **Statistic**	**P201 Part B 50 µg mRNA-1273 Booster**		
	≥18 and <55 years N=131	**≥ 55 years N=164**	**Overall N=295**
Pre-Booster			
n[1]	130	163	293
GMT	52.68	35.46	42.27
95% CI[2]	43.07, 64.44	30.17, 41.67	37.19, 48.04
Median	43.51	33.61	36.87
Min, Max	9.3, 2730.5	9.3, 609.8	9.3, 2730.5
28 Days After Boost Dose			
n[3]	131	164	295
GMT	863.39	758.68	803.51
95% CI[2]	760.91, 979.66	662.07, 869.38	731.42, 882.70
Median	850.98	775.81	801.12
Min, Max	116.0, 4656.8	43.5, 9720.8	43.5, 9720.8
GMFR	16.31	21.40	18.97
95% CI[2]	13.28, 20.05	18.29, 25.03	16.72, 21.53
Participants Achieving Seroresponse Comparing to Pre-booster, n (Seroresponse Rate %)[4]			
N1	130	163	293
n (%)	117 (90.0)	153 (93.9)	270 (92.2)
95% CI[5]	83.5, 94.6	89.0, 97.0	88.5, 95.0

CI = Confidence intervals; GMFR=Geometric Mean Fold-Rise; GMT = Geometric Mean Titer; N1 = Number of subjects with non-missing data at pre-booster and the corresponding visit; nAb = Neutralising antibody.
Note: Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ if actual values are not available. Percentages are based on the number of subjects in the Per-Protocol Set with non-missing data at baseline and the corresponding visit (N1).
1 Number of subjects with non-missing data at pre-booster.
2 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
3 Number of subjects in the Per-Protocol Set with non-missing data at the corresponding visit.
4 Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4xLLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
5 95% CI is calculated using the Clopper-Pearson method.

Non-inferiority analysis to compare the immunogenicity results in study P201 post dose 3 (booster) to the results in efficacy study P301 post dose 2 after the primary series

GMR as Assessed by PsVNA ID50 Titers

The primary analysis population for this co-primary endpoint (in Study P201 Part B) included all PP participants who received a single booster dose of 50 µg mRNA-1273 in Study P201 Part B (i.e. all participants combined regardless of whether they received 50 µg or 100 µg of mRNA-1273 in the primary series).

In comparison to the peak PsVNA ID50 titers in P301 Part A (Day 57, 28 days post dose 2), where efficacy was demonstrated, the GMR (P201 Part B D29 vs. P301 D57, against the original virus strain) was 1.71 (95% CI: 1.519, 1.929) (Table 10). The GMR estimate was 1.71 (above the prespecified threshold of 1.0), with the lower bound of the 95% CI greater than 0.67 (corresponding to NIM=1.5). Hence, this GMR successfully met the prespecified NI criterion. A consistent trend to that observed from the analysis described above, with the 2 prime series groups combined, was also observed in the subgroup analysis (by prime series). In participants who were primed with a 2-dose series of 100 µg of mRNA-1273, the GMR (P201 Part B vs. P301) was 1.76 (95% CI: 1.496, 2.060); and in participants who were primed with a 2-dose series of 50 µg of mRNA-1273, the GMR was 1.66 (95% CI: 1.412, 1.958) (Table 12). The above suggests that the 50 µg booster increases nAb responses regardless of the dose (50 µg vs 100 µg) received in the primary series.

Table 12: Analysis of PsVNA ID50 Titers: mRNA-1273 Post-Dose 3 (all subjects) compared with the P301 primary series peak titers (PP Immunogenicity Set)

	P201 Part B overall 50 µg Booster	**P301 100 µg Primary Series**
28 Days After Booster (P201 Part B) or Completion of Primary Series		
n	295	1053
GLSM	1767.936	1032.698
95% CI	(1586.445, 1970.189)	(974.207, 1094.701)
GMR (P201 Part B vs. P301; model-based)	1.712	
95% CI	(1.519, 1.929)	

Abbreviations: ANCOVA = analysis of covariance; ID50 = 50% inhibitory dilution; GLSM = geometric least squares mean; CI = confidence interval; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
n= number of subjects with non-missing data at the corresponding time point

Table 13 provides the non-inferiority analyses for the comparison of PSVNA ID50 titers according to primary vaccination series. For both vaccination groups (50 µg and 100 µg) the non-inferiority criterion was met.

Table 13: Analysis of PsVNA ID50 Titers: mRNA-1273 Post-Booster Compared with the P301 Primary Series Peak Titers - by Primary Series Groups (PP Immunogenicity Set)

	P201 Part B 50 µg Primary Series + 50 µg Booster N=146	**P301 100 µg Primary Series N=1055**	**P201 Part B 100 µg Primary Series + 50 µg Booster N=149**	**P301 100 µg Primary Series N=1055**
28 Days after Booster (P201 Part B) or Completion of Primary Series				
n	146	1053	149	1053

GLSM	1716.185	1031.948	1802.426	1026.854
95% CI	(1469.496, 2004.286)	(971.974, 1095.622)	(1548.020, 2098.643)	(967.880, 1089.420)
GMR (P201 Part B vs. P301; model-based)	1.66		1.76	
95% CI	(1.412, 1.958)		(1.496, 2.060)	

Abbreviations: ANCOVA = analysis of covariance; ID50 = 50% inhibitory dilution; GLSM = geometric least squares mean; CI = confidence interval; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
Separate ANCOVA modes were used for P201 50 µg priming + 50 µg booster (group variables: P201 50 µg priming, and P301) and P201 100 µg priming + 50 µg booster (group variables: P201 100 µg priming, and P301).

A sensitivity analysis, by excluding the 20 participants who were included in a Day 15 exploratory analysis was conducted. In general, the SAP-specified sensitivity analysis yielded similar results.

Seroresponse rates (SRR) as assessed by PsVNA ID50 Titers

The primary analysis population for this coprimary endpoint (in Study P201 Part B) included all PP participants who received a single booster dose of 50 µg mRNA-1273 in Study P201 Part B (i.e., all participants combined regardless of whether they received 50 µg or 100 µg of mRNA-1273 in the primary series).

The calculated SRR difference (for PsVNA ID50 titers) between P201 Part B Day 29 post-booster and P301 Part A Day 57 was assessed. This analysis was performed using 2 definitions of SRR: (i) an assay-specific definition (3.3-fold rise) proposed by the MAH, and (ii) a 4-fold rise definition as a more conservative approach. The assay-specific SR definition and the rationale for considering this as a relevant approach was provided in Moderna 1273 Biomarker Concordance Analysis Report for Protocol mRNA-1273-P301.

Using the assay-specific definition (3.3-fold rise), the calculated difference in SRR between P201 Part B Day 29 post-boost and P301 Part A Day 57 is -5.3% (95% CI: -8.8%, -2.9%) (Table 14). The lower bound of the 95% CI is -8.8%, meeting the prespecified success criterion of a non-inferiority margin (NIM) of 10%.

Using the 4-fold rise definition, the calculated difference in SRR between P201 Part B Day 29 post-boost and P301 Part A Day 57 is -8.2% (95% CI: -12.2%, -5.2%) (Table 14). The lower bound of the 95% CI is slightly less than -10% (the prespecified NIM of 10%).

*Table 14**:** Analysis of SRR by PsVNA ID50 Assay: mRNA-1273 Post-Booster Compared with the P301 Primary Series Peak Titers - by Prime Series Groups (PP Immunogenicity Set)*

Statistic	**SRR per Assay-Specific Definition [a]**		**SRR per 4-Fold Definition [b]**	
	P201 Part B 50 µg Booster (N=295)	**P301 100 µg Primary Series (N=1055)**	**P201 Part B 50 µg Booster (N=295)**	**P301 100 µg Primary Series (N=1055)**
N1	294	1050	294	1050
Participants achieving seroresponse, n (seroresponse rate %)	275 /294 (93.5)	1038 /1050 (98.9)	265 (90.1)	1033 (98.4)
95% CI [c]	90.1, 96.1	98.0, 99.4	86.1, 93.3	97.4, 99.1
Difference in seroresponse rate (P201 Part B vs. P301) (%)	-5.3		-8.2	

95% CI [d]	-8.8, -2.9		-12.2, -5.2	

Abbreviations: CI = confidence interval; ID50 = 50% inhibitory dilution; LLOQ = lower limit of quantification.
N1 = Number of subjects with non-missing data at both post-baseline timepoint of interest and baseline.
a Seroresponse specific to PsVNA ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
b Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4 × LLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
c 95% CI is calculated using the Clopper-Pearson method.
d 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Analysis of the SRR stratified according to the dose groups for primary vaccination shows that the point estimate for the SRR difference and the non-inferiority criterion are not met for the 100 µg group (-10.5; 95% CI: -16.7, -6.1) using a 4-fold rise definition for SR (Table 15). For the 50 µg priming group a point estimate of -6.6 (95% CI: -11.5, -2.5) for the SRR difference was determined.

No data on the SRR difference stratified to dose group were provided for the assay specific definition of a 3.3-fold rise.

*Table 15**:** Analysis of Seroresponse based on Pseudovirus Neutralising Antibody Titers by Priming groups and 4-fold definition of the SSR (Per-Protocol Immunogenicity Subset) Antibody: Pseudovirus Neutralising Antibody ID50 Titers*

	P201 Part B 50 µg Primary Series + 50 µg Booster N=146	**P301 100 µg Primary Series N=1055**	**P201 Part B 100 µg Primary Series + 50 µg Booster N=149**	**P301 100 µg Primary Series N=1055**
28 Days after Booster (P201 Part B) or Completion of Primary Series				
n	145	1050	149	1050
Participants achieving Seroresponse, n (Seroresponse Rate %) [1]	134 (92.4)	1033 (98.4)	131 (87.9)	1033 (98.4)
95% CI	86.8, 96.2	97.4, 99.1	81.6, 92.7	97.4, 99.1
Difference in seroresponse rate (P201 Part B vs. P301) (%)	-6.0		-10.5	
95% CI	-11.5, -2.5		-16.7, -6.1	

The upper limit of quantification (ULOQ) for selected P301 participants tested previously was different.
CI = Confidence interval.
N1 = Number of subjects with non-missing data at both post-baseline timepoint of interest and baseline.
Percentages are based on N1.
[1] Seroresponse at participant level is defined as a change of titer from below the lower limit of quantification (LLOQ) to equal to or above 4xLLOQ, or a 4-times or higher ratio in participants with titers above LLOQ.
[2] 95% CI is calculated using the Clopper-Pearson method.

[3] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

[P201: LLOQ=18.5, ULOQ=45118; P301: LLOQ=18.5, ULOQ=4404]

In general, the subgroup analysis (by prime series) and the SAP-specified sensitivity analysis (data not displayed) yielded similar results in confirming that the NIM of -10% was not met.

Analysis of the GMR and SRR (4-fold increase criterion) on all P201 subjects stratified according to age group are given in Table 166. No data are available on a subgroup analysis by prime series and by age stratification.

*Table 16**:** Analysis of Neutralising Antibody ID50 Titers and Seroresponse Rate 28 Days After mRNA-1273 Boost (Both Priming Series Groups Combined) by Age Group Compared with the P301 Primary Series Peak Titers*

	Age ≥ 18 to < 65 Years		Age ≥ 65 Years		Overall	
	P201 Part B 50 µg Booster N=219	P301 100 µg Primary Series N=700	P201 Part B 50 µg Booster N=76	P301 100 µg Primary Series N=355	P201 Part B 50 µg Booster N=295	P301 100 µg Primary Series N=1055
Baseline						
n	218	699	76	353	294	1052
GMT	145.57	9.77	82.51	9.35	125.70	9.62
95% CI	126.68, 167.27	9.37, 10.18	64.25, 105.96	9.16, 9.54	111.01, 142.32	9.35, 9.90
28 Days after Booster (P201 Part B) or Completion of Primary Series						
n	219	698	76	355	295	1053
GMT	1940.39	1206.59	1761.77	871.20	1892.71	1081.12
95% CI	1749.49, 2152.12	1125.71, 1293.28	1458.19, 2128.56	785.48, 966.29	1728.80, 2072.16	1019.80, 1146.14
GLSM (Model-Based Est. for GMT)	1940.385	1206.589	1761.773	871.203	1767.936	1032.698
95% CI	1722.315, 2186.067	1128.647, 1289.914	1417.106, 2190.271	787.722, 963.532	1586.445, 1970.189	974.207, 1094.701
GMR (P201 Part B vs. P301; model based)	1.608		2.022		1.712	
95% CI	1.403, 1.844		1.591, 2.570		1.519, 1.929	
Participants Achieving Seroresponse, n (Seroresponse Rate %)						
N1	218	697	76	353	294	1050
n (%)	202 (92.7)	687 (98.6)	73 (96.1)	351 (99.4)	275 (93.5)	1038 (98.9)
95% CI	88.4, 95.7	97.4, 99.3	88.9, 99.2	98.0, 99.9	90.1, 96.1	98.0, 99.4
Seroresponse Rate Difference	-5.9		-3.4		-5.3	
95% CI	-10.2, -2.9		-10.4, -0.5		-8.8, -2.9	

3.3. Supportive data

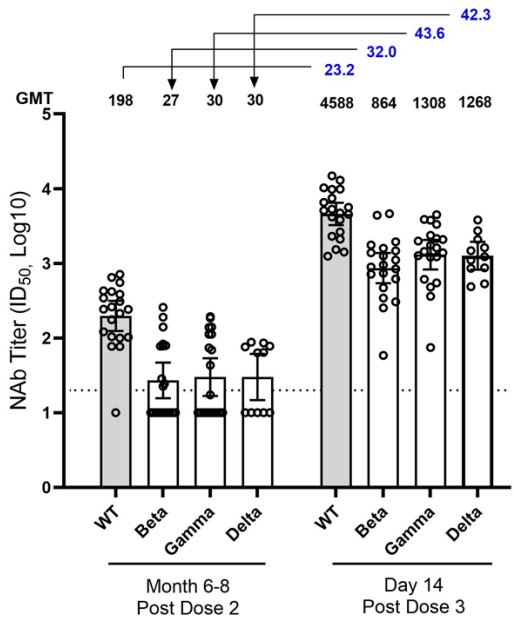
Boosting of Neutralising Antibodies Against Selected Variants

Given the emergence of viral variants, serum from P201 Part B booster recipients was examined for nAb activity against a panel of selected variants using research-grade assays as described in Choi et al 2021. Exploratory analyses of the breadth of neutralising Ab activity were performed on a randomly selected subset of participants in P201 Part B, all of whom had previously (6-8 months prior) received 2 doses of 100 µg in P201 Part A.

Serum samples (collected at Day 1 pre-booster and Day 15 after booster) from a subset of n=20 participants from Study P201 Part B were randomly selected for testing against D614G, B.1.351 and P.1. From this randomly selected subset of 20 participants, serum samples from 11 of the 20 were further selected for testing of variants including for B.1.617.2 – done because the test plates only accommodated a maximum of samples from 11 participants. To achieve a relatively representative sample, the 11 participants selected for testing against additional variants were chosen based on results obtained against the D614G VSV-PsVN assay, selecting participants with results considered 'high' (n=4), "mid" (n=4) and "low" (n = 3). Serum samples obtained 6 months after receipt of the 100 µg doses in Part A ("pre-booster baseline") were compared with serum obtained 2 weeks after the 50 µg booster dose in P201 Part B.

At the time of the 50 µg booster inoculation, approximately 6 months after receipt of 2 doses of 100 mRNA-1273, tested nAb levels had notably declined from peak titers (Day 57 after first of the 2 doses of 100 µg), with titers against variants in some participants falling below the assay LLOQ. Serum collected 2 weeks after receipt of a single dose of 50 µg of mRNA-1273 demonstrated 32- to 44-fold increases in nAb responses against all test variants, including a 42-fold increase against the Delta variant, as depicted in Figure 3 with additional detail for the same analyses provided in Table 17.

Figure 3: Neutralisation of Wild-Type D614G and Variants by Participant Serum Collected Before and After Booster as Measured by the VSV-PsVN Assay



Left-hand panel presents the GMT against the D614G PsV (designated "WT"), and PsV representing Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2) for "Pre-booster baseline" samples obtained at least 6 months after 2 initial doses of 100 µg. Right-hand panel presents the GMT against same PsV measured 2 weeks after the 50 µg booster dose. The neutralising antibody GMTs with 95% confidence intervals are denoted. The GMT fold change (GMR) between "Pre-booster Baseline" and 2 week post-booster is indicated in blue above bars. Results from individual participants are represented as dots on each figure. The horizonal dotted line indicates the LLOQ.

Table 17: Summary of Neutralisation of Wild-Type D614G and Variants by Participant Serum Collected Before and After Booster as Measured by the VSV-PsVN Assay

Parameter	Pseudovirus Spike Variant Assay			
	D614G	**B.1.351**	**B.1.617.2**	**P.1**
N	20	20	11	20
Day 1 (Pre-booster baseline)[1]				
GMT	198	27	30	30
95% CI	124, 314	16, 47	20, 40	17, 53
Day 15 (Post-booster)				
GMT	4588	864	1268	1308
95% CI	3244, 6488	542, 1379	983, 1553	829, 2064
GMFR (D15 vs. D1)	23.2	32.0	42.3	43.6
95% CI	15,36	20, 52	28, 69	27, 72

nAb against the following pseudotyped viruses expressing the designated S proteins was evaluated: D614G represents the Wuhan-Hu-1 isolate, B.1.351 a Beta variant, B.1.617.2 a Delta variant and P.1 a Gamma variant. 1 "Pre-booster baseline" samples were obtained 6 months following receipt of 2 doses of 100 µg in P201 Part A.

3.4. Discussion

The MAH seeks approval of a third dose (0.25 mL, 50 µg/dose) of Spikevax (WT Wuhan-Hu-1 isolate) given intramuscularly at least 6 months after the primary series of 2 doses of 0.5mL (100 µg/dose) of Spikevax. Consequently, an update of sections 2, 4.2, 4.4, 4.8, 5.1, 6.5 and 6.6 of the SmPC to add information on composition, immunogenicity, safety and special precautions for disposal and other handling is proposed.

Immunogenicity of a third dose of Spikevax (50 µg/dose) was evaluated in study P201 in participants who previously received 2 doses of the vaccine (either 50 µg/dose or 100 µg/dose) 28 days apart as primary series. Each dosage group of the primary series comprised 200 adults aged 18 years and older. Following the primary series participants were invited to receive a third dose of 0.25 mL (50 µg/dose) Spikevax. In total, 174 subjects in the 50 µg primary series group and 171 subjects in the 100 µg primary series group agreed to receive a 50 µg dose as booster. The booster dose was given 6-8 months after the primary series and the immune response was evaluated 28 days after the third dose by employing various assay formats including validated neutralisation assays with pseudovirus representing the wild type Wuhan variant or the Delta variant. In addition, supportive data from research grade assays measuring the neutralising antibody responses against other variants of concern were provided on a small subset of participants.

To bridge the immune responses 28 days post dose 3 as measured in study P201 was compared to the immune response elicited 28 days after the primary series in study P301, the pivotal clinical efficacy trial.

Conduct of the study and statistical methods

The study P201 Part B to study the immunogenicity effect of a booster dose was introduced as a substantial amendment with Protocol Amendment 4 (15 January 2021). The immunogenicity objectives for Part B remained quite vague in the protocol. Statistical methods for the primary immunogenicity analyses in Part B were not at all described within the protocol for P201 Part B. Only with the SAP, which was drafted rather late (SAP Version 1.0: 04 June 2021; Version 2.0: 06 August 2021), the statistical methods were properly defined. The primary comparison was a non-inferiority assessment between P201 Part B and P301. The reason to use external controls from P301 to assess non-inferiority per the primary immunogenicity objective instead of conducting an intra-subject comparison (pre vaccination to post primary vaccination vs. pre booster to post booster) is not fully comprehensible as the comparison between trials might be hampered by e.g. selection bias or other sources of bias. However, given the observed results between trials and the reported results within trial P201, this is not considered as an issue in the end for this procedure. The defined statistical methods are overall considered acceptable.

Seroresponse was redefined from SAP V1.0 to V2.0. For subjects with baseline values < LLOQ the initial criterion required a titre ≥ LLOQ. The new criterion was more demanding as a 4-fold increase over the LLOQ was required. For subjects with measurable baseline titres the initial criteria were assay specific. The new criterion is the same for all assays and was more demanding for all but anti-spike ELISA (VAC65 Spike IgG Antibody) where the change from baseline was reduced from a 4.6-fold to a 4-fold increase. Overall this is considered acceptable.

A non-inferiority assessment of nAb titers against WT for subjects from P301 to nAb titres against Delta variant for subjects from P201 was planned in SAP V2.2 but was not provided with this submission. Only the nAb titres against the Delta variant were provided without a formal comparison. This is duly noted but not considered of relevance for the given procedure.

Immunogenicity

Antibody responses following the primary series of 2 doses and a third booster dose of Spikevax were assessed using three different serological assays to measure anti-spike binding and neutralising

antibodies. As demonstrated in in vitro studies and in vivo using monoclonal antibodies, neutralising antibodies against the spike protein play a crucial role in the prevention of COVID-19. Hence, results of the analyses of neutralising antibody responses are key to demonstrate the benefit of a third dose.

Immunogenicity data from study P201 revealed that a third (booster) dose of 50 µg when given 6-8 months after the second dose results in an increase in neutralising antibodies as compared to the pre-booster nAb levels 6-8 months after the primary vaccination series and to peak neutralising antibody levels post dose 2. As to be expected waning of neutralising antibodies occurred over time but ~98% still had detectable nAb after 6 to 8 months. Nonetheless a robust anamnestic response was observed and the antibody response was restored by a third dose to levels even above the peak levels reported post dose 2. The increase was more pronounced in the 50 µg priming group compared to the 100 µg priming group (post dose 3/post dose 2: 2.93 vs 1.53; post-dose 3/pre-dose 3: 17.53 vs 12.99) indicating that lower neutralising antibody responses elicited by a 'suboptimal' dose regimen results in a greater increase in antibody titers after a third dose compared with the approved vaccine 100 µg dose regimen. Stratification according to age and primary vaccination dose reveals that lower antibody levels are elicited 28 days after booster in the age group ≥ 55 years compared to 18-55 years (GMT 100 µg: 1,670 vs 2,001) but that the increase in nAb levels from pre dose 3 to post dose 3 is higher for the older age cohort (GMR: 16.17 vs 12.85). This demonstrates that the older age group might still benefit from a booster dose due to more pronounced waning and good boostability of the nAb response. No data from subgroup analyses according to the planned age categories (<65 vs ≥ 65) and primary dose were submitted. Such data are of interest to better evaluate the effect of waning and of a booster dose in subjects 65 years of age and older (see Section 6). Data on persistence of the antibody response following a third dose of 50 µg are missing to evaluate the durability of the lower booster dose. No immunogenicity data from younger individuals below the age of 18 years are available.

Immunogenicity data using a heterologous variant PSVNT based on the companies assay format indicate that a lower nAb response is reported pre booster and 28 days after a third dose against the Delta variant as compared to the wild type isolate. In this analysis 133 out of the 149 participants (100 µg primary dose) achieved a seroresponse resulting in a SRR of 89.3% with an increase in GMT of ~17 from pre to post dose 3. Information on the antibody response against the Delta variant at other time points (pre-dose 1, post dose 2) was not provided. Only subgroup analyses on the total study population of part B according to various age categories were provided. To compare the immunogenicity results derived from nAb analyses using the wt-virus and Delta variant, further subgroup analyses according to age group (< 65 and ≥ 65) and priming dose (50 µg and 100 µg) are desirable as well as information on the number of subjects in each of the subgroups who had detectable nAbs against the Delta variant pre dose 2 (see section 6.). Data from an exploratory analysis based on 20 randomly selected sera from study P201 (100 µg priming group + 50 µg booster) and using a research grade neutralisation assay (different nt assay format) show a 30- to 40-fold increase in nAb levels against variants of concern including the Delta variant from pre to post 3 confirming a significant increase in cross protective ab elicited by a third dose against globally circulating viruses. However, it is currently not known what level of protection is maintained against the various virus variants. No correlate of protection is defined neither for the wild type nor for any circulating variant. In addition, current vaccine effectiveness data do not indicate a high increase in breakthrough cases especially for severe COVID-19 in the general population. Although the MAH presented an *ad hoc* analysis of vaccine efficacy from the ongoing efficacy study P301 based on the time period of July to August 2021 suggesting a relative reduction in VE due to the circulating Delta variant in the USA, these data need to be interpreted cautiously especially as regards protection of vulnerable groups against severe COVID-19.

The determined neutralising antibody titers and kinetics indicate that the vaccine-induced immune response can be significantly increased by applying a booster dose at least 6 months post completion of primary vaccination. It is noted that currently the actual need and optimal timing of such a booster dose

has not been fully established. However, in view of the waning immune titres observed following primary vaccination it appears reasonable to assume that a third (booster) dose might be beneficial in particular at later time points after primary vaccination. Duration of the antibody responses following a third 50 µg dose and the level of long-term protection are currently not known.

The MAH conducted a non-inferiority analyses comparing nAb titers and response rates determined post dose 3 in study P201 with peak antibody levels of the immunogenicity subset of the pivotal study P301.

These analyses demonstrate that non-inferiority is met when peak PsVNA ID50 titers post dose 2 in the immunogenicity subset of P301 were compared to the nAb titers obtained 28 days post dose 3. The GMR estimate was 1.76 (95% CI 1.496, 2.060) for the 100 µg primary vaccination group and 1.66 (95% CI: 1.412, 1.958) for the 50 µg primary vaccination group. As regards the calculated sero response rate (SRR) difference based on the 4-fold rise criterion for nAb titers the point estimate for SRR was found to be -8.2 for the 100 µg primary dose however the lower non-inferiority margin was not met (95% CI: -12.2, -5.2). Similar results were observed for the 50 µg primary vaccination and the combined groups.

It is noted that formally, the study was not successful according to the pre-planned non-inferiority criteria. According to the SAP, both criteria on GMR and sero-response needed to be demonstrated to conclude on non-inferiority of the booster dose in comparison to the primary vaccination series. No sequence of immunogenicity endpoints was defined in the SAP and the protocol considered the assessment of bAb levels as primary objective followed by the assessment of nAb levels. Non-inferiority was met for all assays based on the GMR. Non-inferiority was not formally met for the ELISA assay and PsVNA ID50 in the 100 µg prime cohort, which is of primary interest. As especially the neutralising antibodies and the increase in antibody titres are considered of primary relevance for the assessment of the immunogenicity of the booster dose, the failure to prove non-inferiority in seroresponse after the booster dose in comparison to the primary vaccination series is not considered of critical importance here.

The observation of lower SRR following a third dose could most likely be explained by the residual high levels of nAb pre booster in study P201 and by the fact that the response rates following a booster dose were compared to peak levels after the primary series in study P301. It should be noted that two different study populations were compared and the nAb levels reported in these populations post dose 2 (GMT: P201 ~1200 vs P301~1000) differ.

In conclusion, a third dose administered 6-8 months after the primary vaccination series was shown to elevate the neutralising antibody responses significantly. The antibody levels determined 28 days post dose 3 are higher when compared to peak antibody levels 28 days post dose 2.

4. Clinical Safety aspects

4.1. Methods – analysis of data submitted

The interval between primary and booster doses selected for the clinical studies was "at least 6 months after the completion of the primary immunisation series." This interval was selected based on the data of waning of immunogenicity against VOCs demonstrated at 6-8 months.

Following safety data have been submitted:

1. Solicited ARs and unsolicited AEs for **P201 Part B** up to Day 29 (data extracted on 11 June 2021); Results are provided for recipients of (i) 100 µg Prime + 50 µg Boost and (ii) 50 µg Prime + 50 µg Boost; and (iii) the combined "50 + 100 µg" Prime + 50 µg Boost.

Table 18: Clinical Studies Supporting the Development of mRNA-1273 50 µg Booster

Study	2-Dose Primary Series	Booster Dose (Dose 3)	Interval Between Dose 2 and 3	N	Status
P201 B	50 µg – mRNA-1273	50 µg – mRNA-1273	≥6 months	173	Data available through Day 29 post-boost
	100 µg – mRNA-1273	50 µg – mRNA-1273	≥6 months	171	

2. Solicited ARs (post-dose 2) from **P201 Part A** (100 µg prime series group) and **P301 Part A**;
3. Unsolicited AEs for 28 days post any dose from **P201 Part A** (100 µg prime series group) and **P301 Part A**;
4. Updated listings of cumulative unsolicited adverse events (AEs), severe adverse events (SAEs), and medically attended adverse events (MAAEs) from participants who received a single booster dose in Study **P201 Part B**, generated from a live ongoing database (data subject to further cleaning; data snapshot date: 16 August 2021).
5. Solicited AR and unsolicited AE (up to study Day 7) for the supportive Study **DMID Study 21-0012**

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.

6. In addition, variant booster candidate vaccines are being evaluated in the ongoing Study mRNA-1273-P205, *A Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants*. Only safety data have been submitted for this study.

This submission is intended to support the use of a booster of mRNA-1273 to all children and adults 12 years and older who received a primary vaccination series with 2 doses of mRNA-1273 (100 µg) at least 6 months prior. Safety data have not been submitted in the current submission dossier for subjects below the age of 18 years which is a limitation.

4.1.1. P201 Part B (assessed as main study)

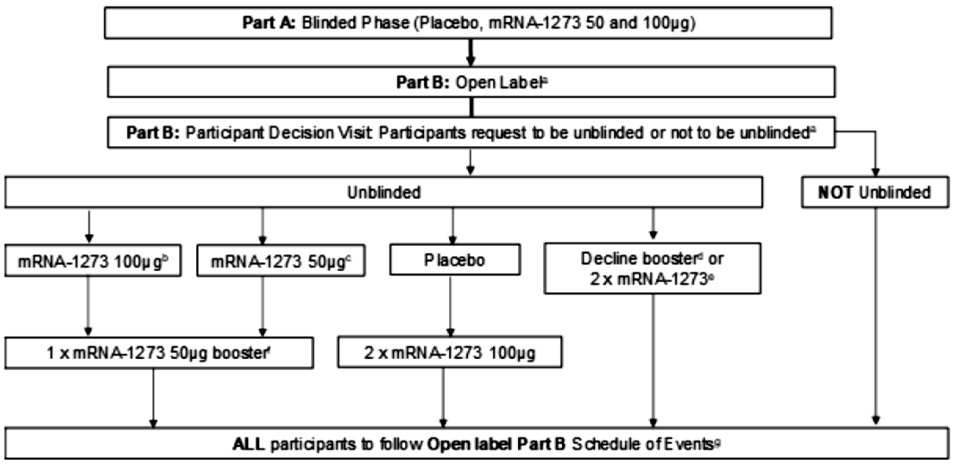
Study mRNA-1273-P201 is an ongoing 3-part, Phase 2a study: Part A, Part B, and Part C.

Part B was designed to offer participants who received placebo in Part A of this study the option to receive 2 injections of open-label mRNA-1273 (100 µg). Participants who received 1 or 2 doses of 50 µg or 100 µg mRNA-1273 in Part A were offered a single booster dose of mRNA-1273 (50 µg) in Part B.

In Part B, a pre-planned analysis for the booster dose at Day 29 has been conducted (database lock date 10 June 2021).

Solicited local and systemic adverse reactions (ARs) were collected for the 7 days following the booster injection (i.e. the day of injection and 6 subsequent days), and unsolicited AEs were collected for the 28 days following each injection (i.e. the day of injection and 27 subsequent days). SAEs, MAAEs, and AEs leading to study discontinuation were recorded for the duration of follow-up.

Figure 4: P201 Part B, Open-Label Schema



[a] All participants will proceed to Part B, Open-Label Interventional Phase; begins with the Participant Decision Visit.
[b] Participants who received 2 injections of mRNA-1273 100 µg during Blinded Part A.
[c] Participants who received 2 injections of mRNA-1273 50 µg during Blinded Part A.
[d] Participants who received 2 injections of mRNA-1273 in Part A and decline booster injection in Part B.
[e] Participants who received placebo in Part A and decline 2 injections of mRNA-1273 in Part B.
[f] Participants who received 2 injections of mRNA-1273 (50 µg or 100 µg) in Part A will receive 1 booster injection of mRNA-1273 50 µg in Part B.

4.1.2. DMID 21-0012 (assessed as supportive study)

DMID Study 21-0012 is a Phase 1/2 heterologous SARS-CoV-2 vaccine dosing (mRNA-1273 booster) study of the various US Emergency Use Authorization (EUA) vaccines (Janssen, Moderna, Pfizer/BioNTech) in participants ≥ 18 years old (NCT04889209). A total of 154 participants have been enrolled and received an mRNA-1273 boost injection (IM; 100 µg) approximately 12-20 weeks after receiving primary vaccination under EUA.

Table 19: EUA-dosed Cohort 1

Group	Sample Size*	EUA Dosing Scheme	Interval (weeks)	Delayed Booster Vaccination	Strategy Tested
1E	50	Previously dosed Janssen – Ad26.COV2-S	12-20	Moderna- mRNA-1273	Same Strain Heterologous platform
2E	50	Previously dosed Moderna – mRNA-1273	12-20	Moderna- mRNA-1273	Control - Same Strain & platform
3E	50	Previously dosed Pfizer/BioNTech – mRNA-BNT162b2	12-20	Moderna- mRNA-1273	Same Strain Similar platform

*Sample cohort size, N = 50, two age strata: 18-55 years (n = 25), 56+ years (n = 25)

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.

4.1.3. P205 Part A (assessed as supportive study)

This is a study not included in the efficacy/immunogenicity analysis in section 3 of this AR.

The MAH is providing these safety data from P205 to support the EUA amendment for a booster indication.

Study P205 is an open-label, Phase 2/3 study to evaluate the immunogenicity, safety, and reactogenicity of SARS-CoV-2 variant-matched vaccines, administered as a booster in adult participants of the mRNA-1273-P301 study who had previously received 2 doses of mRNA-1273 as a primary series. These participants received the second study dose at least 6 months prior to the administration of the booster.

In study P205 part A specifically, participants received either 50 or 100 µg (total mRNA content) of vaccine 1273.211, as a booster. Vaccine 1273.211 is a bivalent vaccine that contains two mRNAs in 1:1 mass ratio: one mRNA encodes for the S-2P of archetype SARS-CoV-2, Wuhan-Hu-1 (same mRNA as in vaccine mRNA-1273), and the other mRNA encodes for the S-2P of the B.1.351 (Beta variant) SARS-CoV-2 variant.

In study P205 part A, 300 participants were enrolled in the 50 µg of mRNA-1273.211 study arm between 28 May 2021 and 04 June 2021 and 596 participants were enrolled in the 100 µg arm of mRNA-1273 between 30 June 2021 and 16 July 2021. These participants constitute the P205 part A Safety Set used in the safety analyses presented herein. As of 20 August 2021, P205 part A participants have accrued approximately 80 and 45 on-study days since administration of the 50 and 100 µg of mRNA-1273.211, respectively (table 14.1.6.1).

4.2. Results

4.2.1. P201 Part B (and where relevant P201 Part A, and P301 Safety Data (Side-by-Side Evaluation))

Disposition

The Solicited Safety Set was used for the analyses of solicited ARs for Part B booster dose, and the Safety Set was used for analysis of safety for Part B booster dose except for the solicited ARs. Among 306 participants in Part B of P201 who received a booster injection and had both baseline and Day 29 immunogenicity assessment, 11 were excluded from the PP Set: 10 because of SARS-CoV-2 infection at baseline, and 1 because of a major protocol deviation.

Table 20 Summary of Reasons for Exclusion from Per-Protocol Set Full Analysis Set (Part b, Open-Label phase)

	Overall mRNA-1273		
	50 µg - Boost (N=150)	100 µg - Boost (N=156)	Total (N=306)
Full Analysis Set	150	156	306
Per-Protocol Set, n (%)	146 (97.3)	149 (95.5)	295 (96.4)
Excluded from Per-Protocol Set, n (%)	4 (2.7)	7 (4.5)	11 (3.6)
Reasons for Exclusion, n (%) [1]			
SARS-CoV-2 Infection at OL Baseline	4 (2.7)	6 (3.8)	10 (3.3)
Had no Immunogenicity Data at OL-Day 29	0	0	0
Non-Study COVID-19 Vaccine prior to OL-Day 29	0	0	0
COVID-19 Related Prohibited Medication prior to OL-Day 29	0	0	0
Had Other Major Protocol Deviations	0	1 (0.6)	1 (0.3)

Demographics and Baseline Characteristics

In the Part B Safety Set for Study P201, across both 50 µg and 100 µg prime series groups, participants were predominantly female (Table 21), had a mean age of approximately 52 years and were predominantly white (95%) and not Hispanic or Latino (94%). Other than a slightly larger proportion of females in the 50 µg prime series group than in the 100 µg prime series group, no apparent differences were observed in baseline demographics across the prime series groups.

Table 21 Study P201 Part B Demographics and Characteristics in P201 Part B of 50 µg and 100 µg Priming Groups (Safety Set)

Characteristic	mRNA-1273 50 µg Primary Series + 50 µg Booster N=173 n (%)	mRNA-1273 100 µg Primary Series + 50 µg Booster N=171 n (%)	P201 Part B mRNA-1273 50 µg Booster Total N= 344
Sex			
Female	124 (71.7)	104 (60.8)	228 (66.3)
Male	49 (28.3)	67 (39.2)	116 (33.7)
Age			
Mean (SD)	52.0 (15.79)	52.0 (15.11)	52.0 (15.44)
Median	56.0	55.0	56.0
Min, Max	18, 87	18, 87	18, 87
Race			
White	164 (94.8)	164 (95.9)	328 (95.3)
Black or African American	3 (1.7)	5 (2.9)	8 (2.3)
Asian	2 (1.2)	1 (0.6)	3 (0.9)
American Indian or Alaska Native	1 (0.6)	1 (0.6)	2 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0	1 (0.3)
Multiracial	1 (0.6)	0	1 (0.3)
Other	1 (0.6)	0	1 (0.3)
Not Reported	0	0	0
Unknown	0	0	0
Ethnicity			
Hispanic or Latino	10 (5.8)	10 (5.8)	20 (5.8)
Not Hispanic or Latino	162 (93.6)	161 (94.2)	323 (93.9)
Not reported	1 (0.6)	0	1 (0.3)
Unknown	0	0	0
Body mass index (kg/m^2)			
Mean (SD)	25.68 (3.309)	25.46 (3.185)	25.57 (3.245)
Median	26.12	25.59	25.76

CHMP comment

Beside a higher proportion of female subjects compared to male subjects, all other characteristics were comparable between both dose groups.

4.2.1.1. Solicited Adverse Reactions

Participants recorded solicited local and systemic ARs in the eDiary on the day of each mRNA-1273 injection and during the 7 days after each mRNA-1273 injection. The reactogenicity profile following a 50 µg booster had a comparable profile for solicited local and systemic ARs among participants primed with 50 µg or those 100 µg. Because these 2 groups were comparable, the combined safety data are presented below. The reactogenicity profile following a single injection of the 50 µg mRNA-1273 booster observed in Study P201 Part B was similar to that observed after the second dose of mRNA-1273 from the primary series in the previously reported P201 Part A and P301 Part A.

Summary of Solicited Local Adverse Reactions

The following local ARs were evaluated in each study within 7 days after injection: pain at injection site, erythema (redness) at injection site, swelling (hardness) at injection site, and localised axillary swelling or tenderness ipsilateral to the injection arm.

The frequency of local ARs in Study P201 Part B following the 50 µg booster dose was numerically similar to that observed following the second injection of the primary series (50 µg or 100 µg)(**Error! Reference source not found.**).

Table 22 Solicited Local Adverse Reactions Reported Within 7 Days After Booster vs Within 7 Days After the 2nd Injection in the Primary Series of P201 Part A and P301 (by Grade): Solicited Safety Set

	mRNA-1273				
	P201 50 µg Prime + 50 µg Booster N=163 n(%)	P201 100 µg Prime + 50 µg Booster N=167 n (%)	P201 Part B 50 µg Booster Total (N=330) n (%)	P201 Part A 100 µg N=198 n (%)	P301 100 µg N= 14691 n (%)
Pain, N1	162	167	329	198	14688
Any	144 (88.9)	140 (83.8)	284 (86.3)	169 (85.4)	12964 (88.3)
Grade 1	111 (68.5)	111 (66.5)	222 (67.5)	140 (70.7)	9508 (64.7)
Grade 2	26 (16.0)	23 (13.8)	49 (14.9)	28 (14.1)	2850 (19.4)
Grade 3	7 (4.3)	6 (3.6)	13 (4.0)	1 (0.5)	606 (4.1)
Erythema (Redness), N1	162	167	329	198	14687
Any	10 (6.2)	8 (4.8)	18 (5.5)	15 (7.6)	1274 (8.7)
Grade 1	4 (2.5)	5 (3.0)	9 (2.7)	7 (3.5)	456 (3.1)
Grade 2	4 (2.5)	2 (1.2)	6 (1.8)	3 (1.5)	531 (3.6)
Grade 3	2 (1.2)	1 (0.6)	3 (0.9)	5 (2.5)	287 (2.0)
Swelling (Hardness), N1	162	167	329	198	14687
Any	12 (7.4)	9 (5.4)	21 (6.4)	21 (10.6)	1807 (12.3)
Grade 1	4 (2.5)	4 (2.4)	8 (2.4)	14 (7.1)	900 (6.1)
Grade 2	7 (4.3)	4 (2.4)	11 (3.3)	6 (3.0)	652 (4.4)
Grade 3	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.5)	255 (1.7)
Lymphadenopathy, N1	162	167	329	198	14687
Any	35 (21.6)	34 (20.4)	69 (21.0)	20 (10.1)	2092 (14.2)
Grade 1	22 (13.6)	30 (18.0)	52 (15.8)	17 (8.6)	1735 (11.8)
Grade 2	13 (8.0)	3 (1.8)	16 (4.9)	3 (1.5)	289 (2.0)
Grade 3	0	1 (0.6)	1 (0.3)	0	68 (0.5)

The most common solicited AR after the 50 µg boost dose was pain. Most solicited local ARs were grade 1 to grade 2 in severity. Pain was the most commonly reported grade 3 local AR in P201 Part B. No grade 4 solicited local ARs were reported in either primary series group in P201 Part B. Local ARs were transient, and most resolved by Day 4. The frequency and severity of solicited local ARs was numerically comparable between age cohorts (18 to <55; ≥55 years of age).

Table 23 Summary of Solicited Adverse reactions within 7 days after booster injection by grade solicited safety set (Part 8, Open-label phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
Solicited Adverse Reaction Category Grade	50 µg - Boost (N=73) n (%)	100 µg - Boost (N=79) n (%)	Total (N=152) n (%)	50 µg - Boost (N=90) n (%)	100 µg - Boost (N=88) n (%)	Total (N=178) n (%)
Solicited Adverse Reactions - N1	73	79	152	90	88	178
Any Solicited Adverse Reactions	68 (93.2)	73 (92.4)	141 (92.8)	84 (93.3)	78 (88.6)	162 (91.0)
95% CI	84.7, 97.7	84.2, 97.2	87.4, 96.3	86.1, 97.5	80.1, 94.4	85.8, 94.8
Grade 1	33 (45.2)	30 (38.0)	63 (41.4)	32 (35.6)	43 (48.9)	75 (42.1)
Grade 2	24 (32.9)	33 (41.8)	57 (37.5)	34 (37.8)	26 (29.5)	60 (33.7)
Grade 3	11 (15.1)	9 (11.4)	20 (13.2)	18 (20.0)	9 (10.2)	27 (15.2)
Grade 4	0	0	0	0	0	0
Solicited Local Adverse Reactions - N1	72	79	151	90	88	178
Any Solicited Local Adverse Reactions	66 (91.7)	69 (87.3)	135 (89.4)	78 (86.7)	74 (84.1)	152 (85.4)
95% CI	82.7, 96.9	78.0, 93.8	83.4, 93.8	77.9, 92.9	74.8, 91.0	79.3, 90.2
Grade 1	49 (68.1)	48 (60.8)	97 (64.2)	53 (58.9)	60 (68.2)	113 (63.5)
Grade 2	13 (18.1)	17 (21.5)	30 (19.9)	20 (22.2)	10 (11.4)	30 (16.9)
Grade 3	4 (5.6)	4 (5.1)	8 (5.3)	5 (5.6)	4 (4.5)	9 (5.1)
Grade 4	0	0	0	0	0	0

CHMP comment

The frequencies of reported solicited local ARs were comparable between booster doses both primarily vaccinated with 50 µg or 100 µg of Spikevax and comparable to the safety profile of primary vaccination schedules in P201 Part A as well as to the safety profile of the primary vaccination schedule in the pivotal study P301. No safety data were provided for children in age of 12 to 17 years. The frequencies of reported solicited local reactions were comparable between both age strata.

Summary of Solicited Systemic Adverse Reactions

The following systemic ARs were evaluated in each study: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, fever, and chills.

Rash was a solicited systemic AR in Study P201 only; therefore, no comparison between P201 and P301 can be made and accordingly rash is not included in Table 18.

The frequency of systemic ARs in Study P201 Part B following the 50 µg booster dose was numerically similar to that observed following the second injection of the primary series in Study P201 Part A and in P301. The most common systemic ARs after the 50 µg booster dose in P201 Part B were fatigue, headache, arthralgia, and myalgia, which occurred at a similar rate between the P201 Part B 50 and 100 µg prime series groups. Because these 2 groups were comparable, the combined safety data are presented below (Table 24). No difference in incidence of the solicited AR of rash (3.7% in the 50 µg vs 1.8% in the 100 µg groups) was observed after the booster dose between the 50 µg and 100 µg prime series. Most solicited systemic adverse reaction in P 201 Part B were grade 1 to grade 2 in severity. Systemic ARs were transient, and most resolved by Day 4. The frequency and severity of solicited systemic ARs was numerically comparable between age cohorts (18 to <55; ≥55 years of age) (P201 Part B: Table 23).

Fatigue, myalgia, headache, and arthralgia were the most commonly reported grade 3 systemic ARs (Table 24). No grade 4 solicited systemic ARs were reported in either prime series group in P201.

Table 24: Solicited Systemic Adverse Reactions Within 7 Days After Booster vs Within 7 Days After the 2nd Injection in the Primary Series of P201 Part A and P301 (by Grade): Solicited Safety Set

	mRNA-1273				
	50 µg Prime + 50 µg Booster (N=163) n (%)	**100 µg Prime + 50 µg Booster N=167 n (%)**	**P201 Part B 50 µg Booster Total (N=330) n (%)**	**P201 Part A 100 µg N=198 n (%)**	**P301 100 µg N=14691 n (%)**
Fever, N1	162	166	328	198	14682
Any	13 (8.0)	11 (6.6)	24 (7.3)	26 (13.1)	2276 (15.5)
Grade 1	12 (7.4)	6 (3.6)	18 (5.5)	19 (9.6)	1363 (9.3)
Grade 2	1 (0.6)	3 (1.8)	4 (1.2)	3 (1.5)	697 (4.7)
Grade 3	0	2 (1.2)	2 (0.6)	4 (2.0)	203 (1.4)
Grade 4	0	0	0	0	13 (<0.1)
Headache, N1	162	167	329	198	14687
Any	97 (59.9)	92 (55.1)	189 (57.4)	104 (52.5)	8637 (58.8)
Grade 1	57 (35.2)	61 (36.5)	118 (35.9)	56 (28.3)	4815 (32.8)
Grade 2	34 (21.0)	29 (17.4)	63 (19.1)	39 (19.7)	3156 (21.5)
Grade 3	6 (3.7)	2 (1.2)	8 (2.4)	9 (4.5)	666 (4.5)
Fatigue, N1	162	167	329	198	14687
Any	103 (63.6)	98 (58.7)	201 (61.1)	128 (64.6)	9607 (65.4)
Grade 1	40 (24.7)	47 (28.1)	87 (26.4)	44 (22.2)	3431 (23.4)
Grade 2	50 (30.9)	44 (26.3)	94 (28.6)	66 (33.3)	4743 (32.3)
Grade 3	13 (8.0)	7 (4.2)	20 (6.1)	18 (9.1)	1433 (9.8)
Myalgia, N1	162	167	329	198	14687
Any	86 (53.1)	82 (49.1)	168 (51.1)	104 (52.5)	8529 (58.1)
Grade 1	40 (24.7)	47 (28.1)	87 (26.4)	35 (17.7)	3242 (22.1)
Grade 2	37 (22.8)	30 (18.0)	67 (20.4)	54 (27.3)	3966 (27.0)
Grade 3	9 (5.6)	5 (3.0)	14 (4.3)	15 (7.6)	1321 (9.0)
Arthralgia, N1	162	167	329	198	14687
Any	66 (40.7)	69 (41.3)	135 (41.0)	77 (38.9)	6303 (42.9)
Grade 1	35 (21.6)	43 (25.7)	78 (23.7)	32 (16.2)	2809 (19.1)
Grade 2	23 (14.2)	21 (12.6)	44 (13.4)	37 (18.7)	2719 (18.5)
Grade 3	8 (4.9)	5 (3.0)	13 (4.0)	8 (4.0)	775 (5.3)
Nausea/Vomiting, N1	162	167	329	198	14687
Any	29 (17.9)	19 (11.4)	48 (14.6)	41 (20.7)	2794 (19.0)
Grade 1	25 (15.4)	16 (9.6)	41 (12.5)	25 (12.6)	2094 (14.3)
Grade 2	4 (2.5)	3 (1.8)	7 (2.1)	16 (8.1)	678 (4.6)
Grade 3	0	0	0	0	21 (0.1)
Grade 4	0	0	0	0	1 (<0.1)
Chills, N1	162	167	329	198	14687
Any	62 (38.3)	59 (35.3)	121 (36.8)	78 (39.4)	6500 (44.3)
Grade 1	32 (19.8)	36 (21.6)	68 (20.7)	30 (15.2)	2907 (19.8)
Grade 2	28 (17.3)	23 (13.8)	51 (15.5)	47 (23.7)	3402 (23.2)
Grade 3	2 (1.2)	0	2 (0.6)	1 (0.5)	191 (1.3)

Table 25 summarised concomitant medication of analgesics and antipyretics, which were taken by the boosted subjects after administration until 14 days post-dose booster. Around 50% of subjects took medication to prevent pain or fever, more dominantly to prevent fever in both age strata.

Table 25 Summary of Analgesics/Antipyretics Use within 2-week after booster vaccination safety set (Part B, Open-label phase

	Overall		
	mRNA-1273		
Preferred Term	50 µg - Boost (N=173) n (%)	100 µg - Boost (N=171) n (%)	Total (N=344) n (%)
Number of Subjects Who Used Analgesic/Antipyretic	66 (38.2)	56 (32.7)	122 (35.5)
IBUPROFEN	34 (19.7)	32 (18.7)	66 (19.2)
PARACETAMOL	29 (16.8)	21 (12.3)	50 (14.5)
ACETYLSALICYLIC ACID;CAFFEINE;PARACETAMOL	1 (0.6)	5 (2.9)	6 (1.7)
ACETYLSALICYLIC ACID	3 (1.7)	2 (1.2)	5 (1.5)
NAPROXEN	4 (2.3)	0	4 (1.2)
DEXTROMETHORPHAN HYDROBROMIDE;DOXYLAMINE SUCCINATE;PARACETAMOL	0	1 (0.6)	1 (0.3)
DEXTROMETHORPHAN HYDROBROMIDE;DOXYLAMINE SUCCINATE;PARACETAMOL;PHENYLEPHRINE HYDROCHLORIDE	1 (0.6)	0	1 (0.3)
DEXTROMETHORPHAN HYDROBROMIDE;GUAIFENESIN;PARACETAMOL;PHENYLEPHRINE HYDROCHLORIDE	1 (0.6)	0	1 (0.3)
ETODOLAC	0	1 (0.6)	1 (0.3)
HYDROCODONE	1 (0.6)	0	1 (0.3)
KETOROLAC	1 (0.6)	0	1 (0.3)
NAPROXEN SODIUM	1 (0.6)	0	1 (0.3)

CHMP *comment*

The frequencies of reported solicited systemic ARs were comparable for booster doses given to subjects after primary vaccination with either 50 µg or 100 µg of Spikevax and comparable to the safety profiles of primary vaccination schedules in P201 Part A as well as to the safety profile of the primary vaccination schedule in the pivotal study P301. Reported frequencies of solicited systemic reactions were comparable between both age strata. The MAH applied for a booster indication for adolescents and adults aged 12 years and above. No data of solicited systemic ARs were provided by the MAH for the age group of adolescents aged 12 to 17 years after a booster dose. Both age strata took medication in comparable amounts to prevent pain around 8 % and to prevent fever around 45 %.

4.2.1.2. Unsolicited Adverse Reactions

In P201 Part B, unsolicited treatment-emergent adverse events (TEAEs) were systematically collected during the 28-day time window after the booster dose.

Adverse events leading to discontinuation from study participation, SAEs, MAAEs, and pregnancies are being collected from Day 1 through the entire study period or until the last day of study participation. Refer to the Study P201 protocol for additional details on the collection of unsolicited AEs.

Per the comments received from the FDA on 28 September 2020, any solicited AR that meets either of the following criteria was included in the analysis of unsolicited AEs: (i) solicited local or systemic AR lasting beyond 7 days post-injection (ii) solicited local or systemic AR meeting SAE criteria.

The frequency of unsolicited AEs following the booster in Study P201 Part B was similar across the 50 µg and 100 µg prime series groups with numerically slight better profile in 50 µg priming group. It was also numerically comparable to or lower than the rates observed post any dose in P201 Part A and P301 Part A (Table 19).

All unsolicited AEs were mild or moderate in severity.

No unsolicited AEs led to study discontinuation.

TEAEs that were considered by the investigator as related to mRNA-1273 were consistent with PT terms solicited as part of the reactogenicity assessment.

There were no SAEs in 201 Part B up to 28 days after booster administration.

Table 20 summarises TEAEs by Preferred Term (PT) for the 28-day follow-up period after booster vaccination, and no unexpected reporting patterns were observed. Some reported TEAEs (e.g., headache and fatigue) are solicited ARs that extended beyond Day 7. The reports with a PT of COVID-19 represent 4 asymptomatic participants who had nasal swabs, collected at scheduled study visits or following potential exposure to SARS-CoV-2, that tested positive for SARS-CoV-2.

As of 16 August 2021 in the live database of this ongoing study (data subject to further cleaning), there were 28 additional unsolicited AEs that were not classified as SAEs or MAAEs (which are both described below) that occurred after Day 29. There was no clinical pattern observed, and none was considered related to mRNA-1273.

Table 26 Summary of unsolicited treatment-emergent adverse events up to 28 days after booster in P201 part B or up to 28 days after any injection in P201 part A and P301: Safety Set

	mRNA-1273				
	50 µg Prime + 50 µg Booster N=173 n (%)	**100 µg Prime + 50 µg Booster N=171 n (%)**	**P201 Part B 50 µg Booster Total (N=344) n (%)**	**P201 Part A 100 µg N=200 n (%)**	**P301 mRNA-1273 (N=15184) n (%)**
Unsolicited TEAEs regardless of relationship to study vaccination					
All	17 (9.8)	22 (12.9)	39 (11.3)	56 (28.0)	4752 (31.3)
Serious	0	0	0	0	98 (0.6)
Fatal	0	0	0	0	2 (<0.1)
Medically-attended	8 (4.6)	12 (7.0)	20 (5.8)	17 (8.5)	1819 (12.0)
Leading to study discontinuation	0	0	0	0	9 (<0.1)
Severe	0	0	0	5 (2.5)	258 (1.7)
Unsolicited TEAEs related to study vaccination					
All	6 (3.5)	7 (4.1)	13 (3.8)	27 (13.5)	2067 (13.6)
Serious	0	0	0	0	8 (<0.1)
Fatal	0	0	0	0	0
Medically-attended	0	2 (1.2)	2 (0.6)	5 (2.5)	198 (1.3)
Leading to study discontinuation	0	0	0	0	1 (<0.1)
Severe	0	0	0	2 (1.0)	83 (0.5)

TEAE = treatment-emergent adverse event.
Source: P201 Part A: Table 14.3.1.7.1, Study P201 Part B: Table 14.3.1.7.3.1; Study P301 Part A CSR Table 14.3.1.7.1.1.

Table 27: Study P201 Part B incidence of unsolicited TEAE by preferred term up to 28 days after booster: safety set

Preferred Term	50 µg Prime + 50 µg Booster N=173 n (%)	100 µg Prime + 50 µg Booster N=171 n (%)	P201 Part B 50 µg Booster Total (N=344) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	17 (9.8)	22 (12.9)	39 (11.3)
Number of Unsolicited Adverse Events	19	27	46
Headache	1 (0.6)	4 (2.3)	5 (1.5)
COVID-19	1 (0.6)	3 (1.8)	4 (1.2)
Fatigue	0	4 (2.3)	4 (1.2)
Arthralgia	1 (0.6)	1 (0.6)	2 (0.6)
Lymphadenopathy	2 (1.2)	0	2 (0.6)
Oropharyngeal pain	1 (0.6)	1 (0.6)	2 (0.6)
Tooth abscess	2 (1.2)	0	2 (0.6)
Abdominal pain	0	1 (0.6)	1 (0.3)
Allergy to arthropod bite	0	1 (0.6)	1 (0.3)
Anxiety	0	1 (0.6)	1 (0.3)
Chills	1 (0.6)	0	1 (0.3)
Dermatitis exfoliative	1 (0.6)	0	1 (0.3)
Dizziness	0	1 (0.6)	1 (0.3)
Facial paralysis	1 (0.6)	0	1 (0.3)
Gastrooesophageal reflux disease	0	1 (0.6)	1 (0.3)
Glycosylated haemoglobin increased	0	1 (0.6)	1 (0.3)
Humerus fracture	0	1 (0.6)	1 (0.3)
Hypertension	1 (0.6)	0	1 (0.3)
Influenza	0	1 (0.6)	1 (0.3)
Injection site erythema	0	1 (0.6)	1 (0.3)
Myalgia	0	1 (0.6)	1 (0.3)
Osteopenia	1 (0.6)	0	1 (0.3)
Pruritus	1 (0.6)	0	1 (0.3)
Rash	0	1 (0.6)	1 (0.3)
Skin laceration	1 (0.6)	0	1 (0.3)
Suspected COVID-19	1 (0.6)	0	1 (0.3)
Tooth fracture	1 (0.6)	0	1 (0.3)
Urinary tract infection	0	1 (0.6)	1 (0.3)
Vertigo	1 (0.6)	0	1 (0.3)
Vitamin D deficiency	0	1 (0.6)	1 (0.3)
Vomiting	1 (0.6)	0	1 (0.3)
Wheezing	0	1 (0.6)	1 (0.3)

Source: P201 Part B: Table 14.3.1.9.3.1.
n/N = number; TEAE = treatment-emergent adverse event.

Following Tables have been submitted in the eCTD158, which however implicate additional tendence of numerically slightly better profile of unsolicited AEs if boosting occurred after 50 µg dose priming vs. 100 µg dose priming (see section 6.):

Table 14.3.1.10.3.1
Subject Incidence of Unsolicited TEAE by System Organ Class, Preferred Term, and Severity up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Overall		
	mRNA-1273		
System Organ Class Preferred Term Severity	50 µg - Boost (N=173) n (%)	100 µg - Boost (N=171) n (%)	Total (N=344) n (%)
Musculoskeletal and connective tissue disorders (cont.)			
Myalgia	0	1 (0.6)	1 (0.3)
Mild	0	1 (0.6)	1 (0.3)
Moderate	0	0	0
Severe	0	0	0
Osteopenia	1 (0.6)	0	1 (0.3)
Mild	1 (0.6)	0	1 (0.3)
Moderate	0	0	0
Severe	0	0	0
General disorders and administration site conditions	1 (0.6)	5 (2.9)	6 (1.7)
Mild	1 (0.6)	5 (2.9)	6 (1.7)
Moderate	0	0	0
Severe	0	0	0

Unsolicited TEAEs, Dose and Age group

Table 14.3.1.7.3.1
Summary of Unsolicited TEAE up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Unsolicited TEAEs Regardless of Relationship to Study Vaccination						
All	10 (12.5)	5 (6.1)	15 (9.3)	7 (7.5)	17 (19.1)	24 (13.2)
Serious	0	0	0	0	0	0
Fatal	0	0	0	0	0	0
Medically-Attended	4 (5.0)	4 (4.9)	8 (4.9)	4 (4.3)	8 (9.0)	12 (6.6)
Leading to Study Discontinuation	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Unsolicited TEAEs Related to Study Vaccination						
All	5 (6.3)	1 (1.2)	6 (3.7)	1 (1.1)	6 (6.7)	7 (3.8)
Serious	0	0	0	0	0	0
Fatal	0	0	0	0	0	0
Medically-Attended	0	0	0	0	2 (2.2)	2 (1.1)
Leading to Study Discontinuation	0	0	0	0	0	0
Severe	0	0	0	0	0	0

Table 14.3.1.8.3.1
Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	10 (12.5)	5 (6.1)	15 (9.3)	7 (7.5)	17 (19.1)	24 (13.2)
Number of Unsolicited Adverse Events	11	7	18	8	20	28
Infections and infestations	2 (2.5)	2 (2.4)	4 (2.5)	2 (2.2)	2 (2.2)	4 (2.2)
COVID-19	1 (1.3)	2 (2.4)	3 (1.9)	0	1 (1.1)	1 (0.5)
Tooth abscess	1 (1.3)	0	1 (0.6)	1 (1.1)	0	1 (0.5)
Influenza	0	0	0	0	1 (1.1)	1 (0.5)
Suspected COVID-19	0	0	0	1 (1.1)	0	1 (0.5)
Urinary tract infection	0	1 (1.2)	1 (0.6)	0	0	0
Blood and lymphatic system disorders	2 (2.5)	0	2 (1.2)	0	0	0
Lymphadenopathy	2 (2.5)	0	2 (1.2)	0	0	0
Immune system disorders	0	1 (1.2)	1 (0.6)	0	0	0
Allergy to arthropod bite	0	1 (1.2)	1 (0.6)	0	0	0

Some Tables have been copied below to support statements in the discussion..

Table 14.3.1.9.3.1
Subject Incidence of Unsolicited TEAE by Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
Preferred Term	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	10 (12.5)	5 (6.1)	15 (9.3)	7 (7.5)	17 (19.1)	24 (13.2)
Number of Unsolicited Adverse Events	11	7	18	8	20	28
Headache	1 (1.3)	1 (1.2)	2 (1.2)	0	3 (3.4)	3 (1.6)
COVID-19	1 (1.3)	2 (2.4)	3 (1.9)	0	1 (1.1)	1 (0.5)
Fatigue	0	1 (1.2)	1 (0.6)	0	3 (3.4)	3 (1.6)
Arthralgia	1 (1.3)	0	1 (0.6)	0	1 (1.1)	1 (0.5)
Lymphadenopathy	2 (2.5)	0	2 (1.2)	0	0	0
Oropharyngeal pain	0	0	0	1 (1.1)	1 (1.1)	2 (1.1)
Tooth abscess	1 (1.3)	0	1 (0.6)	1 (1.1)	0	1 (0.5)
Abdominal pain	0	0	0	0	1 (1.1)	1 (0.5)
Allergy to arthropod bite	0	1 (1.2)	1 (0.6)	0	0	0
Anxiety	0	1 (1.2)	1 (0.6)	0	0	0
Chills	0	0	0	1 (1.1)	0	1 (0.5)
Dermatitis exfoliative	1 (1.3)	0	1 (0.6)	0	0	0
Dizziness	0	0	0	0	1 (1.1)	1 (0.5)
Facial paralysis	1 (1.3)	0	1 (0.6)	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	1 (1.1)	1 (0.5)

Table 14.3.1.9.3.1
Subject Incidence of Unsolicited TEAE by Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
Preferred Term	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Glycosylated haemoglobin increased	0	0	0	0	1 (1.1)	1 (0.5)
Humerus fracture	0	0	0	0	1 (1.1)	1 (0.5)
Hypertension	0	0	0	1 (1.1)	0	1 (0.5)
Influenza	0	0	0	0	1 (1.1)	1 (0.5)
Injection site erythema	0	0	0	0	1 (1.1)	1 (0.5)
Myalgia	0	0	0	0	1 (1.1)	1 (0.5)
Osteopenia	0	0	0	1 (1.1)	0	1 (0.5)
Pruritus	1 (1.3)	0	1 (0.6)	0	0	0
Rash	0	0	0	0	1 (1.1)	1 (0.5)
Skin laceration	0	0	0	1 (1.1)	0	1 (0.5)
Suspected COVID-19	0	0	0	1 (1.1)	0	1 (0.5)
Tooth fracture	1 (1.3)	0	1 (0.6)	0	0	0
Urinary tract infection	0	1 (1.2)	1 (0.6)	0	0	0
Vertigo	1 (1.3)	0	1 (0.6)	0	0	0
Vitamin D deficiency	0	0	0	0	1 (1.1)	1 (0.5)
Vomiting	0	0	0	1 (1.1)	0	1 (0.5)
Wheezing	0	0	0	0	1 (1.1)	1 (0.5)

Table 14.3.1.10.3.1
Subject Incidence of Unsolicited TEAE by System Organ Class, Preferred Term, and Severity up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
System Organ Class / Preferred Term / Severity	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	10 (12.5)	5 (6.1)	15 (9.3)	7 (7.5)	17 (19.1)	24 (13.2)
Mild	5 (6.3)	3 (3.7)	8 (4.9)	6 (6.5)	11 (12.4)	17 (9.3)
Moderate	5 (6.3)	2 (2.4)	7 (4.3)	1 (1.1)	6 (6.7)	7 (3.8)
Severe	0	0	0	0	0	0
Number of Unsolicited Adverse Events	11	7	18	8	20	28
Mild	5	5	10	7	13	20
Moderate	6	2	8	1	7	8
Severe	0	0	0	0	0	0
Infections and infestations	2 (2.5)	2 (2.4)	4 (2.5)	2 (2.2)	2 (2.2)	4 (2.2)
Mild	1 (1.3)	2 (2.4)	3 (1.9)	1 (1.1)	1 (1.1)	2 (1.1)
Moderate	1 (1.3)	0	1 (0.6)	1 (1.1)	1 (1.1)	2 (1.1)
Severe	0	0	0	0	0	0
COVID-19	1 (1.3)	2 (2.4)	3 (1.9)	0	1 (1.1)	1 (0.5)
Mild	1 (1.3)	2 (2.4)	3 (1.9)	0	1 (1.1)	1 (0.5)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0

Table 14.3.1.10.3.1
Subject Incidence of Unsolicited TEAE by System Organ Class, Preferred Term, and Severity up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
System Organ Class / Preferred Term / Severity	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Nervous system disorders	2 (2.5)	1 (1.2)	3 (1.9)	0	4 (4.5)	4 (2.2)
Mild	0	1 (1.2)	1 (0.6)	0	1 (1.1)	1 (0.5)
Moderate	2 (2.5)	0	2 (1.2)	0	3 (3.4)	3 (1.6)
Severe	0	0	0	0	0	0
Headache	1 (1.3)	1 (1.2)	2 (1.2)	0	3 (3.4)	3 (1.6)
Mild	0	1 (1.2)	1 (0.6)	0	1 (1.1)	1 (0.5)
Moderate	1 (1.3)	0	1 (0.6)	0	2 (2.2)	2 (1.1)
Severe	0	0	0	0	0	0
Dizziness	0	0	0	0	1 (1.1)	1 (0.5)
Mild	0	0	0	0	0	0
Moderate	0	0	0	0	1 (1.1)	1 (0.5)
Severe	0	0	0	0	0	0
Facial paralysis	1 (1.3)	0	1 (0.6)	0	0	0
Mild	0	0	0	0	0	0
Moderate	1 (1.3)	0	1 (0.6)	0	0	0
Severe	0	0	0	0	0	0
Ear and labyrinth disorders	1 (1.3)	0	1 (0.6)	0	0	0
Mild	1 (1.3)	0	1 (0.6)	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0

Table 14.3.1.10.3.1
Subject Incidence of Unsolicited TEAE by System Organ Class, Preferred Term, and Severity up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
System Organ Class Preferred Term Severity	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Musculoskeletal and connective tissue disorders (cont.)						
Myalgia	0	0	0	0	1 (1.1)	1 (0.5)
Mild	0	0	0	0	1 (1.1)	1 (0.5)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Osteopenia	0	0	0	1 (1.1)	0	1 (0.5)
Mild	0	0	0	1 (1.1)	0	1 (0.5)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
General disorders and administration site conditions	0	1 (1.2)	1 (0.6)	1 (1.1)	4 (4.5)	5 (2.7)
Mild	0	1 (1.2)	1 (0.6)	1 (1.1)	4 (4.5)	5 (2.7)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0

Table 14.3.1.10.3.1
Subject Incidence of Unsolicited TEAE by System Organ Class, Preferred Term, and Severity up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
System Organ Class Preferred Term Severity	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
General disorders and administration site conditions (cont.)						
Fatigue	0	1 (1.2)	1 (0.6)	0	3 (3.4)	3 (1.6)
Mild	0	1 (1.2)	1 (0.6)	0	3 (3.4)	3 (1.6)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Chills	0	0	0	1 (1.1)	0	1 (0.5)
Mild	0	0	0	1 (1.1)	0	1 (0.5)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Injection site erythema	0	0	0	0	1 (1.1)	1 (0.5)
Mild	0	0	0	0	1 (1.1)	1 (0.5)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Investigations	0	0	0	0	1 (1.1)	1 (0.5)
Mild	0	0	0	0	0	0
Moderate	0	0	0	0	1 (1.1)	1 (0.5)
Severe	0	0	0	0	0	0

Table 14.3.1.11.3.1
Subject Incidence of Unsolicited Treatment-Related TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	5 (6.3)	1 (1.2)	6 (3.7)	1 (1.1)	6 (6.7)	7 (3.8)
Number of Unsolicited Adverse Events	5	2	7	2	6	8
Blood and lymphatic system disorders	2 (2.5)	0	2 (1.2)	0	0	0
Lymphadenopathy	2 (2.5)	0	2 (1.2)	0	0	0
Nervous system disorders	1 (1.3)	1 (1.2)	2 (1.2)	0	2 (2.2)	2 (1.1)
Headache	1 (1.3)	1 (1.2)	2 (1.2)	0	2 (2.2)	2 (1.1)
Gastrointestinal disorders	0	0	0	1 (1.1)	0	1 (0.5)
Vomiting	0	0	0	1 (1.1)	0	1 (0.5)
Skin and subcutaneous tissue disorders	1 (1.3)	0	1 (0.6)	0	1 (1.1)	1 (0.5)
Pruritus	1 (1.3)	0	1 (0.6)	0	0	0
Rash	0	0	0	0	1 (1.1)	1 (0.5)

In elderly, medically-attended TEAEs have higher incidence after 100 µg prime. Unsolicited TEAEs appear to be equal frequented in 50 µg cohort and 100 µg cohort in younger subjects, but appear more frequently in the elderly vaccinated with 100 µg prime dose comparing to 50 µg. This seems to maintained in elderly also if only treatment-related TEAEs are considered, but safety in younger Cohort 1 seems to be more in favour of 50 µg priming dose. This discrepant finding should also be clarified. (see section 6.)

Unsolicited TEAEs in SARS-CoV-2 infected or COVID-19

Table 14.3.1.23.2.1
Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase) - Subjects with SARS-CoV-2 Infection or COVID-19

	Overall		
	mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=7) n (%)	100 µg - Boost (N=10) n (%)	Total (N=17) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	4 (57.1)	5 (50.0)	9 (52.9)
Number of Unsolicited Adverse Events	4	6	10
Infections and infestations	1 (14.3)	3 (30.0)	4 (23.5)
COVID-19	1 (14.3)	3 (30.0)	4 (23.5)
Urinary tract infection	0	1 (10.0)	1 (5.9)
Blood and lymphatic system disorders	1 (14.3)	0	1 (5.9)
Lymphadenopathy	1 (14.3)	0	1 (5.9)
Immune system disorders	0	1 (10.0)	1 (5.9)
Allergy to arthropod bite	0	1 (10.0)	1 (5.9)
Metabolism and nutrition disorders	0	1 (10.0)	1 (5.9)
Vitamin D deficiency	0	1 (10.0)	1 (5.9)

Table 14.3.1.23.2.1
Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase) - Subjects with SARS-CoV-2 Infection or COVID-19

	Overall		
	mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=7) n (%)	100 µg - Boost (N=10) n (%)	Total (N=17) n (%)
Skin and subcutaneous tissue disorders	1 (14.3)	0	1 (5.9)
Pruritus	1 (14.3)	0	1 (5.9)
Musculoskeletal and connective tissue disorders	1 (14.3)	0	1 (5.9)
Arthralgia	1 (14.3)	0	1 (5.9)

Table 14.3.1.23.2.1
Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase) - Subjects with SARS-CoV-2 Infection or COVID-19

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=6) n (%)	100 µg - Boost (N=6) n (%)	Total (N=12) n (%)	50 µg - Boost (N=1) n (%)	100 µg - Boost (N=4) n (%)	Total (N=5) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	4 (66.7)	3 (50.0)	7 (58.3)	0	2 (50.0)	2 (40.0)
Number of Unsolicited Adverse Events	4	4	8	0	2	2
Infections and infestations	1 (16.7)	2 (33.3)	3 (25.0)	0	1 (25.0)	1 (20.0)
COVID-19	1 (16.7)	2 (33.3)	3 (25.0)	0	1 (25.0)	1 (20.0)
Urinary tract infection	0	1 (16.7)	1 (8.3)	0	0	0
Blood and lymphatic system disorders	1 (16.7)	0	1 (8.3)	0	0	0
Lymphadenopathy	1 (16.7)	0	1 (8.3)	0	0	0
Immune system disorders	0	1 (16.7)	1 (8.3)	0	0	0
Allergy to arthropod bite	0	1 (16.7)	1 (8.3)	0	0	0
Metabolism and nutrition disorders	0	0	0	0	1 (25.0)	1 (20.0)
Vitamin D deficiency	0	0	0	0	1 (25.0)	1 (20.0)

Table 14.3.1.23.2.1
Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase) - Subjects with SARS-CoV-2 Infection or COVID-19

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=6) n (%)	100 µg - Boost (N=6) n (%)	Total (N=12) n (%)	50 µg - Boost (N=1) n (%)	100 µg - Boost (N=4) n (%)	Total (N=5) n (%)
Skin and subcutaneous tissue disorders	1 (16.7)	0	1 (8.3)	0	0	0
Pruritus	1 (16.7)	0	1 (8.3)	0	0	0
Musculoskeletal and connective tissue disorders	1 (16.7)	0	1 (8.3)	0	0	0
Arthralgia	1 (16.7)	0	1 (8.3)	0	0	0

CHMP comment:

No relevant difference in unsolicited TEAEs is observed between adults and elderly subjects in infected subjects.

Unsolicited TEAEs up to 28 days after booster dose that were serious, led to discontinuation or were severe

No such events were noted.

Unsolicited, medically attended TEAEs up to 28 days

Table 14.3.1.18.3.1
Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55) mRNA-1273			Cohort 2 (Age >= 55) mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Number of Subjects Reporting Unsolicited Adverse Events	4 (5.0)	4 (4.9)	8 (4.9)	4 (4.3)	8 (9.0)	12 (6.6)
Number of Unsolicited Adverse Events	5	4	9	4	8	12
Infections and infestations	2 (2.5)	2 (2.4)	4 (2.5)	1 (1.1)	1 (1.1)	2 (1.1)
COVID-19	1 (1.3)	2 (2.4)	3 (1.9)	0	0	0
Tooth abscess	1 (1.3)	0	1 (0.6)	1 (1.1)	0	1 (0.5)
Influenza	0	0	0	0	1 (1.1)	1 (0.5)
Immune system disorders	0	1 (1.2)	1 (0.6)	0	0	0
Allergy to arthropod bite	0	1 (1.2)	1 (0.6)	0	0	0
Metabolism and nutrition disorders	0	0	0	0	1 (1.1)	1 (0.5)
Vitamin D deficiency	0	0	0	0	1 (1.1)	1 (0.5)
Psychiatric disorders	0	1 (1.2)	1 (0.6)	0	0	0
Anxiety	0	1 (1.2)	1 (0.6)	0	0	0

Table 14.3.1.18.3.1
Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55) mRNA-1273			Cohort 2 (Age >= 55) mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Nervous system disorders	1 (1.3)	0	1 (0.6)	0	2 (2.2)	2 (1.1)
Headache	0	0	0	0	2 (2.2)	2 (1.1)
Facial paralysis	1 (1.3)	0	1 (0.6)	0	0	0
Ear and labyrinth disorders	1 (1.3)	0	1 (0.6)	0	0	0
Vertigo	1 (1.3)	0	1 (0.6)	0	0	0
Vascular disorders	0	0	0	1 (1.1)	0	1 (0.5)
Hypertension	0	0	0	1 (1.1)	0	1 (0.5)
Gastrointestinal disorders	0	0	0	0	1 (1.1)	1 (0.5)
Gastrooesophageal reflux disease	0	0	0	0	1 (1.1)	1 (0.5)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (1.1)	1 (0.5)
Rash	0	0	0	0	1 (1.1)	1 (0.5)
Musculoskeletal and connective tissue disorders	0	0	0	1 (1.1)	0	1 (0.5)
Osteopenia	0	0	0	1 (1.1)	0	1 (0.5)

Table 14.3.1.18.3.1
Subject Incidence of Unsolicited Medically-Attended TEAE by System Organ Class and Preferred Term up to 28 Days after Booster Vaccination
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55) mRNA-1273			Cohort 2 (Age >= 55) mRNA-1273		
System Organ Class Preferred Term	50 µg - Boost (N=80) n (%)	100 µg - Boost (N=82) n (%)	Total (N=162) n (%)	50 µg - Boost (N=93) n (%)	100 µg - Boost (N=89) n (%)	Total (N=182) n (%)
Investigations	0	0	0	0	1 (1.1)	1 (0.5)
Glycosylated haemoglobin increased	0	0	0	0	1 (1.1)	1 (0.5)
Injury, poisoning and procedural complications	1 (1.3)	0	1 (0.6)	1 (1.1)	1 (1.1)	2 (1.1)
Humerus fracture	0	0	0	0	1 (1.1)	1 (0.5)
Skin laceration	0	0	0	1 (1.1)	0	1 (0.5)
Tooth fracture	1 (1.3)	0	1 (0.6)	0	0	0

CHMP comment:

Medically attended TEAEs seem to be slightly more frequent in the 100 µg priming cohort than in 50 µg cohort (n=12 vs. 8). However, as also events like influenza, allergy to arthropod bite vitamin D deficiency

and anxiety were counted into these TEAEs, this difference seems to be a coincidence and it may be concluded that no difference has been observed between 100 and 50 µg cohorts if medically attended TEAEs are considered in general.

Unsolicited medically-attended TEAEs up to 28 days were more frequent in subjects above 55 years old in 100 µg cohort (9 %) than in 50 µg cohort (4.3%). This effect was not observed in subjects younger than 55 years old.

An MAAE was an AE that led to an unscheduled visit (including a telemedicine visit) to a healthcare practitioner (including unscheduled visits to the study site). The incidence of MAAEs during the 28-day time window was numerically higher in P201 Part A than in P201 Part B, including when assessed by the investigator as related to treatment (Table 19), which is consistent to the longer follow-up period due to receipt of 2 doses in Part A versus 1 dose in Part B.

No participants experiencing MAAE considered related to mRNA-1273 in the 50 µg prime series group but 2 (1.2%) in the 100 µg prime series group (grade 2 headache and grade 1 rash).

The review of cumulative MAAEs among P201 Part B participants who received a booster as of 16 August 2021 in the live ongoing database comprises 110 events.

There were 5 serious MAAEs, which are described below as "SAEs"

Deaths

No deaths were reported in Study P201 Part A (P201 Part A: CSR Addendum) or among P201 Part B booster participants (Table 19).

SAEs

There were no SAEs reported within the 28-day time window post-booster in P201 Part B or within the 28-day time window post any injection in P201 Part A.

The review of cumulative SAEs among P201 Part B participants who received a booster in the live clinical database as of 16 August 2021 shows 5 SAEs, in 4 participants (2 in each of the 50 µg and 100 µg priming groups) were reported, and all were considered by the investigator to be not related to mRNA-1273 (P201 Part B: Ad-hoc Listing 16.2.7.8; snapshot date: 16 August 2021).

In the 100 µg priming group, there was a 20-29-year-old with a tendon rupture that occurred 93 days after the booster and a 20-29-year-old female with previous pregnancies resulting in live births who experienced a spontaneous abortion 52 days after vaccination. This study participant subsequently became pregnant again 114 days after vaccination and this second pregnancy is ongoing. Two study participants in the 50 µg priming series had SAEs. A 70-79-year-old-male with relevant past medical history significant for hypertension reported a pulmonary embolism and deep vein thrombosis 79 days after booster. An 80-89-year-old female with a history of hypothyroidism, hypercholesterolemia, osteoarthritis, grade 1 diastolic dysfunction and chronic bradycardia, developed worsening of chronic bradycardia 44 days post-dose 2. Approximately 60 days post-dose 2 of the 50 µg priming series, she was hospitalised for pacemaker placement and was discharged in stable condition. A serious event of pericarditis was reported 89 days after booster vaccination and lasted 6 days along with a grade 2 event of angina lasting 1 day. Of note, the study participant also reported grade 2 pericarditis (not reported as serious) again from Day 122-127 after the booster. Both events of pericarditis were considered not related to vaccination.

AEs leading to discontinuation

There was no study discontinuation due to an adverse event in P201 Part B (Table 19).

AEs of clinical interest

Ad-hoc analyses of AEs of clinical interest were performed in Study P201 Part B up to Day 29 by searching the database using Standardised Medical Dictionary for Regulatory Activities Queries (SMQs) for the following events of interest: angioedema, arthritis, cardiomyopathy, central nervous system (CNS) vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis.

In addition, given the newly identified risk of myocarditis/pericarditis, the MAH searched the live clinical database up to 16 August 2021 for reported cases of myocarditis and pericarditis and individual symptoms or abnormalities that may be associated with these events (i.e. TEAEs of angina pectoris, chest pain, dyspnoea, palpitations, and syncope) as well as electrocardiogram (ECG) with ST elevation or PR depression, troponin elevation, pericardial rub on examination, and echocardiographic abnormalities (Gargano et al 2021).

The results of this analysis showed that no participants had AEs of interest in the SMQs of vasculitis, peripheral neuropathy, demyelination, convulsions, CNS haemorrhage and cerebrovascular conditions, embolic and thrombotic events, thrombophlebitis, hematopoietic cytopenias, or cardiomyopathy.

In P201 Part B, 2 participants (1 in the 50 µg priming series and 1 in the 100 µg priming series) had an AE of arthralgia that was captured in the arthritis SMQ. The 2 participants in the 50 µg priming series group were: a 40-49-year-old male who had joint aches in several joints from Day 1 to Day 7 after the boost, which was considered related to mRNA-1273; and a 60-69-year-old female who experienced moderate "joint aches" on Day 1 and 2 after the boost, which was considered related and which both resolved.

Table 14.3.1.22.3.2.2
Subject Incidence of Unsolicited Adverse Event of Special Interest after Booster Vaccination - Arthritis by SMQ (Narrow and Broad Scope)
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
	50 µg - Boost (N=80)	100 µg - Boost (N=82)	Total (N=162)	50 µg - Boost (N=93)	100 µg - Boost (N=89)	Total (N=182)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects Reporting Arthritis [1]	1 (1.3)	0	1 (0.6)	0	1 (1.1)	1 (0.5)
Number of Arthritis [1]	1	0	1	0	1	1
Arthralgia	1 (1.3)	0	1 (0.6)	0	1 (1.1)	1 (0.5)

In P201 Part B, there was **1 event** of wheezing in the broad **angioedema** SMQ after the booster in the 100 µg priming series cohort: a 60-69-year-old female developed mild left lower lobe wheezing on Day 1 after the boost, which was considered unrelated.

Table 14.3.1.22.4.2.2
Subject Incidence of Unsolicited Adverse Event of Special Interest after Booster Vaccination - Angioedema by SMQ (Narrow and Broad Scope)
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
	50 µg - Boost (N=80)	100 µg - Boost (N=82)	Total (N=162)	50 µg - Boost (N=93)	100 µg - Boost (N=89)	Total (N=182)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects Reporting Angioedema [1]	0	0	0	0	1 (1.1)	1 (0.5)
Number of Angioedema [1]	0	0	0	0	1	1
Wheezing	0	0	0	0	1 (1.1)	1 (0.5)

In P201 Part B, there were **2 events** in the SMQ **hypersensitivity after the 50 µg** booster: a 30-39-year-old male had mild pruritis (itching on the hand) on the day after booster; the event lasted 1 day and was considered related; and a 40-49-year-old female had mild exfoliative dermatitis of the face, which occurred 12 days after the boost and immediately following a spa treatment . The event lasted 1 day, was not medically-attended, and was considered unrelated.

There were **2 hypersensitivity events after the 100 µg** priming series group: a 60-69-year-old female had mild rash on her trunk and bilateral arms Day 2 to Day 30 after the booster, which was considered related; and there was a case of mild left lower lobe wheezing and as described above in the angioedema SMQ.

Table 14.3.1.22.2.2.2
Subject Incidence of Unsolicited Adverse Event of Special Interest after Booster Vaccination - Hypersensitivity by SMQ (Narrow and Broad Scope)
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
	50 µg - Boost (N=80)	100 µg - Boost (N=82)	Total (N=162)	50 µg - Boost (N=93)	100 µg - Boost (N=89)	Total (N=182)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects Reporting Hypersensitivity [1]	2 (2.5)	0	2 (1.2)	0	2 (2.2)	2 (1.1)
Number of Hypersensitivity [1]	2	0	2	0	2	2
Dermatitis exfoliative	1 (1.3)	0	1 (0.6)	0	0	0
Pruritus	1 (1.3)	0	1 (0.6)	0	0	0
Rash	0	0	0	0	1 (1.1)	1 (0.5)
Wheezing	0	0	0	0	1 (1.1)	1 (0.5)

In the broad SMQ **hearing and vestibular disorders**, **2 cases were captured, both in the 50 µg** prime group: a 30-39-year-old female had mild vertigo on Day 1 to Day 8 after the booster ; and a 40-49-year-old female reported grade 2 moderate "Bell's palsy"/facial paralysis 5 hours after receiving the booster, which resolved 25 days after vaccination and was considered unrelated . One individual above 55 years in the 100 µg prime group was reported.

Table 14.3.1.22.10.2.2
Subject Incidence of Unsolicited Adverse Event of Special Interest after Booster Vaccination - Hearing and Vestibular Disorders by SMQ (Narrow and Broad Scope)
Safety Set (Part B, Open-Label Phase)

	Cohort 1 (Age >= 18 and age < 55)			Cohort 2 (Age >= 55)		
	mRNA-1273			mRNA-1273		
	50 µg - Boost (N=80)	100 µg - Boost (N=82)	Total (N=162)	50 µg - Boost (N=93)	100 µg - Boost (N=89)	Total (N=182)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects Reporting Hearing and Vestibular Disorders [1]	2 (2.5)	0	2 (1.2)	0	1 (1.1)	1 (0.5)
Number of Hearing and Vestibular Disorders [1]	2	0	2	0	1	1
Dizziness	0	0	0	0	1 (1.1)	1 (0.5)
Facial paralysis	1 (1.3)	0	1 (0.6)	0	0	0
Vertigo	1 (1.3)	0	1 (0.6)	0	0	0

Within the 28-day time window post-booster in P201 Part B, no cases of myocarditis or pericarditis have been reported. No TEAEs were identified for the relevant clinical symptoms and abnormalities: chest pain, palpitations, dyspnoea, syncope, troponin elevation, ECG with ST elevation or PR depression, pericardiac rub, or echocardiographic findings.

In the live clinical database up to 16 August 2021 among P201 Part B participants who received a booster, review of SAEs and MAAEs as well as reported unsolicited AEs shows no myocarditis events. One SAE of pericarditis and AE of angina pectoris was reported in an 80-89-year-old female; onset was 89 days for both events after the booster in the 50 µg prime group. The case was assessed as unrelated to mRNA-1273.

Two study participants in the 50 µg prime group had adverse events mapping to relevant clinical symptoms for the evaluation of myocarditis or pericarditis; however, in both cases, the events occurred beyond 7 days following the booster, and were not associated with other reported myocarditis/pericarditis symptoms as described above. The first case concerned a nonserious grade 2 dyspnoea on exertion in a 60-69-year-old female 78 days after the booster, which resolved 112 days after the booster dose. The second case was reported in a 70-79-year-old female with nonserious premature ventricular contractions, assessed as unrelated by the investigator to mRNA-1273, which started 92 days after the booster and were ongoing as of 16 August 2021.

Pregnancies

There were no pregnancies reported following on-study testing in P201 Part B within the 28-day time window post-booster in P201 Part B or within the 28-day time window post any injection in P201 Part A. 3 pregnancies outside these time windows.

One reported case concerns a 30-39-year-old, female subject with medical history of polycystic ovarian disease, who became pregnant, 4 months 14 days after the first dose and 3 months 16 days after the last dose of the blinded study vaccine administration. This was her second pregnancy with history of one prior pregnancy which ended in a live birth. . At 8 weeks gestation, the subject experienced a spontaneous abortion. The investigator assessed the event of spontaneous abortion as not related to the study drug and not related to the study procedure.

A second case of product exposure during pregnancy was reported in a 30-39-year-old female. At week 6 the patient had a miscarriage. No further details provided. The investigator assessed the event, miscarriage, as not related to study drug and not related to study procedure

A third case concerns a 20-29-year-old, female subject with no prior medical history, who experienced drug exposure before pregnancy and spontaneous abortion. The subject did use contraception. The subject was unblinded and received 2 doses of mRNA-1273 during the trial and one booster dose after unblinding. The event of spontaneous abortion occurred 10 months and 11 days after the first dose of blinded vaccine administration and 9 months and 12 days after the second dose of blinded vaccine administration and 1 month, 24 days after booster dose. The investigator assessed the event, miscarriage, as not related to study drug or study procedure. The same participant reported a subsequent pregnancy 115 days after the booster.

In fact, based on the limited clinical information and the small population without appropriate control group, a final conclusion on relatedness of vaccination and spontaneous abortion is not possible. Spontaneous abortion is a frequent event in the early stage of pregnancy (approximately at least 20% of early pregnancies end in spontaneous abortion). A potential association between the vaccine and the event of spontaneous abortion can only be estimated in the broader Pharmacovigilance context. So far, mRNA COVID-19 vaccines are not associated with harm for pregnancy outcomes. No signal has been observed yet.

4.2.2. DMID 21-0012

4.2.2.1. Solicited 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 28 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[8]				
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

CHMP comment

Subjects reported with a higher frequency solicited local ARs after priming with Janssen-vaccine and boost with Spikevax compared to both other groups where priming and boost were administered mRNA-vaccines. Only induration was reported with a lower frequency in the Janssen group compared to the Comirnaty and Spikevax groups.

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 29).

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 Moderna, Boost Moderna and Dosed Pfizer/BioNTech, Boost Moderna) tended to report more solicited systemic AEs post vaccination compared with participants in the Dosed Janssen, Boost Moderna group.

Table 29 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)

CHMP comment

Beside fever all other solicited systemic ARs were more frequently reported after the heterologous booster with a vector-based as primary series followed by an mRNA-vaccine. The safety profile was

comparable of primary series with an mRNA vaccine followed by Spikevax regarding solicited systemic events.

4.2.2.2. Unsolicited Adverse Reactions

Most participants experienced mild or moderate AEs. The most common AE related to study vaccine was lymphadenopathy.

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 Janssen, boost Moderna) 18 participants reported 21 unsolicited AEs (Table 4a, Figures 1a and 2a). From the 51 participants in group 2E (EUA dosed Moderna, boost Moderna) 16 participants reported 22 unsolicited AEs (Table 4b, Figures 1b and 2b). From the 50 participants in Group 3E (EUA dosed Pfizer/BioNTech, boost Moderna) 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).

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%)

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

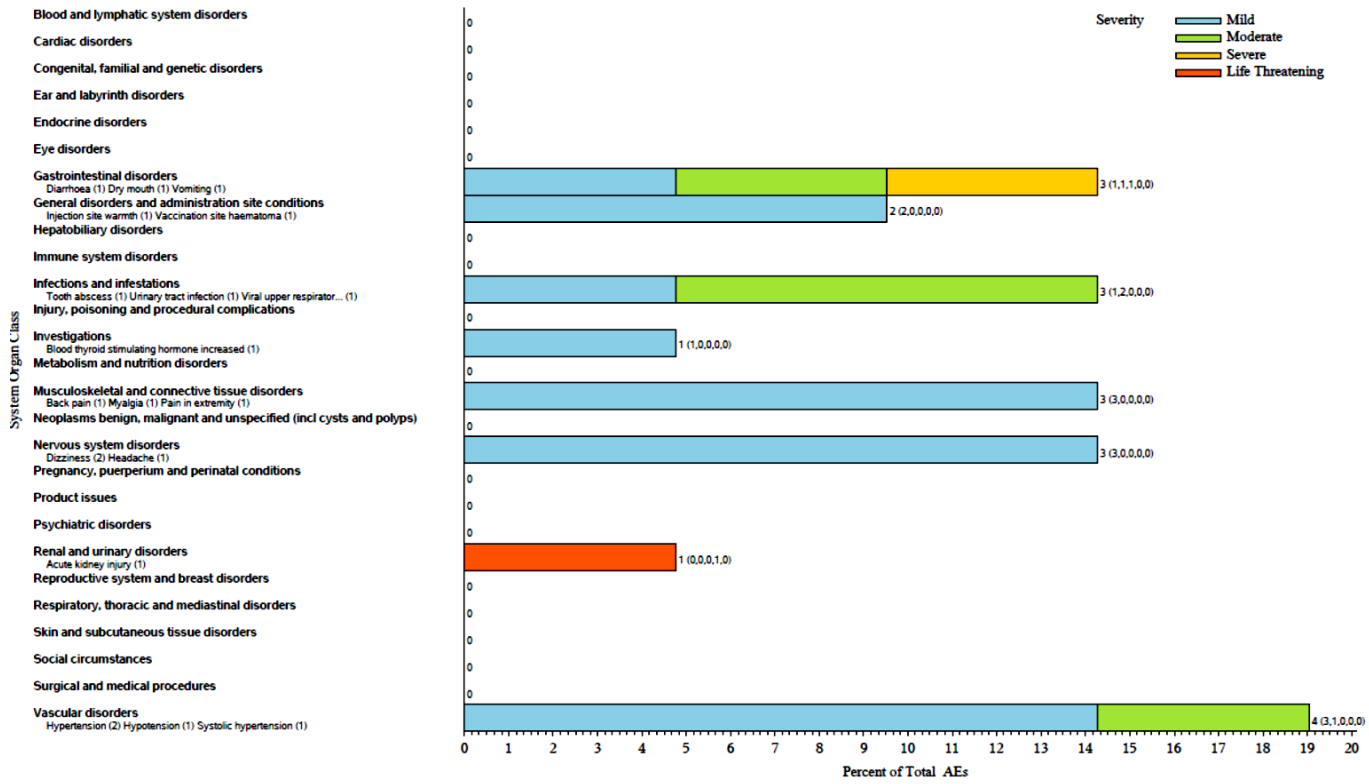


Figure 1b - All Unsolicited Adverse Events by MedDRA System Organ Class and Severity, Group 2E (Dosed Moderna)
Number of Enrolled Participants = 51
Total Number of Participants with one or more AE = 16

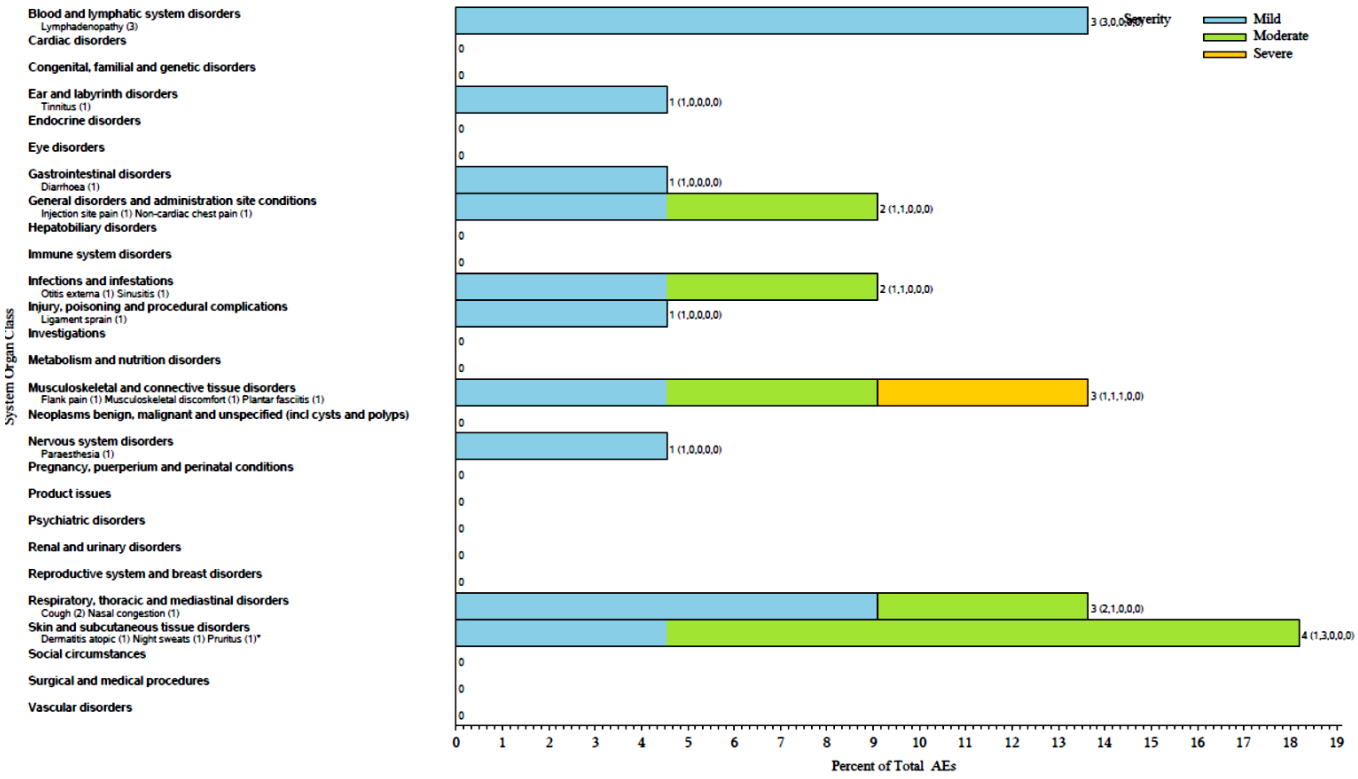


Figure 1c - All Unsolicited Adverse Events by MedDRA System Organ Class and Severity, Group 3E (Dosed Pfizer/BioNTech)
Number of Enrolled Participants = 50
Total Number of Participants with one or more AE = 20

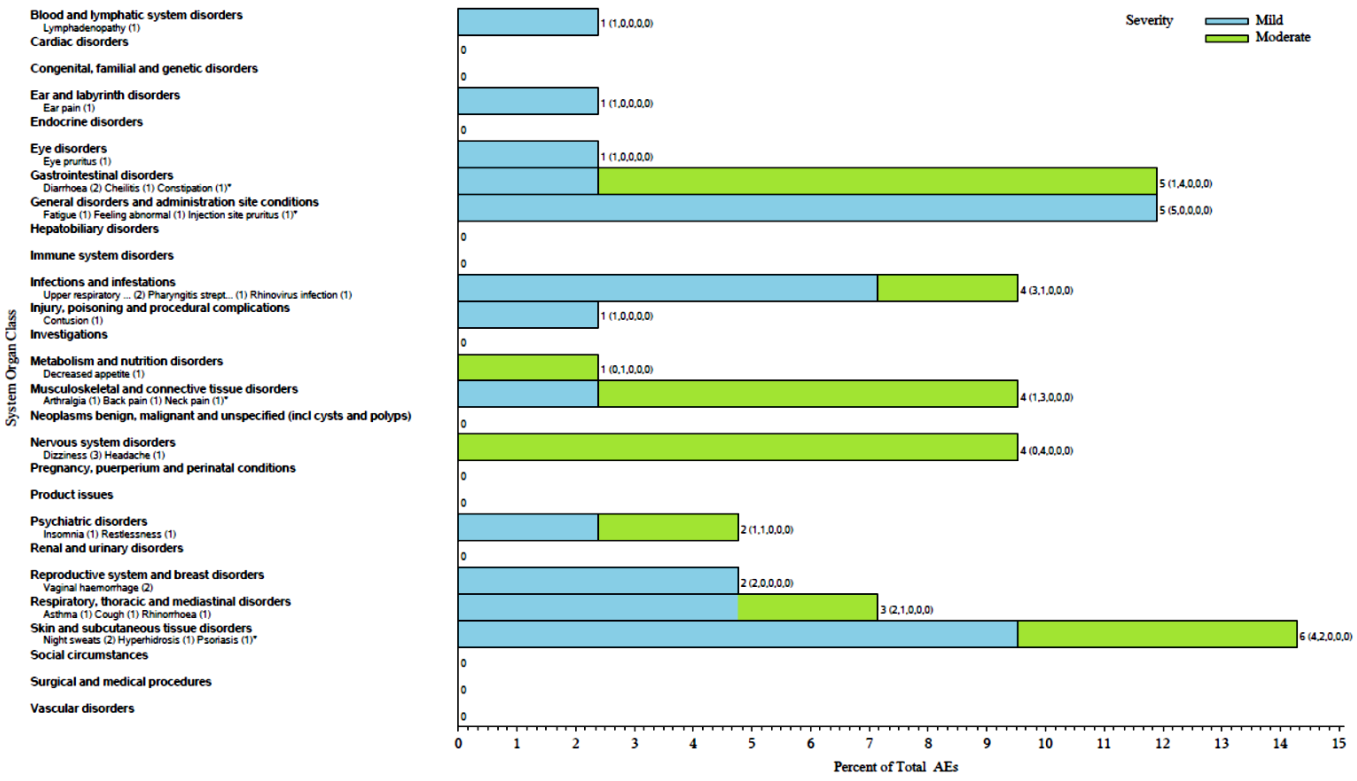


Figure 2a - All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 1E (Dosed Janssen)
Number of Enrolled Participants = 53
Total Number of Participants with one or more AE = 18

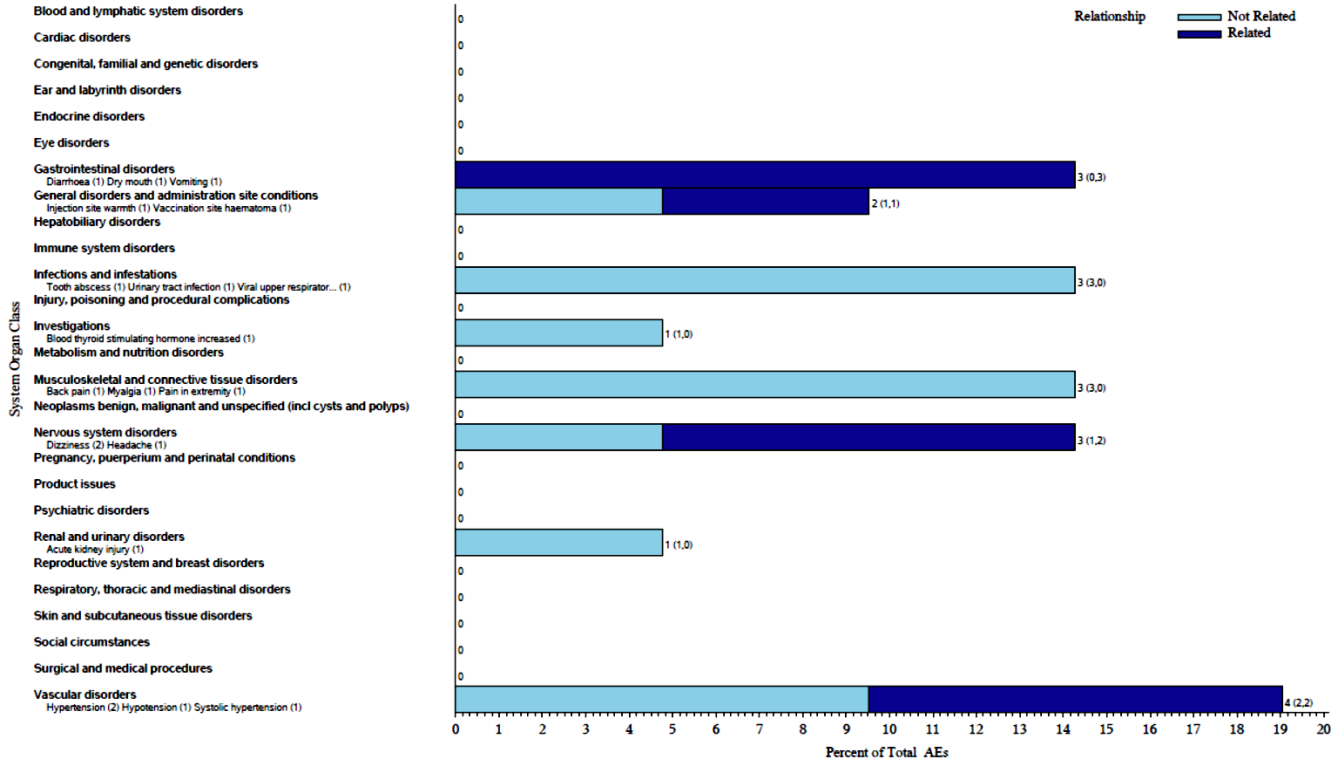


Figure 2b - All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 2E (Dosed Moderna)
Number of Enrolled Participants = 51
Total Number of Participants with one or more AE = 16

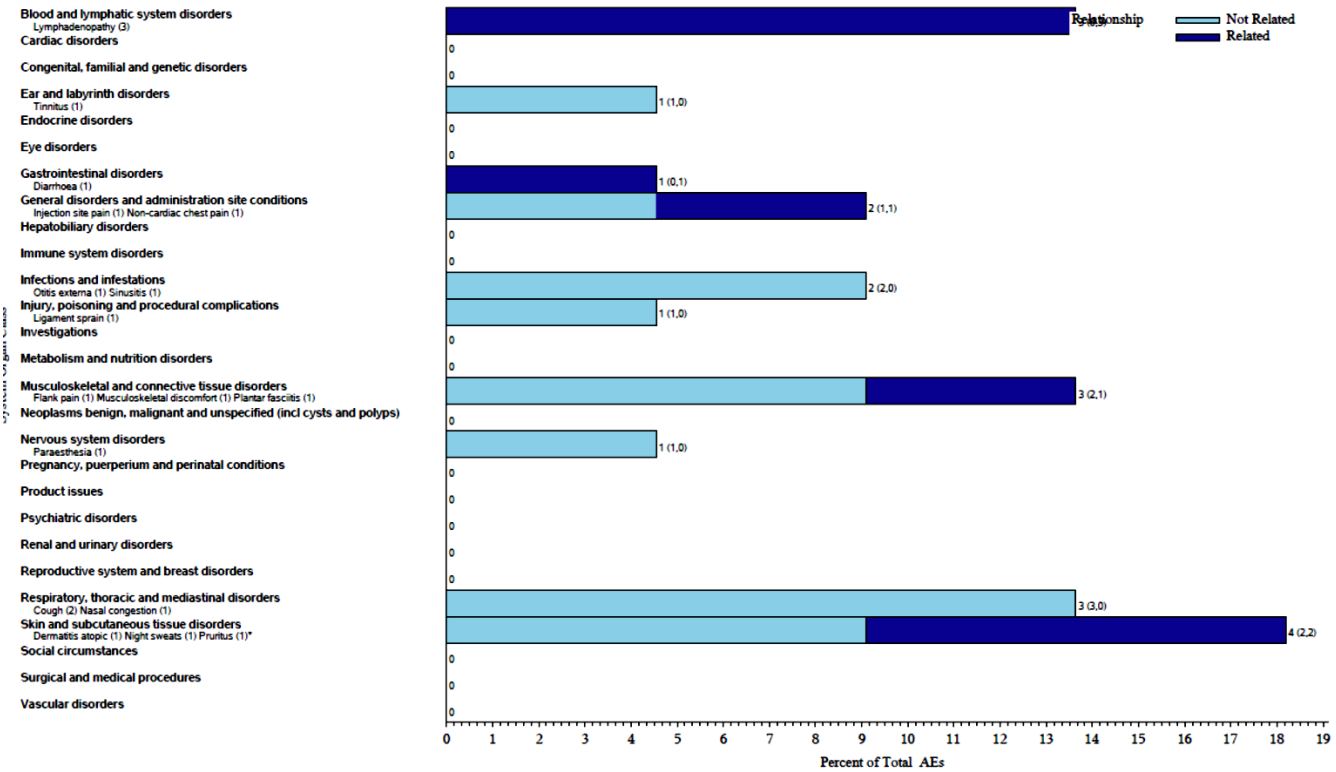
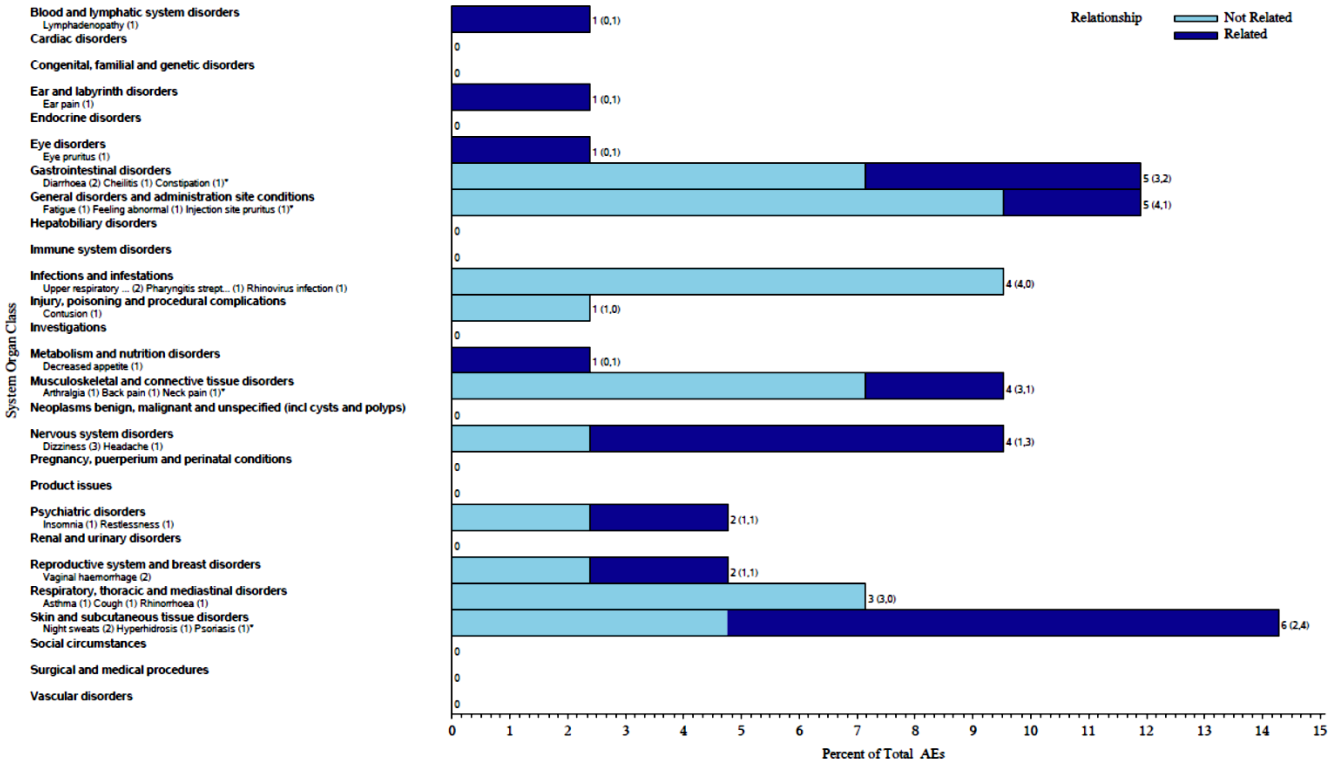


Figure 2c - All Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Product, Group 3E (Dosed Pfizer/BioNTech)
Number of Enrolled Participants = 50
Total Number of Participants with one or more AE = 20



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%)

Severe 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).

Any unsolicited 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 (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).

4.2.3. P205 Part A

As summarised below, no new safety signals have been observed in P205 Part A (as of 20 August 2021). The safety profile observed following the 50 µg or 100 µg mRNA-1273.211 booster in Study P205 Part A is consistent with the safety profile that has been observed for mRNA-1273 in study P201 Part A and in P301 Part A.

Serious Adverse Events (SAE)

Table 14.3.1.12.1
Subject Incidence of Serious TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	 mRNA-1273.211 100 ug (N=596) n (%)	 Total mRNA-1273.211 (N=896) n (%)
Number of Subjects Reporting Serious TEAEs	0	6 (1.0)	6 (0.7)
Number of Serious TEAEs	0	11	11
Infections and infestations	0	3 (0.5)	3 (0.3)
Urinary tract infection	0	2 (0.3)	2 (0.2)
Cellulitis	0	1 (0.2)	1 (0.1)
Urosepsis	0	1 (0.2)	1 (0.1)
Nervous system disorders	0	3 (0.5)	3 (0.3)
Transient ischaemic attack	0	2 (0.3)	2 (0.2)
Dizziness	0	1 (0.2)	1 (0.1)
Cardiac disorders	0	1 (0.2)	1 (0.1)
Bradycardia	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	1 (0.1)
Hypoxia	0	1 (0.2)	1 (0.1)
Hepatobiliary disorders	0	1 (0.2)	1 (0.1)
Cholelithiasis	0	1 (0.2)	1 (0.1)

Table 14.3.1.12.1
Subject Incidence of Serious TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	 mRNA-1273.211 100 ug (N=596) n (%)	 Total mRNA-1273.211 (N=896) n (%)
Investigations	0	1 (0.2)	1 (0.1)
Myocardial necrosis marker increased	0	1 (0.2)	1 (0.1)

Table 14.3.1.12.1 shows the incidence and type of SAEs by system organ class and preferred term within the follow up period of this data extraction. There were no fatal events and the overall incidence of SAEs was equal to 1% (100 µg arm) or below 1% (0% for 50 µg arm, 0.7% for 50 and 100 µg combined). According to the provided Table, SAEs have been reported ONLY in 100 µg dose arm and not in 50 µg Arm.

SAEs of bradycardia at Day 14 post-boost and myocardial necrosis marker increased (reported term: elevated cardiac enzyme) at Day 29 post-boost were reported in one participant in the 100µg arm. This participant is a 70-79- year-old female with risk factors for cardiac disease (hypertension, diabetes mellitus, dyslipidaemia) and a history of chronic sinus bradycardia; she had dizziness in the setting of bradycardia and subsequently had detectable troponins in blood. The events of bradycardia and cardiac enzyme elevation resolved, and the investigator reported the elevated cardiac enzyme as related. There were no ST changes reported in an electrocardiogram and no diagnosis of pericarditis or myocarditis. The event of cardiac enzyme elevation did not occur in the risk period for vaccine-associated myocarditis or pericarditis. Given the multiple cardiac disease risk factors and the history of sinus bradycardia, the MAH assessed the events as unrelated.

The same events of bradycardia and elevated cardiac enzyme (in the same participant) also appear in the MAAE and SAE tables. Otherwise causality was reported by investigators as non-related for all other SAEs.

Unsolicited Medically Attended Adverse Events (MAAE)

Table 14.3.1.17.2
Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

	Part A		
System Organ Class Preferred Term	mRNA-1273.211 50 ug (N=300) n (%)	mRNA-1273.211 100 ug (N=596) n (%)	Total mRNA-1273.211 (N=896) n (%)
Number of Subjects Reporting Unsolicited Medically-Attended TEAEs	46 (15.3)	69 (11.6)	115 (12.8)
Number of Unsolicited Medically-Attended TEAEs	58	101	159
Infections and infestations	22 (7.3)	31 (5.2)	53 (5.9)
Upper respiratory tract infection	3 (1.0)	5 (0.8)	8 (0.9)
Urinary tract infection	3 (1.0)	5 (0.8)	8 (0.9)
Rhinovirus infection	7 (2.3)	0	7 (0.8)
Bronchitis	1 (0.3)	2 (0.3)	3 (0.3)
Suspected COVID-19	0	3 (0.5)	3 (0.3)
Cellulitis	0	2 (0.3)	2 (0.2)
Otitis media acute	0	2 (0.3)	2 (0.2)
Parainfluenzae virus infection	1 (0.3)	1 (0.2)	2 (0.2)
Sinusitis	0	2 (0.3)	2 (0.2)
Tooth abscess	0	2 (0.3)	2 (0.2)
Viral infection	2 (0.7)	0	2 (0.2)
Acute sinusitis	1 (0.3)	0	1 (0.1)
Bacterial vaginosis	1 (0.3)	0	1 (0.1)
COVID-19	1 (0.3)	0	1 (0.1)
Cystitis	1 (0.3)	0	1 (0.1)
Furuncle	0	1 (0.2)	1 (0.1)

Table 14.3.1.17.2
Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	Part A mRNA-1273.211 100 ug (N=596) n (%)	Part A Total mRNA-1273.211 (N=896) n (%)
Infections and infestations (Cont.)			
Gastroenteritis	0	1 (0.2)	1 (0.1)
Gastroenteritis viral	0	1 (0.2)	1 (0.1)
Helicobacter infection	0	1 (0.2)	1 (0.1)
Hordeolum	0	1 (0.2)	1 (0.1)
Impetigo	1 (0.3)	0	1 (0.1)
Nail infection	0	1 (0.2)	1 (0.1)
Otitis media	1 (0.3)	0	1 (0.1)
Pharyngitis streptococcal	1 (0.3)	0	1 (0.1)
Respiratory syncytial virus infection	0	1 (0.2)	1 (0.1)
Tonsillitis	1 (0.3)	0	1 (0.1)
Urosepsis	0	1 (0.2)	1 (0.1)
Viral upper respiratory tract infection	0	1 (0.2)	1 (0.1)
Vulvovaginal candidiasis	0	1 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.2)	1 (0.1)
Malignant melanoma in situ	0	1 (0.2)	1 (0.1)
Blood and lymphatic system disorders	0	3 (0.5)	3 (0.3)
Anaemia	0	1 (0.2)	1 (0.1)
Leukocytosis	0	1 (0.2)	1 (0.1)

Table 14.3.1.17.2
Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	Part A mRNA-1273.211 100 ug (N=596) n (%)	Part A Total mRNA-1273.211 (N=896) n (%)
Blood and lymphatic system disorders (Cont.)			
Lymphadenopathy mediastinal	0	1 (0.2)	1 (0.1)
Immune system disorders	1 (0.3)	0	1 (0.1)
Allergy to chemicals	1 (0.3)	0	1 (0.1)
Endocrine disorders	1 (0.3)	2 (0.3)	3 (0.3)
Hypothyroidism	1 (0.3)	2 (0.3)	3 (0.3)
Metabolism and nutrition disorders	3 (1.0)	6 (1.0)	9 (1.0)
Hypercholesterolaemia	1 (0.3)	3 (0.5)	4 (0.4)
Type 2 diabetes mellitus	0	2 (0.3)	2 (0.2)
Hyperlipidaemia	1 (0.3)	0	1 (0.1)
Hypokalaemia	0	1 (0.2)	1 (0.1)
Hypomagnesaemia	0	1 (0.2)	1 (0.1)
Lactic acidosis	0	1 (0.2)	1 (0.1)
Vitamin D deficiency	1 (0.3)	0	1 (0.1)
Psychiatric disorders	4 (1.3)	3 (0.5)	7 (0.8)
Anxiety	2 (0.7)	2 (0.3)	4 (0.4)
Depression	2 (0.7)	1 (0.2)	3 (0.3)

Table 14.3.1.17.2
Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	Part A mRNA-1273.211 100 ug (N=596) n (%)	Part A Total mRNA-1273.211 (N=896) n (%)
Nervous system disorders	2 (0.7)	5 (0.8)	7 (0.8)
Headache	2 (0.7)	0	2 (0.2)
Transient ischaemic attack	0	2 (0.3)	2 (0.2)
Dizziness	0	1 (0.2)	1 (0.1)
Migraine	1 (0.3)	0	1 (0.1)
Neuropathy peripheral	0	1 (0.2)	1 (0.1)
New daily persistent headache	0	1 (0.2)	1 (0.1)
Eye disorders	0	2 (0.3)	2 (0.2)
Blepharitis allergic	0	1 (0.2)	1 (0.1)
Keratitis	0	1 (0.2)	1 (0.1)
Ear and labyrinth disorders	0	1 (0.2)	1 (0.1)
Ear pain	0	1 (0.2)	1 (0.1)
Cardiac disorders	1 (0.3)	2 (0.3)	3 (0.3)
Bradycardia	0	1 (0.2)	1 (0.1)
Mitral valve incompetence	1 (0.3)	0	1 (0.1)
Palpitations	0	1 (0.2)	1 (0.1)
Vascular disorders	4 (1.3)	3 (0.5)	7 (0.8)
Hypertension	3 (1.0)	1 (0.2)	4 (0.4)

Table 14.3.1.17.2
Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	Part A mRNA-1273.211 100 ug (N=596) n (%)	Part A Total mRNA-1273.211 (N=896) n (%)
Vascular disorders (Cont.)			
Aortic arteriosclerosis	0	1 (0.2)	1 (0.1)
Hypotension	1 (0.3)	0	1 (0.1)
Thrombosis	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	3 (1.0)	4 (0.7)	7 (0.8)
Asthma	1 (0.3)	0	1 (0.1)
Cough	0	1 (0.2)	1 (0.1)
Emphysema	0	1 (0.2)	1 (0.1)
Hypoxia	0	1 (0.2)	1 (0.1)
Paranasal sinus discomfort	1 (0.3)	0	1 (0.1)
Pulmonary mass	0	1 (0.2)	1 (0.1)
Rhinorrhoea	1 (0.3)	0	1 (0.1)
Gastrointestinal disorders	1 (0.3)	2 (0.3)	3 (0.3)
Gastrooesophageal reflux disease	0	2 (0.3)	2 (0.2)
Diarrhoea	1 (0.3)	0	1 (0.1)
Hepatobiliary disorders	0	1 (0.2)	1 (0.1)
Cholelithiasis	0	1 (0.2)	1 (0.1)

Table 14.3.1.17.2
Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	 mRNA-1273.211 100 ug (N=596) n (%)	 Total mRNA-1273.211 (N=896) n (%)
Skin and subcutaneous tissue disorders	1 (0.3)	5 (0.8)	6 (0.7)
Rash	1 (0.3)	1 (0.2)	2 (0.2)
Hidradenitis	0	1 (0.2)	1 (0.1)
Precancerous skin lesion	0	1 (0.2)	1 (0.1)
Pruritus	0	1 (0.2)	1 (0.1)
Rosacea	0	1 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders	5 (1.7)	10 (1.7)	15 (1.7)
Arthralgia	1 (0.3)	2 (0.3)	3 (0.3)
Muscle spasms	0	2 (0.3)	2 (0.2)
Osteoarthritis	0	2 (0.3)	2 (0.2)
Back pain	0	1 (0.2)	1 (0.1)
Fibromyalgia	1 (0.3)	0	1 (0.1)
Musculoskeletal chest pain	0	1 (0.2)	1 (0.1)
Myalgia	0	1 (0.2)	1 (0.1)
Neck pain	1 (0.3)	0	1 (0.1)
Osteoporosis	0	1 (0.2)	1 (0.1)
Pain in extremity	1 (0.3)	0	1 (0.1)
Rotator cuff syndrome	0	1 (0.2)	1 (0.1)
Spondylitis	1 (0.3)	0	1 (0.1)

Table 14.3.1.17.2
Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	 mRNA-1273.211 100 ug (N=596) n (%)	 Total mRNA-1273.211 (N=896) n (%)
Renal and urinary disorders	1 (0.3)	0	1 (0.1)
Bladder mass	1 (0.3)	0	1 (0.1)
Reproductive system and breast disorders	1 (0.3)	0	1 (0.1)
Benign prostatic hyperplasia	1 (0.3)	0	1 (0.1)
General disorders and administration site conditions	0	4 (0.7)	4 (0.4)
Fatigue	0	1 (0.2)	1 (0.1)
Pain	0	1 (0.2)	1 (0.1)
Pyrexia	0	1 (0.2)	1 (0.1)
Vaccination site lymphadenopathy	0	1 (0.2)	1 (0.1)
Investigations	1 (0.3)	3 (0.5)	4 (0.4)
Blood pressure increased	0	1 (0.2)	1 (0.1)
Cardiac murmur	0	1 (0.2)	1 (0.1)
Lipids abnormal	1 (0.3)	0	1 (0.1)
Myocardial necrosis marker increased	0	1 (0.2)	1 (0.1)
White blood cell count increased	0	1 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	2 (0.7)	4 (0.7)	6 (0.7)
Concussion	1 (0.3)	1 (0.2)	2 (0.2)

Table 14.3.1.17.2
Subject Incidence of Unsolicited Medically-Attended TEAEs by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

System Organ Class Preferred Term	Part A mRNA-1273.211 50 ug (N=300) n (%)	 mRNA-1273.211 100 ug (N=596) n (%)	 Total mRNA-1273.211 (N=896) n (%)
Injury, poisoning and procedural complications (Cont.)			
Ligament sprain	1 (0.3)	1 (0.2)	2 (0.2)
Tooth fracture	0	2 (0.3)	2 (0.2)
Spinal column injury	0	1 (0.2)	1 (0.1)

Table 14.3.1.17.2 shows the incidence and type of unsolicited MAAEs by system organ class and preferred term within the follow up period of the data extraction for study P205 part A. The overall incidence of unsolicited MAAE was 12.8% in both arms combined (15.3 % in the 50 µg arm, 11.6% in the 100 µg arm).

There were three events of suspected COVID-19 which had a negative SARS-CoV-2 PCR and therefore these events are not confirmed COVID-19. An additional event of COVID-19 occurred 22 days post-boost in a study participant who was reported to be asymptomatic.

An event of intermittent palpitations was reported in one study participant (100 µg arm) approximately 14 days after the booster. Palpitations were reported as non-serious and not related in the setting of a concussion and cervical spine injury in this participant. Lastly, causality was reported by investigators as non-related for all MAAEs except for an event of fever, an event of worsening of hypothyroidism and an event of supraclavicular lymphadenopathy.

Adverse Events of Special Interest (AESI)

Table 14.3.1.19.2
Subject Incidence of TEAEs of Special Interest (mRNA1273-205 Protocol-Specified) by System Organ Class and Preferred Term up to the Data Cutoff Date
Safety Set

	Part A		
System Organ Class Preferred Term	mRNA-1273.211 50 ug (N=300) n (%)	mRNA-1273.211 100 ug (N=596) n (%)	Total mRNA-1273.211 (N=896) n (%)
Number of Subjects Reporting TEAEs of Special Interest	2 (0.7)	2 (0.3)	4 (0.4)
Number of TEAEs of Special Interest	2	2	4
Infections and infestations	1 (0.3)	1 (0.2)	2 (0.2)
COVID-19	1 (0.3)	1 (0.2)	2 (0.2)
Vascular disorders	1 (0.3)	0	1 (0.1)
Hypotension	1 (0.3)	0	1 (0.1)
Investigations	0	1 (0.2)	1 (0.1)
Myocardial necrosis marker increased	0	1 (0.2)	1 (0.1)

Table 14.3.1.19.2 shows the incidence and type of AESIs by system organ class and preferred term within the follow up period of the data extraction for study P205 part A. The incidence of AESI was 0.4% for both dose arms combined (0.7% in the 50µg arm and 0.3% in 100µg arm).

Two events of COVID-19 are shown in the AESI table: (i) one event occurring 82 days after the 50µg dose of mRNA-1273.211. The event was reported as mild and has resolved and, (ii) an event, which corresponded to a study P205 screening PCR test, therefore this event reflects a pre-booster SARS-CoV-2 infection.

Other AEs of clinical relevance

The MAH searched for PTs as angioedema, arthritis, cardiomyopathy, central nervous system (CNS) vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis.

No participants had events in the SMQs of vasculitis, demyelination, or convulsions. An event of swollen tongue was reported in the 50µg arm approximately 7 days after administration of the booster. The event was reported as non-serious, unrelated and it resolved. Two events of transient ischemic attack (TIA) were reported, both in the 100 µg arm. In one study participant TIA was reported approximately 15 days after the booster as serious and non-related and it resolved. The participant was a 50-59 year old female with complex medical history, including among others relevant chronic conditions like insulin resistant, Hashimoto thyroiditis, migraine, hypoadrenalism, anxiety, major depression, anaemia, and hyperlipidaemia. The concomitant medication consisted of more than 20 drugs including amphetamine, and progesterone. In the other study participant TIA was reported as serious and non-related approximately one month after the booster and it also resolved. The subject was a 60-69 year old male. The subject's medical history, as provided by the investigator, included sinus surgery, nasal polyp, and

gout. Concomitant medications included baking soda. The events of thrombosis and thrombophlebitis were reported in a 50-59-year-old female (100µg arm) with a leg blood clot approximately 18 days after the booster. Medical history, as provided by the investigator, included chronic obstructive pulmonary disease, depression, bilateral knee pain, neuropathy (bilateral). Concomitant medications reported included escitalopram oxalate, tramadol, pregabalin, fluticasone furoate, umeclidinium, vilanterol and paracetamol. Per the investigator, medical records did not support a diagnosis of deep vein thrombosis. The events were non-serious, considered as being non-related by the investigator and were reported to be resolving.

Palpitations were reported in two study participants (100 µg arm). Information is provided under the MAAE section for one study participant. The event of palpitations in the other participant was non-serious and not medically attended.

P205 Part A - Conclusion

Overall, the adverse event data extracted on 20 August 2021 from study P205 part A (50 and 100 µg arm of booster mRNA-1273.211, which contains 25 and 50 µg of mRNA 1273 in the two arms respectively) support that the safety profile of the mRNA-173.211 is consistent with the safety profile of mRNA-1273 in studies P201 and P301, regardless of the dose level. Administration of the booster vaccine was well tolerated by the P205 part A study participants.

4.3. Discussion

Three studies have been submitted to support the current type II variation.

P201 Part B (considered as main study for this variation)

In the Phase 2 Study P201 Part B, which is pivotal for this variation, and was conducted at 8 sites in US, 344 participants who had received 2 doses of 50 µg (n=171) or 100 µg (N=173), respectively, were administered a third dose of 50 µg of mRNA-1273 approximately 6 months after primary vaccination for the evaluation of safety.

Beside a higher proportion of female subjects compared to male subjects, all other characteristics were comparable between both dose groups.

All actively enrolled participants aged 18 years and above were followed-up more than 4.5 months of safety, and there is ongoing safety follow-up of the participants. Data from P201 Part B participants until Day 29 were summarised, as well as SAEs, MAAEs, and any additional reported unsolicited AEs from the live, ongoing database through 16 August 2021.

The Phase 2a study included 2 age cohorts: Cohort 1 ≥ 18 to < 55 years old and Cohort 2 ≥ 55 years old. No children or adolescents were enrolled in the booster studies.

Solicited

Solicited local and systemic reaction were followed-up up to seven days after the booster dosage of 50 µg of mRNA-1273 in study P201.

The frequencies of reported solicited local and systemic ARs in study P201 were comparable between booster doses both primarily vaccinated with 50 µg or 100 µg of Spikevax and comparable to the safety profile of primary vaccination schedules in P201 Part A as well as to the safety profile of the primary vaccination schedule in the pivotal study P301 except of lymphadenopathy (local) of low grade, which has had a higher incidence in P201 Part B after booster dose. In case of fever, myalgia and nausea (all systemic) booster dose could have even numerically better safety profile. As numbers of subjects are low

in P201 Part B, generally the safety profile in terms of solicited AEs seems comparable to what is already known from other studies.

Reported frequencies of solicited systemic reactions were comparable also between both age strata. This is also indirectly noticeable as both age strata took medication in comparable amounts to prevent pain around 8 % and to prevent fever around 45 %.

The MAH applies for a booster indication for adolescents and adults aged 12 years and above. However, no safety data were provided by the MAH for the age group of adolescents aged 12 to 17 years after a booster dose. The CHMP is therefore of the opinion that the age limit should be adapted to the population studied in the provided dossier.

Unsolicited

Unsolicited treatment-emergent adverse events (TEAEs) were systematically collected during the 28-day time window after the booster dose.

Additionally, adverse events leading to discontinuation from study participation, SAEs, MAAEs, and pregnancies are being collected from Day 1 through the entire study period or until the last day of study participation.

Unsolicited TEAEs were infrequent and mild to moderate in severity. Some commonly reported unsolicited TEAEs were solicited events that continued beyond Day 7, such as headache and fatigue.

From the data overall it appears that the booster caused less AE after priming with 50 µg dose compared to 100 µg priming dose. This observation is not further pursued as the evidence on VE is limited to the 100 µg priming doses.

No cases of myocarditis, pericarditis, or relevant AEs suggestive of any of these conditions were observed up to Day 29 in P201 Part B.

There were no SAEs or AEs leading to study discontinuation. Review of SAEs and MAAEs from the live clinical database up to 16 August 2021 (after the 28-day window) showed 4 participants with 5 SAEs, all of which were assessed as unrelated to study vaccine. These included 1 SAE of pericarditis, which started the same day as angina pectoris in an 80-89-year-old female participant 89 days after the booster of a 50 µg prime group and which resolved 95 days after booster and then recurred from 122-127 days after the booster. Both pericarditis events were deemed unrelated to mRNA-1273. The SAE of pericarditis is not consistent with the characteristics of post-authorisation cases of pericarditis possibly related to vaccination. Myocarditis and pericarditis are risks that are under investigation as described in the mRNA-1273 Risk Management Plan (RMP).

No deaths were reported in Study P201 Part A (P201 Part A: CSR Addendum) or among P201 Part B booster participants.

The following were considered AEs of clinical interest and did not occur: angioedema, arthritis, cardiomyopathy, central nervous system (CNS) vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis. In addition, myocarditis and pericarditis have been actively searched for.

No participants had AEs of clinical interest of vasculitis, peripheral neuropathy, demyelination, convulsions, CNS haemorrhage and cerebrovascular conditions, embolic and thrombotic events, thrombophlebitis, hematopoietic cytopenias, or cardiomyopathy. There were 2 related cases of suspected arthritis, 1 unrelated event of angioedema, 2 cases of hypersensitivity, 1 of which was related and manifested with long-lasting rash from day 2 to day 30 post booster, 3 hearing and vestibular disorders, 1 of them was vertigo that could be related. Within the 28-day time window post-booster in P201 Part B,

no cases of myocarditis or pericarditis were confirmed. Two participants in the 50 µg prime group had adverse events mapping to relevant clinical symptoms for the evaluation of myocarditis or pericarditis; however, in both cases, the events occurred in participants 60-79 years old, beyond 7 days following the booster. The first case is a nonserious grade 2 dyspnoea on exertion in a 60-69-year-old female 78 days after the booster, which resolved 112 days after the booster dose. The second participant is a 70-79-year-old female with nonserious premature ventricular contractions, assessed as unrelated by the investigator to mRNA-1273, which started 92 days after the booster and were ongoing as of 16 August 2021. It is acknowledged that myo- and pericarditis in Part B of Study 201 did not raise any concerns.

There were no pregnancies reported following on-study testing in P201 Part B within the 28-day time window post-booster in P201 Part B or within the 28-day time window post any injection in P201 Part A. After this period 3 pregnancies were noted. 2 of them ended with miscarriage and one as spontaneous abortion. All events were considered not related to the booster.

DMID Study 21-0012 (considered supportive)

DMID 21-0012 is considered to be a supportive study only as here heterologous vaccination has been evaluated.

Safety profile of solicited and unsolicited ARs was evaluated in the supportive DMID Study 21-0012 with heterologous/homologues (Moderna) SARS-CoV-2 vaccine dosing (mRNA-1273 booster) study of the various EUA vaccines (Janssen, Moderna, Pfizer/BioNTech) in participants' ≥ 18 years old. A total of 154 participants have been enrolled and received an mRNA-1273 boost injection (IM; 100 µg) approximately 12-20 weeks after receiving primary vaccination under EUA.

It must be noted, that even the homologues Moderna-arm in DMID Study 21-0012 is not comparable to the proposed booster dose of 50 µg of mRNA-1273 (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). Therefore, results must be taken as supportive only.

Solicited

Solicited local and systemic reaction were followed-up up to seven days after the booster dosage of 100 µg of mRNA-1273.

Subjects reported with a higher frequency solicited local ARs after priming with Janssen-vaccine and boost with Spikevax compared to both other groups where priming and boost were administered mRNA-vaccines. Only induration was reported with a lower frequency in the Janssen group compared to the Comirnaty and Spikevax groups.

Beside fever all other solicited systemic ARs were more frequently reported after the heterologous booster with a vector-based as primary series followed by an mRNA-vaccine. The safety profile was however comparable of primary series with an mRNA vaccine followed by Spikevax regarding solicited systemic events.

Unsolicited

Most participants experienced mild or moderate AEs. The most common AE related to study vaccine was lymphadenopathy.

From the 53 participants in group 1E (EUA dosed Janssen, boost Moderna) 18 participants reported 21 unsolicited AEs.

From the 51 participants in group 2E (EUA dosed Moderna, boost Moderna) 16 participants reported 22 unsolicited AEs.

From the 50 participants in Group 3E (EUA dosed Pfizer/BioNTech, boost Moderna) 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. That could mean that homologous boosting with Spikevax has had the best safety profile.

As to severe AEs there was 1 grade 3 AE of vomiting after boosting in the Janssen 1E cohort and in neither arm any grade 4 or grade 5 AEs.

No deaths and no SAEs had occurred at the time of the data snapshot. Also, no participants have withdrawn early for any reason. No pregnancies have been noted.

P205 Part A (considered supportive)

This is a study not included in the efficacy/immunogenicity analysis in section 6 of this AR and is assessed only as supportive in the safety analysis.

Study P205 is an open-label, Phase 2/3 study to evaluate the immunogenicity, safety, and reactogenicity of SARS-CoV-2 variant-matched vaccines, administered as a booster in adult participants of the mRNA-1273-P301 study who had previously received 2 doses of mRNA-1273 as a primary series. These participants received the second study dose at least 6 months prior to the administration of the booster.

In study P205 part A specifically, participants received either 50 or 100 µg (total mRNA content) of vaccine 1273.211, as a booster. As this booster has had another compound comparing to the P201 study, results are only supportive and actually not really valid for the currently requested extension of indication.

From scientific point of view, it is considered interesting to compare two booster doses 50 µg vs. 100 µg, considering the limitations above. Patients have been randomised 2:1 (100 µg vs. 50 µg).

No new safety signals have been observed in P205 Part A.

SAEs have been observed more frequently in 100 µg Arm than in the 50 µg arm (n= 11 vs. 0), which per extrapolation favours the 50 µg dose chosen in the study 201 part B.

There were no fatal events.

SAEs of bradycardia at Day 14 post-boost and myocardial necrosis marker increased (reported term: elevated cardiac enzyme) at Day 29 post-boost were reported in 1 participant in the 100 µg arm. This participant is a 70-79- year-old female with risk factors for cardiac disease (hypertension, diabetes mellitus, dyslipidaemia) and a history of chronic sinus bradycardia. The investigator reported the elevated cardiac enzyme as related, however the MAH assessed the events as unrelated.

The percentage (considering the randomisation 2:1) of unsolicited medically –attended TEAEs and also subjects reporting them was similar between 50 and 100 µg (15.3% vs 11.6% of subjects).

The MAH clarified an event of intermittent palpitations that was reported in one study participant (100µg arm) approximately 14 days after the booster. Palpitations were reported as non-serious and not related in the setting of a concussion and cervical spine injury in this participant. Lastly, causality was reported by investigators as non-related for all MAAEs except for an event of fever, an event of worsening of hypothyroidism and an event of supraclavicular lymphadenopathy. No other MAAE with higher frequency is considered relevant to discuss here.

Considering AESIs, one participant in the 50 µg arm had COVID-19 with mild event. 1 subject has hat hypotension and 1 non-related myocardial necrosis marker. No participants had events in the SMQs of

vasculitis, demyelination, or convulsions. An unrelated and resolved event of swollen tongue in the 50 µg arm approximately 7 days after administration of the booster. Two events of unrelated transient ischemic attack (TIA) were reported in 2 participants, both in the 100µg arm. The events of thrombosis and thrombophlebitis were reported in one study participant (100 µg arm) with a leg blood clot approximately 18 days after the booster. The events were non-serious and non-related and were reported to be resolving. Palpitations were reported in two participants (100µg arm). One event was MAAE and the other one not medically attended.

Conclusions

To date, the reactogenicity and safety profile of the booster seems to be consistent with that observed following the primary series in P301, which included 30,346 study participants, and P201 Part A. No new unexpected safety concerns have been identified from a booster dose. Slight imbalances however, in unsolicited AEs have been noted related to the priming dose but this is not considered relevant for this procedure.

As to the appropriateness of 50 µg booster dose, as part of initial dose ranging of mRNA-1273 (P201 Part A), both 50 and 100 µg were evaluated. Both dosages induced substantial neutralising antibody. While the 100 µg dosage was advanced to the pivotal trial (P301), it was postulated that a 50 µg booster dose would be effective in briskly activating recall responses. The trend toward lower reactogenicity observed for the 50 µg dose in P201 Part A also supported this selection. Finally, there is precedence for a booster dose to be lower than the priming vaccine dose. For example, Tdap, the booster for the DTaP vaccine, has a reduced dose of the diphtheria and pertussis vaccines and is intended to boost the immunity that wanes after primary vaccination. The rationale to recommend the lower 50 µg dose for boosting seems to be supported also by the fact that this dose has had numerically better safety in elderly comparing to 100 µg.

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 mRNA-1273 further seem to support a similar reactogenicity and safety profile within the 7 days following the administration of the booster dose.

In the post-authorisation period, a total of 301,035,380 doses have been distributed worldwide. Rare cases of anaphylaxis, myocarditis, and pericarditis events have been reported during the post-authorisation period from healthcare professionals and spontaneously reported from patients. The risk of these events after a booster dose cannot be determined due to the sample size that can be achieved prior to an approval.

The MAH commits to amend Study P301 (COVE, the pivotal efficacy and safety study) to administer the booster dose, after which participants will continue to be followed for breakthrough disease. The MAH would also amend Study P901, the effectiveness study that is currently ongoing with Kaiser Permanente Southern California to follow effectiveness after the booster dose, which will also contribute extensive information on future protection against VOC.

Given the urgency of investigating the safety and effectiveness of booster doses as the epidemiological landscape of the pandemic evolves, it was too early to evaluate participants primed more than 9 months ago. The MAH considers that it is reasonable to assume that the booster effect regarding immunogenicity will be similar in people who received their primary series more than 6-8 months prior to their booster (for this, please see the efficacy assessment). Following a request from the CHMP during the evaluation, the MAH confirmed, that two large, population-based studies ("real-world" settings), one in the US and one in the EU (mRNA-1273-P903 and mRNA-1273-P904), are planned to be conducted to evaluate the safety after any dose of Spikevax. Study mRNA-1273-P904 is listed in the EU RMP with applicable timelines. In addition, the pivotal efficacy trial mRNA-1273-P301 Part C will evaluate the immunogenicity

and safety of a booster dose given approximately 8 months to 12 months after the primary series. Recent amendments to the study protocol incorporated Part C, which is the booster Dose Phase. The 2 large population based studies are not per se designed to evaluate a booster dose of Spikevax as primary objective. The primary objective is to assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group (Study protocol P904 has been reviewed as part of MEA 004). The quality and amount of data to assess the safety of a booster dose can therefore not be profoundly estimated so far for these 2 studies. However, in combination with Part C of Study P301 it can be expected that meaningful safety and immunogenicity data over time can be provided, also for individuals who did not receive the booster vaccination exactly 6 months after primary immunisation.

Finally, it can be concluded that the reactogenicity profile of the third dose regarding solicited and unsolicited ARs seems to be in line with the data reported after administration of the second dose. However, the submitted data is limited in terms of the numbers of vaccinees included in the study and the duration of follow up does therefore not allow any firm conclusions regarding the pattern and incidence of uncommon or rare AEs/SAEs.

Additionally, safety data have not been submitted in any study in the current submission dossier for subjects below the age of 18 years, which is a limitation for safety and immunogenicity.

4.4. Other information

To support the withdrawal of a maximum of 20 doses of 0.25 mL each from the 5 mL multidose vial respective studies were performed. The presented data support a maximum of 20 punctures per vial. No change to the in use stability conditions given in the product information are proposed with this variation. This is considered acceptable by the CHMP.

5. Changes to the Product Information

As a result of this variation, sections 2, 4.2, 4.4, 4.8, 5.1, 6.5 and 6.6 of the SmPC are being updated to provide information on a booster dose in individuals aged 18 years and older. The labelling and the Package Leaflet (PL) are updated accordingly. Please refer to Attachment 1.

6. Request for supplementary information

6.1. Other concerns

Clinical aspects

Efficacy

1. The MAH is asked to provide additional subgroup analysis to conclude on the benefit of a third dose in different age groups. The following subgroup analysis should be provided:

- For study P201 part B a subgroup analyses of the nAb response stratified according to age (≥18-<65 years and ≥65 years) and by priming dose (50 µg dose and 100 µg dose group separately) employing the WT based Pseudovirus neutralisation assay.
- For study P201 part B a subgroup analyses of the nAb response stratified according to age (≥18-<55 years and ≥55 years) and by priming dose (50 µg dose and 100 µg dose group separately) employing the Delta based Pseudovirus neutralisation assay.

- For study P201 part B a subgroup analyses of the nAb response stratified according to age (≥18-<65 years and ≥65 years) and by priming dose (50 µg dose and 100 µg dose group separately) employing the Delta based Pseudovirus neutralisation assay.
- For study P201 part B information on the number of subjects who still had a detectable nAb antibody response to the Delta variant pre dose 3 should be provided.
- For the non-inferiority analyses of the SRR based on the assay specific 3.3-fold criterion the subgroup analysis stratified according to primary dose series should be provided. This analysis could not be located in the submitted tables although the MAH's claims that NI was established for the 100 µg primary dosing group based on the 3.3-fold criterion.

2. Currently no data are available on the durability of a 50 µg booster dose or immunogenicity data comparing directly the response of a 100 µg and 50 µg booster dose. The MAH should discuss the appropriateness of the 50 µg dose and whether any plans are in place to evaluate the durability of the nAb response over time.
3. Data in younger subjects below 18 years are missing. The MAH is invited to discuss whether there are any plans to evaluate a third dose in children and adolescents.

Safety

4. The MAH considers that it is reasonable to assume that the booster effect regarding immunogenicity will be similar in people who received their primary series more than 6-8 months prior to the booster. As a post-approval commitment, the MAH is asked to collect and submit upcoming safety and immunogenicity data from subjects having received their booster dose more than 6 months post primary vaccination.
5. The MAH is asked to comment on plans that are in place to evaluate safety data and the immune response over time.
6. In the ongoing trial P205 two events of TIA occurred in 2 subjects and thrombosis and thrombophlebitis in one subject. In the submitted dossier no clinical information could be found. The MAH is asked to provide narratives or any clinical information available so far. (Q added following comments received)

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

7.1. Other concerns

Clinical aspects

Efficacy

Question 1

Summary of the MAH's response

The requested outputs were provided with this submission and are summarised below:

nAb responses against the parental strain according to priming group:

Table 14.2.2.1.4.1.2
Summary of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers after Booster Injection by Age Group (<65, >=65)
Per-Protocol Set (Part B, Open-Label Phase)
Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118)

Timepoint Data Category Statistic	Overall mRNA-1273 50 µg - Boost (N=146)	 100 µg - Boost (N=149)	 Total (N=295)
Baseline (OL-Day 1)			
n[1]	145	149	294
GMT	104.658	150.224	125.696
95% CI [2]	88.282, 124.070	125.726, 179.495	111.011, 142.325
Median	126.159	138.385	131.032
Min, Max	9.25, 2238.93	9.25, 4393.49	9.25, 4393.49

Timepoint Data Category Statistic	Overall mRNA-1273 50 µg - Boost (N=146)	 100 µg - Boost (N=149)	 Total (N=295)
OL-Day 29			
n[3]	146	149	295
GMT	1834.309	1951.735	1892.708
95% CI [2]	1600.233, 2102.623	1729.606, 2202.392	1728.800, 2072.157
Median	1861.152	2001.124	1968.267
Min, Max	147.58, 16923.82	468.88, 45929.62	147.58, 45929.62
N1	145	149	294
GMFR	17.53	12.99	15.06
95% CI [2]	14.94, 20.56	11.04, 15.29	13.43, 16.89
Seroconversion [4]			
n[5] (%)	134 (92.4)	131 (87.9)	265 (90.1)
95% CI [6]	86.8, 96.2	81.6, 92.7	86.1, 93.3
Seroresponse [7]			
n[5] (%)	139 (95.9)	136 (91.3)	275 (93.5)
95% CI [6]	91.2, 98.5	85.5, 95.3	90.1, 96.1
>=2-fold Increase from Baseline [8]			
n[5] (%)	143 (98.6)	146 (98.0)	289 (98.3)
95% CI [6]	95.1, 99.8	94.2, 99.6	96.1, 99.4
>=3-fold Increase from Baseline [8]			
n[5] (%)	140 (96.6)	141 (94.6)	281 (95.6)
95% CI [6]	92.1, 98.9	89.7, 97.7	92.6, 97.6
>=4-fold Increase from Baseline [8]			
n[5] (%)	134 (92.4)	131 (87.9)	265 (90.1)
95% CI [6]	86.8, 96.2	81.6, 92.7	86.1, 93.3

nAb responses against the parental strain according to priming group and age group:

Table 14.2.2.1.4.1.2
Summary of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers after Booster Injection by Age Group (<65, >=65)
Per-Protocol Set (Part B, Open-Label Phase)
Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118)

Timepoint Data Category Statistic	Cohort 1 (Age >= 18 and age < 65) mRNA-1273 50 µg - Boost (N=107)	 100 µg - Boost (N=112)	 Total (N=219)	Cohort 2 (Age >= 65) mRNA-1273 50 µg - Boost (N=39)	 100 µg - Boost (N=37)	 Total (N=76)
Baseline (OL-Day 1)						
n[1]	106	112	218	39	37	76
GMT	118.224	177.246	145.567	75.144	91.051	82.507
95% CI [2]	97.666, 143.111	145.536, 215.865	126.677, 167.273	52.690, 107.165	63.085, 131.415	64.248, 105.956
Median	132.879	161.754	145.607	63.844	104.407	93.991
Min, Max	9.25, 2238.93	9.25, 4393.49	9.25, 4393.49	9.25, 909.62	9.25, 1043.04	9.25, 1043.04

Timepoint Data Category Statistic	Cohort 1 (Age >= 18 and age < 65) mRNA-1273 50 µg - Boost (N=107)	100 µg - Boost (N=112)	Total (N=219)	Cohort 2 (Age >= 65) mRNA-1273 50 µg - Boost (N=39)	100 µg - Boost (N=37)	Total (N=76)
OL-Day 29						
n[3]	107	112	219	39	37	76
GMT	1813.744	2069.624	1940.385	1891.934	1634.259	1761.773
95% CI [2]	1552.715, 2118.655	1800.990, 2378.327	1749.486, 2152.116	1409.873, 2538.820	1277.127, 2091.257	1458.189, 2128.561
Median	1811.035	2138.687	1966.021	2446.904	1902.578	1987.464
Min, Max	230.54, 16923.82	539.95, 45929.62	230.54, 45929.62	147.58, 10066.56	468.88, 9888.53	147.58, 10066.56
N1	106	112	218	39	37	76
GMFR	15.34	11.68	13.33	25.18	17.95	21.35
95% CI [2]	12.68, 18.57	9.77, 13.96	11.70, 15.20	19.25, 32.93	12.40, 25.97	17.06, 26.73
Seroconversion [4]						
n[5] (%)	96 (90.6)	98 (87.5)	194 (89.0)	38 (97.4)	33 (89.2)	71 (93.4)
95% CI [6]	83.3, 95.4	79.9, 93.0	84.1, 92.8	86.5, 99.9	74.6, 97.0	85.3, 97.8
Seroresponse [7]						
n[5] (%)	100 (94.3)	102 (91.1)	202 (92.7)	39 (100)	34 (91.9)	73 (96.1)
95% CI [6]	88.1, 97.9	84.2, 95.6	88.4, 95.7	91.0, 100.0	78.1, 98.3	88.9, 99.2
>=2-fold Increase from Baseline [8]						
n[5] (%)	104 (98.1)	109 (97.3)	213 (97.7)	39 (100)	37 (100)	76 (100)
95% CI [6]	93.4, 99.8	92.4, 99.4	94.7, 99.3	91.0, 100.0	90.5, 100.0	95.3, 100.0
>=3-fold Increase from Baseline [8]						
n[5] (%)	101 (95.3)	106 (94.6)	207 (95.0)	39 (100)	35 (94.6)	74 (97.4)
95% CI [6]	89.3, 98.5	88.7, 98.0	91.2, 97.5	91.0, 100.0	81.8, 99.3	90.8, 99.7

Timepoint Data Category Statistic	Cohort 1 (Age >= 18 and age < 65) mRNA-1273 50 µg - Boost (N=107)	100 µg - Boost (N=112)	Total (N=219)	Cohort 2 (Age >= 65) mRNA-1273 50 µg - Boost (N=39)	100 µg - Boost (N=37)	Total (N=76)
>=4-fold Increase from Baseline [8]						
n[5] (%)	96 (90.6)	98 (87.5)	194 (89.0)	38 (97.4)	33 (89.2)	71 (93.4)
95% CI [6]	83.3, 95.4	79.9, 93.0	84.1, 92.8	86.5, 99.9	74.6, 97.0	85.3, 97.8

nAb responses against the Delta variant according to priming group and age group:

Table 7.6.1
Summary of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers Against New Variant Strain [B.1.617.2] for Subjects in the 100 ug Priming Group - By Age Group 2
Per-Protocol Immunogenicity Subset

Antibody: Pseudovirus Neutralizing Antibody ID80 Titers [LLOQ=14.3, ULOQ=10232]

Timepoint Data Category Statistic	P201 Part B 50 µg mRNA-1273 booster after 100 ug priming ≥18 and <55 years old (N=68)	≥55 years old (N=81)	Overall (N=149)
Pre-Booster			
n [1]	68	81	149
GMT	20.05	15.98	17.72
95% CI [2]	15.76, 25.50	13.35, 19.13	15.31, 20.51
Median	16.78	15.38	16.13
Min, Max	7.2, 457.6	7.2, 96.6	7.2, 457.6
28 days after booster dose			
n [3]	68	81	149
GMT	323.50	291.88	305.91
95% CI [2]	278.62, 375.61	250.52, 340.08	274.99, 340.30
Median	329.11	342.55	332.48
Min, Max	71.5, 1881.5	61.0, 1797.5	61.0, 1881.5
GMFR	16.14	18.26	17.26
95% CI [2]	12.82, 20.31	14.90, 22.39	14.84, 20.08
Participants achieving Seroresponse comparing to pre-booster, n (Seroresponse Rate %) [4]			
N1	68	81	149
n (%)	63 (92.6)	77 (95.1)	140 (94.0)
95% CI [5]	83.7, 97.6	87.8, 98.6	88.8, 97.2

Table 7.6.1
Summary of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers Against New Variant Strain [B.1.617.2] for Subjects in the 100 ug Priming Group - By Age Group 2
Per-Protocol Immunogenicity Subset

Antibody: Pseudovirus Neutralizing Antibody ID50 Titers [LLOQ=18.5, ULOQ=45118]

	P201 Part B 50 µg mRNA-1273 booster after 100 ug priming		
Timepoint Data Category Statistic	≥18 and <55 years old (N=68)	≥55 years old (N=81)	Overall (N=149)
Pre-Booster			
n [1]	68	81	149
GMT	57.96	40.80	47.89
95% CI [2]	42.70, 78.69	32.35, 51.45	39.68, 57.79
Median	43.51	36.53	38.81
Min, Max	9.3, 2730.5	9.3, 609.8	9.3, 2730.5
28 days after booster dose			
n [3]	68	81	149
GMT	894.04	775.95	827.77
95% CI [2]	757.35, 1055.39	661.90, 909.65	738.48, 927.86
Median	847.20	749.04	792.27
Min, Max	141.0, 4656.8	124.2, 5587.5	124.2, 5587.5
GMFR	15.42	19.02	17.28
95% CI [2]	11.48, 20.73	15.05, 24.03	14.38, 20.77
Participants achieving Seroresponse comparing to pre-booster, n (Seroresponse Rate %) [4]			
N1	68	81	149
n (%)	59 (86.8)	74 (91.4)	133 (89.3)
95% CI [5]	76.4, 93.8	83.0, 96.5	83.1, 93.7

Table 7.5.1
Summary of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers Against New Variant Strain [B.1.617.2] for Subjects in the 100 ug Priming Group- By Age Group 1
Per-Protocol Immunogenicity Subset

Antibody: Pseudovirus Neutralizing Antibody ID50 Titers [LLOQ=18.5, ULOQ=45118]

	P201 Part B 50 µg mRNA-1273 booster after 100 ug priming		
Timepoint Data Category Statistic	≥18 and <65 years old (N=112)	≥65 years old (N=37)	Overall (N=149)
Pre-Booster			
n [1]	112	37	149
GMT	54.82	31.82	47.89
95% CI [2]	43.98, 68.33	22.64, 44.72	39.68, 57.79
Median	43.91	27.74	38.81
Min, Max	9.3, 2730.5	9.3, 204.3	9.3, 2730.5
28 days after booster dose			
n [3]	112	37	149
GMT	872.39	706.13	827.77
95% CI [2]	770.78, 987.41	538.55, 925.87	738.48, 927.86
Median	829.27	646.93	792.27
Min, Max	141.0, 5587.5	124.2, 3601.1	124.2, 5587.5
GMFR	15.91	22.19	17.28
95% CI [2]	12.88, 19.67	15.25, 32.30	14.38, 20.77
Participants achieving Seroresponse comparing to pre-booster, n (Seroresponse Rate %) [4]			
N1	112	37	149
n (%)	98 (87.5)	35 (94.6)	133 (89.3)
95% CI [5]	79.9, 93.0	81.8, 99.3	83.1, 93.7

Table 7.5.1
Summary of Pseudovirus Neutralising Antibody ID50 and ID80 Titers Against New Variant Strain [B.1.617.2] for Subjects in the 100 ug Priming Group- By Age Group 1
Per-Protocol Immunogenicity Subset

Antibody: Pseudovirus Neutralising Antibody ID80 Titers [LLOQ=14.3, ULOQ=10232]

	P201 Part B 50 µg mRNA-1273 booster after 100 ug priming		
Timepoint Data Category Statistic	≥18 and <65 years old (N=112)	≥65 years old (N=37)	Overall (N=149)
Pre-Booster			
n [1]	112	37	149
GMT	19.87	12.53	17.72
95% CI [2]	16.68, 23.68	9.91, 15.84	15.31, 20.51
Median	16.87	7.15	16.13
Min, Max	7.2, 457.6	7.2, 80.7	7.2, 457.6
28 days after booster dose			
n [3]	112	37	149
GMT	318.85	269.85	305.91
95% CI [2]	284.20, 357.73	208.67, 348.98	274.99, 340.30
Median	348.30	306.46	332.48
Min, Max	71.5, 1881.5	61.0, 1556.5	61.0, 1881.5
GMFR	16.04	21.54	17.26
95% CI [2]	13.53, 19.02	15.54, 29.86	14.84, 20.08
Participants achieving Seroresponse comparing to pre-booster, n (Seroresponse Rate %) [4]			
N1	112	37	149
n (%)	104 (92.9)	36 (97.3)	140 (94.0)
95% CI [5]	86.4, 96.9	85.8, 99.9	88.8, 97.2

Information regarding the number of subjects with detectable nAb titers against the Delta variant pre-boost

The MAH clarified that the pseudovirus neutralising antibody against the Delta variant currently are only available at pre-booster and 28 days post-booster in Study P201 Part B. The table below shows the number of subjects who still have a detectable nAb titer (PsVNA ID50) to the Delta variant pre-booster dose.

Summary of Pre-Booster Pseudovirus Neutralising Antibody ID50 Titers Against Delta Variant Strain [B.1.617.2] in Study P201 Part B, Per-Protocol Immunogenicity Set

	P201 Part B 50 µg mRNA-1273 booster after 50 µg priming (N=146) n(%)	**P201 Part B 50 µg mRNA-1273 booster after 100 µg priming (N=149) n(%)**
Pre-Booster N1 GMT 95% CI [a]	144 37.14 31.25, 44.15	149 47.89 39.68, 55.79
Number of subjects with pre-booster titer < LLOQ ≥ LLOQ	33 (22.6) 111 (76.0)	25 (16.8) 124 (83.2)

LLOQ= lower limit of quantification; ULOQ= upper limit of quantification; N1= Number of subjects with non-missing data at pre-booster.
a 95% CI is calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
Note: Pseudovirus Neutralising Antibody ID50 Titers (LLOQ=18.5, ULOQ=45118).

Information regarding the non-inferiority analysis of the SSR.

The MAH clarified that regarding the non-inferiority analysis of the SRR based on the assay specific 3.3-fold criterion, the non-inferiority claim was based on all participants in the Per-Protocol Set who received

a single booster dose of 50 µg mRNA-1273 in Study P201 Part B (i.e., all participants combined regardless of whether they received 50 µg or 100 µg of mRNA1273 in the primary series).

In the 100µg primary series group using the 3.3-fold criterion, the difference of SRR is -7.6% (95% CI: -13.2%, -3.9%), as shown in Table 6.1.2 below.

Analysis of Seroresponse (Assay Specific Definition) based on Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Priming groups
Per-Protocol Immunogenicity Subset

Antibody: Pseudovirus Neutralizing Antibody ID50 Titers [P201: LLOQ=18.5, ULOQ=45118; P301: LLOQ=18.5, ULOQ=4404]

	201 Part B 50 µg mRNA-1273 booster after 50 µg priming		201 Part B 50 µg mRNA-1273 booster after 100 µg priming		Overall	
Statistic	P201 Part B 50 µg mRNA-1273 booster (N=146)	P301 mRNA-1273 100 µg primary series (N=1055)	P201 Part B 50 µg mRNA-1273 booster (N=149)	P301 mRNA-1273 100 µg primary series (N=1055)	P201 Part B 50 µg mRNA-1273 booster (N=295)	P301 mRNA-1273 100 µg primary series (N=1055)
N1	145	1050	149	1050	294	1050
Participants achieving Seroresponse, n (Seroresponse Rate %) [1]	139 (95.9)	1038 (98.9)	136 (91.3)	1038 (98.9)	275 (93.5)	1038 (98.9)
95% CI [2]	91.2, 98.5	98.0, 99.4	85.5, 95.3	98.0, 99.4	90.1, 96.1	98.0, 99.4
Difference in Seroresponse Rate(P201 Part B vs. P301) (%)	-3.0		-7.6		-5.3	
95% CI [3]	-7.6, -0.6		-13.2, -3.9		-8.8, -2.9	

Assessment of the MAH's response

The MAH provided further information on the the nAb responses using the parental strain as requested. The data confirm that the increase in nAb levels is generally higher in older subjects with a SRR of 89.2% and GMFR of 17.95 post dose 3 in the age category ≥65-85 yoa compared to a SRR of 87.5% and GMFR of 11.68 in the group of 18-<65 yoa.

As regards the nAb responses against the Delta variant the data indicate that 83.2% of subjects in the 100 µg primary group had still detectable antibodies 6-8 months after the primary series before the booster dose and 89.3% showed a seroresponse post dose 3 (criterion: 4-fold increase). Analysis of the immune response according age group indicates that the nAb responses (GMT) is slightly higher in the 18-<55 yoa (894.04) and 18-<65 yoa (872.39) group compared to the age categories of ≥55-85 yoa (775.95) and ≥65-85 yoa (706.13) but with higher GMFRs (19.02 and 22.19, respectively) and SRRs (91.4% and 94.6%) in the older age categories compared to the younger age group (GMFR: 15.42 and 15.91; SRR: 86.8% and 87.5%). This might be explained by the lower pre-booster antibody levels that are generally lower in the age categories ≥55-85 yoa and ≥65-85 yoa.

It is acknowledged that the NI evaluation conducted by the MAH was performed based on all subjects enrolled in the primary series regardless of the dose they received, however for the interpretation of any immunobridging data only the approved vaccine dose for the primary series is relevant. Using the 3.3-fold criterion the difference of the SRR between P201 subjects post dose 3 and P301 subjects post dose 2 was -7.6 (95% CI: -13.2; -3.9) not fulfilling the NI criterion as the lower limit of the 95% CI is -13.2.

Conclusion: Issue resolved.

Question 2

Summary of the MAH's response

A 50 µg dose was selected as the candidate booster vaccine dose due to the immune responses observed in the dose confirmation study following the primary series using various RNA concentrations, results of the NI assessment with study P301 and dose sparing considerations.

Additionally, the MAH currently has plans in place to evaluate the durability of nAb response over time of the 50 µg booster dose at a timepoint of Day 181 (Month 6) in Study P201 Part B and in Study P301 Part C (study evaluating safety and effectiveness of a 50 µg booster dose in P301 study subjects).

Study P301 is a 3-part Phase 3 study, comprising Part A, Part B, and Part C. Participants in Part A, the blinded phase of this study were blinded to their treatment assignment. Given that the primary efficacy endpoint for mRNA-1273 against COVID-19 was met per the protocol-defined interim analysis (IA), Part B, the Open-Label Observational Phase of this study, was designed to offer participants who received placebo in Part A of this study an option to request open-label mRNA-1273 while investigational vaccine was still available. Part C is designed to offer eligible participants in Part B the option to request a booster dose of 50 µg of mRNA-1273. The main objectives for Study P301 Part C are to evaluate the safety and the immunogenicity of a booster dose (BD) of mRNA-1273.

Assessment of the MAH's response

The rationale to choose a 50 µg booster dose is accepted. The MAH confirmed that the durability of the immune response of a 50 µg booster dose will be assessed over time in study P201 and in study P301 in participants who received a primary series of two 100 µg doses and a 50 µg booster dose. Immunogenicity results should be provided with the final study reports for Part B of study P201 and Part C of study P301.

Conclusion: Issue resolved.

Question 3

Summary of the MAH's response

The MAH is planning to update Study Protocol P203, A Phase 2/3, Randomised, Observer- Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 Years of Age, in order to evaluate a 50 µg booster dose in adolescents (P203 Part C). In children below 12 years of age, the MAH is conducting a Ph2/3 study (P204) exploring the primary dose series and believes it may be premature to evaluate a booster dose, in advance of those results.

Assessment of the MAH's response and conclusion

The MAH provided information on his current plans to assess a booster dose in children and adolescents as requested.

Conclusion: Issue resolved.

Safety

Question 4

MAH's response:

In both the US and EU Post-Authorisation Safety Studies (protocols mRNA-1273-P903 and mRNA-1273-P904 respectively), subgroup analyses will be presented describing the incidence of Adverse Events of Special Interest (AESI) and assessing any increases in risk for individuals by dose. Recent amendments

to the study protocols specified that booster doses will be evaluated via this mechanism. These studies will provide real-world evidence concerning safety of booster doses in the setting of large, population-based studies. The Interim and Final Study Report dates are listed in RMP v2.3 for mRNA-1273-P903 (Final Study Report: 30 June 2023) and for mRNA-1273-P904 (Final Study Report: 31 December 2023). Additionally, Study mRNA-1273-P301 Part C will evaluate the immunogenicity and safety of a booster dose given approximately 8 months to 12 months after the primary series. Recent amendments to the study protocol incorporated Part C, the Booster Dose Phase. Study P301 Part C began to enrol subjects on 23 September 2021 and is estimated to be completed on June 2022. The Interim Study Report for Part C will be available in December 2022 and Final Study Report in July 2023.

Assessment of response:

Two large, population-based studies ("real-world" settings), one in the US and one in the EU, are planned to be conducted to evaluate the safety after any dose of Spikevax. In addition, the pivotal efficacy trial mRNA-1273-P301 Part C will evaluate the immunogenicity and safety of a booster dose given approximately 8 months to 12 months after the primary series. Recent amendments to the study protocol incorporated Part C, which is the booster Dose Phase. The 2 large population based studies are not per se designed to evaluate a booster dose of Spikevax. The primary objective is to assess whether vaccination with Spikevax, by dose number where feasible and for any dose, including booster dose is associated with increased rates of the AESI compared with the expected rates (Study protocol P904 has not been submitted within the response to RSI, but is available). The quality and amount of data to assess the safety of a booster dose cannot be profoundly estimated so far for these 2 studies. However, in combination with Part C of Study P301 it can be expected that meaningful safety (and immunogenicity) data over time can be provided, also for individuals who did not receive the booster vaccination exactly 6 months after primary immunisation.

Conclusion: Issue resolved.

Question 5

MAH's response:

As noted in response to Item 4, the MAH will evaluate safety data in real-world settings via the US and EU Post-Authorisation Safety Studies (protocols mRNA-1273-P903 and mRNA-1273- P904 respectively) and will evaluate immunogenicity as well as safety in Study mRNA-1273-P301 Part C.

Assessment of response:

Please refer to comment on question 4.

Conclusion: Issue resolved.

Question 6

In the ongoing trial P205 two events of TIA occurred in 2 subjects and thrombosis and thrombophlebitis in one subject. In the submitted dossier no clinical information could be found. The MAH is asked to provide narratives or any clinical information available so far.

MAH's response
Case 1:

This is a 50-59-year-old, female subject participating in the Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants of Concern (mRNA-1273-P205). Subject's medical history, as provided by the investigator, included chronic obstructive pulmonary disease, depression, bilateral knee pain, neuropathy (bilateral legs) (sensory), complete hysterectomy and menorrhagia. Concomitant medications reported included escitalopram oxalate, tramadol, pregabalin, fluticasone furoate, umeclidinium, vilanterol and paracetamol.

The subject received a booster dose of mRNA-1273.211, 100 micrograms intramuscularly in the right arm in part A of the study. Nineteen days later the subject experienced blood clots leg; per the investigator, medical records did not support a diagnosis of deep vein thrombosis. Treatment for the event included oral rivaroxaban.

The investigator assessed the event, blood clots leg, as not related to study drug.

Case 2:

This is a 50-59-year-old, female subject participating in the Phase 2/3 study to Evaluate the Immunogenicity and Safety of mRNA-1273.211 Vaccine for SARS-CoV-2 Variants of Concern (mRNA-1273-P205). The subject's medical history, as provided by the investigator, included insulin resistant, Hashimoto thyroiditis, migraine, hypoadrenalism, anxiety, hyperlipidaemia, menopause and anaemia. Concomitant medications included semaglutide, metformin, rosuvastatin, levothyroxine, ubrogepant, progesterone, ondansetron, folic acid, iron, multivitamin, botulinum toxin type A, oestradiol, and paracetamol.

The subject received a single booster shot dose of mRNA-1273.211, 100 micrograms intramuscular (one-time dose) in the left arm, in Part A of the study. Fifteen days later the subject experienced a transient ischemic attack and was admitted to the hospital. The subject reported undergoing a computerised tomography scan of the head and neck which was within normal limits. Two days later the subject underwent an echocardiogram and magnetic resonance imaging, which were within normal limits. On the same day, the subject was discharged from the hospital. Treatment for the event included oral paracetamol, oral clopidogrel bisulphate, subcutaneous enoxaparin sodium, and oral atorvastatin. The event, transient ischemic attack, was reported as resolved that same day.

The investigator assessed the event, transient ischemic attack, as not related to study drug and not related to study procedure.

Case 3:

This is a report for a 60-69-year-old, male subject participating in the Phase 2/3 study to Evaluate the Immunogenicity and Safety of mRNA-1273.211 Vaccine for SARSCoV- 2 Variants of Concern (mRNA-1273-P205). The subject's medical history, as provided by the investigator, included sinus surgery, nasal polyp, and gout. Concomitant medications included baking soda.

The subject received the single booster shot dose of mRNA-1273.211, 100 micrograms (one-time dose) intramuscularly, in the left arm, in Part A of the study for prophylaxis of COVID-19 infection. Twenty-nine days later the subject started to experience symptoms of dizziness, unsteadiness, word finding difficulty and was diagnosed with transient ischemic attack on the same day. Three days later the subject went to the emergency department (ED) and was subsequently admitted to the hospital. On the same day, chest x-ray revealed widening of superior mediastinum, most likely vascular in nature, and lungs clear of acute infiltrates. Computerised tomogram (CT) of the head without (w/o) contrast revealed no CT evidence of acute intracranial findings. CT angioma of chest and pelvis revealed mediastinal and hilar lymphadenopathy, mildly enlarged lymph nodes at base of neck and axilla, no aortic dissection or aneurysm. Labs were within normal limits included haemoglobin 15.4, haematocrit 48.1, platelets 232, white blood cell count 8, creatinine 1, blood urea nitrogen (BUN) 14, sodium 140, potassium 3.7, chloride

102, calcium 9.4, total protein 7.2, total bilirubin 0.5, creatine phosphokinase 147 (30-200), troponin I <0.01 (normal), and magnesium 2.3 (1.6-2.6).

Additional labs included glucose 206 (76-100), aspartate aminotransferase 62 (10-58), alanine aminotransferase 56 (5-50), total cholesterol 226 (0-199), high-density lipoprotein (HDL) 34 (greater than 40), low-density lipoprotein 156 (0-129), non-HDL cholesterol calculated 192 (0-159), triglycerides 182 (0-149), thyroid-stimulating hormone 1.403 (0.350-4.940), free thyroxine 0.84 (0.70-1.48), and haemoglobin A1C 6.9 (less than 6.5). Respiratory panel was negative.

SARS-CoV-2 test was negative. Blood pressure was 150s/90-100s. Transthoracic echocardiogram was negative study. Urine analysis was normal except glucose 50 (negative) and specific gravity 1.051 (1.001-1.035).

Tests conducted the next day of bilateral carotid artery ultrasound and magnetic resonance imaging (MRI) w/o contrast of brain provided negative results. Ventricles and cisterns were normal. No parenchyma abnormalities seen. No abnormalities on the diffusion-weighted images to suggest a recent infarct. No hydrocephalus or mass effect. Mild inflammatory changes throughout paranasal sinuses. On the same day, the subject was discharged from the hospital in a stable condition with a direction to follow-up with his primary care physician (PCP). Treatment for the event included subcutaneous enoxaparin and oral acetylsalicylic acid.

The investigator assessed the event, transient ischemic attack, as not related to study drug.

Assessment of response

The MAH submitted the narratives as requested. All events were considered being not vaccine related by the investigator. The events of TIA and blood clot did not occur in young subjects. Two of the three participants are on medication with several drugs and have chronic medical condition. On the basis of the three individual cases, relatedness cannot be established. Thrombotic events are followed in the PSURs. In the 8th MSSR (MEA 11.7), the MAH was requested to present and discuss cases of stroke and thromboembolism reported in subjects < 18 years old.

Conclusion: Issue resolved.

☒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 MAH is seeking approval of a third dose (0.25 mL, 50 µg/dose) of Spikevax (WT Wuhan-Hu-1 isolate) given intramuscularly at least 6 months after the primary series of 2 doses of 0.5 mL (100 µg/dose) Spikevax in adults. The submission to update the product information on composition, immunogenicity, safety and handling is supported by information on quality aspects as well as immunogenicity and safety data.

The MAH has submitted immunogenicity and safety data of a third 50 µg dose Spikevax (WT) administered to participants of study P201, which is an ongoing dose confirmation study conducted in the USA. In Part A of the study 400 participants (two age groups 18-55 years and 55-85 years) enrolled in this study were randomised to receive either a primary vaccination series of two doses of 50 µg or two doses of 100 µg dose given 28 days apart. Following unblinding the participants were invited to receive a third (booster) dose of 50 µg 6-8 months after the second dose. Safety and immunogenicity evaluations

28 days post dose 3 were performed. The MAH provided data on the neutralising antibody responses post dose 3 tested against wild type (Wuhan-Hu-1 isolate) and the Delta variant.

Moreover, the immune responses of study P201 participants measured 28 days post dose 3 were compared to peak antibody levels determined in a subset of participants of the pivotal study P301 post dose 2.

Immunogenicity

Immunogenicity data on a third 50 µg dose of Spikevax given 6-8 months after a primary series of the approved 100 µg dose indicate elevated neutralising antibody titers when compared to pre-dose 3 or post dose 2 antibody levels in the current study in adults aged 18 and above. Waning of antibody titers is observed over time following the primary immunisation series but the vast majority of subjects still had detectable neutralising antibody levels against the wild type and the Delta variant at 6-8 months. Administration of a third dose results in an anamnestic response with a significant increase in neutralising antibody titers above the levels observed post dose 2 in subjects 18-85 years of age. Generally, a higher increase in neutralising antibody levels post dose 3 is reported in subjects 55 years of age or older than in subjects (18-<55 years of age). The increase in neutralising antibodies was more pronounced in this age group which had lower neutralising antibody titers pre-dose 3. This is further supported by data from participants having received two 50 µg doses in the primary series followed by a third 50 µg dose. Similar results were shown for the Delta variant although generally lower antibody titers were observed pre or post dose 3 compared to the WT levels.

From a scientific perspective it appears reasonable to assume that a third dose of 50 µg of Spikevax is capable to maintain/restore protective immunity including cross-neutralising antibody titers against variants of concern. Duration of the antibody responses following a third 50 µg dose are presently unknown. The MAH confirmed that the durability of the antibody response over time will be further assessed in the ongoing studies P201 and P301.

There are no data on a third dose in children and adolescents below 18 years of age.

The pivotal VE data have demonstrated that Spikevax is highly efficacious in preventing COVID-19. However, preliminary data of a more recent *ad hoc* analysis suggest a reduction of effectiveness both against COVID-19 and severe COVID-19 over time in particular due to the circulation of the Delta variant. The full extent of decline in VE, however, remains unclear. Thus, it is currently not possible to conclude on a specific recommendation, at which time point a third dose should be given.

The benefit of a third 50 µg dose administered 6-8 months after a primary series of two 100 µg doses of Spikevax is demonstrated as it results in an elevated neutralising antibody response 28 days post dose 3 compared to peak antibody levels post dose 2.

Safety

To date, the reactogenicity and safety profile of the booster seems to be consistent with that observed following the primary series in study P301, which included 30,346 study participants, and study P201, Part A. No new unexpected safety concerns have been identified from a booster dose.

As to the appropriateness of 50 µg booster dose, as part of initial dose ranging of mRNA-1273 (P201 Part A), both 50 and 100 µg were evaluated. Both dosages induced substantial neutralising antibody titers. While the 100 µg dosage was advanced to the pivotal trial (P301), it was postulated that a 50 µg booster dose would be effective in activating recall responses. The trend toward lower reactogenicity observed for the 50 µg dose in P201 Part A also supported this selection. Finally, there is precedence for a booster dose to be lower than the priming vaccine dose. For example, Tdap, the booster for the DTaP vaccine, has a reduced dose of the diphtheria and pertussis vaccines and is intended to boost the immunity that wanes after primary vaccination. The rationale to recommend the lower 50 µg dose for boosting seems to

be supported also by the fact that this dose has demonstrated a slightly better safety profile in elderly comparing to 100 µg.

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.

In the post-authorisation period, a total of 301,035,380 Spikevax doses have been distributed worldwide. Rare cases of anaphylaxis, myocarditis, and pericarditis events have been reported during the post-authorisation period from healthcare professionals and spontaneously reported from patients.

Following a signal evaluation finalised by the PRAC in July 2021, the Spikevax PI was updated to state that very rare cases of myocarditis and pericarditis have been observed following primary vaccination with Spikevax. These cases 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 primary vaccination is not different from myocarditis or pericarditis in general.

Based on the available data, these cases cannot be extrapolated to the use of a third half-dose of Spikevax. To this effect, it is important to note that the clinical setting is different than the primary vaccination and that only half a dose of the vaccine is administered. With regard to the risk of myocarditis after a third half-dose of Spikevax, at least six months after the primary vaccination series, no cases of myocarditis considered to be vaccine-related have been reported in the submitted clinical trials. This risk has therefore not yet been characterised based on the available data. The EMA closely monitors this aspect; in addition, the MAH will generate and submit to the EMA additional data as described in the Risk Management Plan. These considerations have been taken into account in the benefit-risk assessment of the booster half-dose including for younger persons above the age of 18 years old.

The EMA will take any new emerging data into consideration, including the outcome of the currently ongoing reopened signal on the risk of myocarditis and pericarditis after the primary vaccination series and will take regulatory actions accordingly if relevant.

Following future approval of the 50µg booster dose, the MAH commits to amend the protocol of Study P301 (COVE, the pivotal efficacy and safety study) to administer the booster dose, after which participants will continue to be followed for breakthrough disease. The MAH also intends to amend the protocol of Study P901, i.e. the VE study that is currently ongoing with Kaiser Permanente Southern California, to follow VE after the booster dose, which will also contribute extensive information on future protection against VOC. In addition, subjects initially enrolled in study P301 will be invited to receive a booster dose approximately 8 months to 12 months after the primary series (Part C) and will be followed up for approximately 6 months post booster dose for safety.

At the present point in time it is not possible to evaluate participants primed more than 9 months ago as broad vaccination has only begun in December 2020. The MAH considers that it is reasonable to assume that the booster effect regarding immunogenicity will be similar in people who received their primary series more than 6-8 months prior to their booster (for this, please see the efficacy assessment).

No data on the safety of the booster have been submitted in the current submission dossier for subjects below the age of 18 years. Therefore, a booster dose for individuals below 18 years of age is not supported at the present point in time.

Conclusion

In summary, there is evidence for a correlation of neutralising antibodies and protection against COVID-19. The submitted immunogenicity data in adults above the age of 18 clearly demonstrated that a booster

dose is capable to restore waning neutralising antibody titers. A booster dose given 6 to 8 months after primary vaccine series results in an elevated neutralising antibody response 28 days post dose 3 compared to peak antibody levels post dose 2. This could translate into an increased duration of protection, and possibly increased protection against variants of concern, which provide a substantial potential benefit in some epidemiological situations. However, as no threshold for a definite correlate of protection is yet established, the relevance of restoring the waning can currently not be robustly estimated. Data on vaccine efficacy and waning of protection over time have not been evaluated within this procedure. More information on the durability of the antibody response over time will be collected as part of the ongoing studies P201 and P301 as described in the Risk Management Plan.

The CHMP discussed whether there is merit in defining populations at an increased risk for either severe COVID-19 disease or long-term effects from having been infected (e.g., diabetes, myocarditis, cognitive dysfunction etc.), and for whom such a booster could therefore be of particular benefit. In this respect, the CHMP considered that it is currently not appropriate to define such sub-populations. Vaccine trials in general and the trials supporting this variation are conducted in unselected populations as the vaccines are intended for broad populations and not for individuals 'at risk'. At the moment the understanding of risk factors in the general population is still too limited and the CHMP therefore sees no scientific rationale to restrict the 3rd booster dose to certain populations. On the contrary, any such restrictions may exclude populations who would benefit from the potentially increased duration of protection and possibly increased protection against variants of concern provided by a 3rd booster dose.

The reactogenicity profile of the third dose regarding solicited and unsolicited ARs seems to be in line with the data reported after administration of the second dose. However, the submitted data is limited in terms of the numbers of vaccinees included in the study and the duration of follow up which does not allow any firm conclusions regarding the pattern and incidence of uncommon or rare AEs/SAEs.

In summary, based on the presently available data, the benefit-risk balance of a third dose of Spikevax, given at least six months after the second dose, has been shown to be positive in all adults above the age of 18 years old, provided that its implementation is appropriately guided by vaccine efficacy data supporting its utility, taking into account remaining uncertainties and the continuously emerging data on effectiveness and safety as reflected in official recommendations.

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	I, IIIA and IIIB

To update sections 2, 4.2, 4.4, 4.8, 5.1, 6.5 and 6.6 of the SmPC to include a booster dose for Spikevax, based on new clinical data from studies mRNA-1273-P201, a Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older (NCT04405076), mRNA-1273-P301, an ongoing Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older (NCT04470427) and DMID 21-0012, a Phase 1/2 Study of Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines (NCT04889209). The labelling and the package leaflet are updated accordingly.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes 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 (0.25 mL, containing 50 micrograms mRNA, which is half of the primary dose) of Spikevax may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of Spikevax should be made based on available vaccine effectiveness data, taking into account limited safety data.

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, reactogenicity, and immunogenicity of a booster dose of Spikevax are evaluated in an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL, 100 micrograms 1 month apart) of the Spikevax vaccine primary series. In an open-label phase of this study, participants received a single booster dose (0.25 mL, 50 micrograms) at least 6 months after receiving the second dose of the primary series. The solicited adverse reaction profile for the booster dose was similar to that after the second dose in the primary series. A single booster dose was shown to result in a geometric mean fold rise (GMFR) of 12.99 (95% CI: 11.04, 15.29) in neutralising antibodies from pre-booster compared to 28 days after the booster dose. The GMFR in neutralising antibodies was 1.53 (95% CI: 1.32, 1.77) when compared 28 days post dose 2 (primary series) to 28 days after the booster dose.

For more information, please refer to the Summary of Product Characteristics.

Please refer to Scientific Discussion ‘Spikevax/H/C/005791/II/34’

APPENDIX 1

DIVERGENT POSITION DATED 25 October 2021

DIVERGENT POSITION DATED 25 October 2021

Spikevax EMEA/H/C/005791/II/0034

The undersigned members of the CHMP did not agree with the CHMP's positive opinion for the above-mentioned procedure.

The reason for divergent opinion was the following:

Following a signal evaluation, which was finalised by the PRAC in July 2021, myocarditis is an established risk for Spikevax, which is higher in younger men. Recently emerging data has prompted another, currently ongoing signal assessment by the PRAC. As concluded in July 2021, the risk of myocarditis is higher after a second dose compared to a first dose. The absolute risk as well as clinical consequences of myocarditis are currently uncertain. Moreover, the nature of the risk after a third dose is not known.
The benefits of a booster dose of Spikevax in persons who are young and with no specific risk factors for severe covid-19, are also unclear at this time.
Consequently, we find there is a need for further in-depth discussion of these issues before it is possible to conclude on the benefit/risk balance of a Spikevax booster dose for a population encompassing all adults, regardless of age and underlying risk of severe covid-19.
Since the benefit/risk balance has not been shown to be positive for the proposed extent of booster use, the benefit/risk balance is presently negative.

Alar Irs (Estonia)

Kristina Dunder (Sweden)

APPENDIX 2

DIVERGENT POSITION DATED 25 October 2021

DIVERGENT POSITION DATED 25 October 2021

Spikevax EMEA/H/C/005791/II/0034

The undersigned member of the CHMP did not agree with the CHMP's positive opinion for the above-mentioned procedure.

The reason for divergent opinion was the following:

Following a signal evaluation, which was finalised by the PRAC in July 2021, myocarditis is an established risk for Spikevax, which is higher in younger men. Recently emerging data has prompted another, currently ongoing signal assessment by the PRAC. As concluded in July 2021, the risk of myocarditis is higher after a second dose compared to a first dose. The absolute risk as well as clinical consequences of myocarditis are currently uncertain. Moreover, the nature of the risk after a third dose is not known.
The benefits of a booster dose of Spikevax in persons who are young and with no specific risk factors for severe covid-19, are also unclear at this time.
Consequently, we find there is a need for further in-depth discussion of these issues before it is possible to conclude on the benefit/risk balance of a Spikevax booster dose for a population encompassing all adults, regardless of age and underlying risk of severe covid-19.
Since the benefit/risk balance has not been shown to be positive for the proposed extent of booster use, the benefit/risk balance is presently negative.

Ingrid Wang (Norway)