EMA/686295/2022
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/005791/II/0057

Invented name: Spikevax

International non-proprietary name: elasomeran

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

Note

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

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Timetable	Date
Start of procedure	07 Mar 2022
CHMP Rapporteur Assessment Report	01 April 2022
CHMP members comments	05 Apr 2022
ETF discussion	07 April 2022
Updated CHMP Rapporteur Assessment Report /RSI	08 April 2022
Request for supplementary information	22 Apr 2022
Start of procedure	27 Apr 2022
CHMP Rapporteur Assessment Report	09 May 2022
CHMP members comments	10 May 2022
ETF discussion	12 May 2022
Updated CHMP Rapporteur Assessment Report /RSI	13 May 2022
2nd Request for supplementary information	19 May 2022
Start of procedure	29 Jun 2022
CHMP Rapporteur Assessment Report	06 Jul 2022
CHMP members comments	11 Jul 2022
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Updated CHMP Rapporteur Assessment Report /RSI	15 Jul 2022
Opinion	21 Jul 2022

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List of abbreviations

Ab	antibody
AE	adverse event
AESI	adverse events of special interest
AR	adverse reaction
bAb	binding antibodies
CDC	US Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CoVs	Coronaviruses
COVID-19	Coronavirus disease 2019
DSMB	Data Safety Monitoring Board
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
FAS	Full Analysis Set
FDA	Food and Drug Administration
GM	geometric mean
GMT	geometric mean titer
GMR	geometric mean ratio
IA	interim analysis
ID50	50% inhibitory dose
IgG	immunoglobulin
IP	investigational product
IS/ID	Immunostimulation/Immunodynamic
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically-attended adverse events
MIS-C	multisystem inflammatory syndrome in children
mITT1	modified intent-to-treat 1
mRNA	messenger ribonucleic acid
nAb	neutralising antibody
NIAID	National Institute of Allergy and Infectious Diseases
NIM	noninferiority margin
NP	nasopharyngeal
PIP	paediatric investigation plan
PP	per-protocol
PSP	paediatric study plan
PsVNA	pseudotyped virus neutralising assay
PT	preferred term
RBD	receptor-binding domain
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SMQ	standard Medical Dictionary for Regulatory Activities queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULOQ	upper limit of quantification
VE	vaccine efficacy

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 22 February 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type II	I and IIIB

Update of section 4.2 of the Spikevax SmPC to include a 50 µg booster dose for adolescents 12 to 18 years of age, based on the extrapolation of safety and efficacy data from young adults (18 to 24 years of age). The package leaflet is updated accordingly.

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

2. Introduction

Spikevax (also referred to as COVID-19 Vaccine Moderna and mRNA-1273) is currently indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older. Spikevax is administered as a course of two 100 microgram doses to individuals 12 years of age and older and to children 6 through 11 years of age as a course of two 50 microgram doses, which is half of the primary dose for individuals 12 years and older. A third dose of Spikevax may be given at least 28 days after the second dose to individuals 12 years of age and older (100 micrograms) and children 6 through 11 years (50 micrograms) who are severely immunocompromised.

A booster dose of Spikevax (50 µg) given at least 3 months after completion of the primary series is currently approved for adults 18 years of age and older.

Within the present submission the MAH requests to extend the use of a 50 µg booster dose of Spikevax to adolescents (12 to < 18 years) at a dosing interval of at least 3 months after completion of the primary series with Spikevax (homologous boost) to prevent COVID-19. The submission is mostly based on the extrapolation of safety, immunogenicity and efficacy data from young adults (18 to 25 years of age) to the adolescent target age group.

3. Clinical Efficacy aspects

3.1. Summary of Immunogenicity and Efficacy Results by the MAH

The MAH presents immunogenicity and efficacy data from clinical studies and post-licensure data:

- Established efficacy of a primary vaccination series in adults and young adults from clinical study P301 of 93% (from interim CSR dated 05 April 2021).
- Immunogenicity results in young adults (≥18 to 25 years of age) receiving booster doses in clinical studies P201B, DMID Study 21-0012, P301, and post-licensure.
- Immunobridging of the primary vaccination in adolescents using immunogenicity data from study P203 (12 to <18 years of age) to young adults in study P301 (≥18 to 25 years of age).

Primary Series Adults ≥18 Years in Study P301

The safety and efficacy of mRNA-1273 to prevent COVID-19 was demonstrated in adults 18 years and older in Study P301. The final efficacy analysis of Part A (blinded phase) based on a database lock of 04 May 2021 demonstrated VE of 93.2% (95% CI: 91.0, 94.8, $p < 0.0001$), which was consistent with results of the interim and primary analyses, confirming persistent, high efficacy over a substantially larger case database and over a median 5.3-month blinded observation period from randomisation in Part A.

Booster Vaccination in Adults and Young Adults - Study P201B

Serum neutralising titers were measured after the 50 µg booster vaccination, meeting pre-specified criteria for non-inferiority (NI) in terms of GMTs (relative to neutralising titers observed after a 2-dose primary series with 100 µg mRNA-1273 in P301). In addition, if assay-specific definitions for seroresponse were employed, both coprimary endpoints met the pre-specified success criteria for NI, indicating the primary immunogenicity objective was met. A single dose of 50 µg of mRNA-1273 in the P201B study also demonstrated 32- to 44 fold increases in nAb responses against all test variants as compared to pre-boost nAB titers, including a 42-fold increase against the Delta variant.

Table 2 summarises serum nAb (PsVNA median infectious dose [ID50], D614G) titers 28 days after the 50 µg booster in P201 Part B. Among all participants previously receiving 2 doses of 100 µg mRNA-1273, the 50 µg booster led to an increase in baseline titers, GMFR (28 days post booster to pre-dose 1) of 12.99 (95% CI: 11.04, 15.29). In a recent ad-hoc analysis focusing on the 18- to 25-year age group, although containing a small number of participants (n=7), the 50 µg booster post 100 µg primary series led to an increase in baseline titers, with GMFR (28 days post booster to pre-dose 1) of 16.32 (95% CI: 4.53, 58.81).

Table 2 Summary of Pseudovirus Neutralizing Antibody ID_{50} Titers After 50 µg Booster Injection

	mRNA-1273		
	P201B 100 µg Primary Series + 50 µg Booster (all age groups) (N=149)	P201 Part B 50 µg mRNA-1273 Booster After 100 µg priming (18-25 yo) (N=7)	P201 Part B 50 µg mRNA-1273 Booster After 100 µg priming (18-55 yo) (N=68)
Baseline (pre booster), n[a]	149	7	68
GMT	150.224	147.69	172.69
95% CI[b]	125.726, 179.495	29.45, 740.63	132.58, 224.93
28 days post-booster dose, n	149	7	68
GMT	1951.735	2410.31	2052.03
95% CI[b]	1729.606, 2202.392	1324.97, 4384.69	1732.47, 2430.54
N1[d]	149	--	68
GMFR	12.99	16.32	11.88
95% CI	11.04, 15.29[b]	4.53, 58.81[b]	9.38, 15.06

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise (post-baseline vs baseline titers); GMT = geometric mean titer; ID_{50} = median infectious dose; LLOQ = lower limit of quantification; N1 = number of participants with nonmissing data at baseline and the corresponding visit; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values that are greater than the ULOQ are converted to the ULOQ if actual values are not available. Percentages are based on the number of participants in the Per-Protocol Set with nonmissing data at baseline and the corresponding visit (N1).

[a] Number of participants with nonmissing baseline.

[b] 95% CI was 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.

[c] 95% CI was calculated using the Clopper-Pearson method.

[d] Number of participants in the Per-Protocol Set with non-missing data at the corresponding visit.

Source: Study P201 Part B: Table 14.2.2.1.4.1.1, Ad Hoc Table 7.1.0.2 and Table 7.1.0.1

Immunobridging: Comparison of P201 Part B Booster to P301 Primary Series Against the Original Virus Strain

In comparison to the peak PsVNA ID_{50} titers in P301 Part A (Day 57), where efficacy was demonstrated, the geometric mean ratio detected in P201 Part B (GMR; P201 Part B D29 vs P301 D57, against the original virus strain) was 1.71 (95% CI: 1.519, 1.929). The GMR estimate of 1.71 (above the pre-specified threshold of 1.0), with the lower bound of the 95% CI greater than 0.67 (corresponding to NIM=1.5) met the pre-specified 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 3).

Table 3 Analysis of PsVNA ID_{50} Titers: mRNA-1273 Post-booster Compared With the P301 Primary Series Peak Titers - by Prime Series Groups (PP Immunogenicity Set)

	P201 Part B 50 µg mRNA-1273 Booster After 100 µg Primary Series N=149	P301 mRNA-1273 100 µg Primary Series N=1055
28 Days After Booster (P201 Part B) or Completion of Primary Series		
n	149	1053
GLSM	1802.426	1026.854
95% CI	(1548.020, 2098.643)	(967.880, 1089.420)
GMR (P201 Part B vs P301; model based)	1.76	
95% CI	(1.496, 2.060)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GMR = geometric mean ratio; ID50 = 50% inhibitory dilution or median infectious dose; LLOQ = lower limit of quantification; PP = per protocol; PsVNA = pseudotyped virus neutralizing assay; 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 models 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).
Source: P201 CSR Addendum, Table 5.1.

DMID 21-0012 Study

Results of the DMID 21-0012 study using a booster dose of mRNA-1273 both 50 µg and 100 µg, (i) reinforce findings observed after the 50 µg boosting dose (P201 Part B), and (ii) demonstrate the utility of mRNA-1273 regardless of the COVID-19 vaccine initially administered.

Comparing GMT obtained 12 - 20 weeks after 2 doses of 100 µg mRNA-1273 with GMT obtained 14 days after a 100 µg booster dose, show a significant increase in nAb titers with a GMFR of 10.17 following the booster dose (95%: 8.05, 12.85). This GMFR is consistent with that observed in earlier sections for the 50 µg booster, (GMFR 12.99, 95% CI: 11.04, 15.29).

Data from this study also illustrate that a booster dose of mRNA-1273 can significantly enhance nAb responses induced by alternate primary vaccination regimens, regardless of the vaccine used for priming. Study participants had completed authorised regimens of the Janssen (n=52 participants) or Pfizer/BioNTech (n=50 participants) 12-20 weeks prior to obtaining a "baseline" serum sample. Of note, these "baseline" GMTs measured in these groups were lower than that following the authorised 2-dose Moderna regimen (366.31 following Moderna compared with 36.81 following Janssen and 102.44 following Pfizer/BioNTech). Regardless of the initial vaccine regimen, boosting with 50 or 100 µg dose of mRNA-1273 resulted in a significant increase in nAb titer.

In line with the results from P201 Part B, the older adult cohort aged ≥56 years had a GMFR consistent with the younger age cohort 18-55 years of age.

GMFRs comparing GMT after different primary vaccination schemes prior to the 100 µg mRNA-1273 booster to the GMT 14 days after mRNA-1273 booster were 75.91 (prime Janssen), 10.17 (prime Moderna) and 31.69 (prime Pfizer/BioNTech). These results emphasise that fold increase is influenced by baseline titers: 2 doses of mRNA-1273 achieved relatively high "baseline" titers (366.31) compared with "baseline" titers achieved by either the Janssen or Pfizer/BioNTech vaccines (36.81 and 102.44, respectively). The relatively higher titers achieved after 2 doses of 100 µg of mRNA-1273 result in a relatively lower GMFR than for participants initially given Janssen or Pfizer/BioNTech vaccines (86% vs 100%, respectively).

Post-licensure Booster Vaccine Effectiveness

A prospective cohort study at Kaiser Permanente Southern California was conducted to determine the real-world vaccine effectiveness of mRNA-1273 in preventing COVID-19 infection and severe disease. Individuals aged ≥ 18 years receiving 2 doses of mRNA-1273 ≥ 24 days apart (18 Dec 2020 - 31 Mar 2021) were 1:1 matched to randomly selected unvaccinated individuals by age, sex, and race/ethnicity, with follow-up through 30 Jun 2021. Vaccine efficacy against COVID-19 infection was 87.4% (84.8%-89.6%). Vaccine efficacy against COVID-19 hospitalisation and hospital death was 95.8% (90.7%-98.1%) and 97.9% (66.9%-99.9%), respectively. Vaccine efficacy was higher against symptomatic (88.3% [98.3% CI: 86.1%-90.2%]) than asymptomatic COVID-19 (72.7% [53.4%-84.0%]), but was generally similar across age, sex, and racial/ethnic subgroups. Vaccine efficacy among individuals with history of COVID-19 ranged from 8.2% to 33.6%. Among those aged 14 to 44 years at index date, the incidence per 1000 person-years was 3.58 (2.92-4.39) among mRNA-1273 vaccinated participants with an adjusted VE of 87.2% (83.6%-90.1%) The most prevalent variants were Alpha (41.6%), Epsilon (17.5%), Delta (11.5%), and Gamma (9.1%), with Delta increasing to 54.0% of variants by June 2021.

A retrospective cohort study conducted in Qatar among over 2.2 million persons vaccinated with 2 doses was conducted to investigate the effectiveness of booster vaccination against symptomatic SARS-CoV-2. For mRNA-1273, cumulative symptomatic infection incidence was 1.9% (95% CI: 1.7-2.2) in the booster-dose cohort and 3.5% (95% CI: 3.2-3.9) in the primary series cohort, after 35 days of follow-up. The adjusted hazard ratio for symptomatic infection was 0.49 (95% CI: 0.43-0.57). Booster effectiveness relative to primary series was 50.8% (95% CI: 43.4-57.3). There were fewer cases of severe COVID-19 in booster dose cohorts than in primary series cohorts, but cases of severe COVID-19 were rare in all cohorts indicating booster vaccination is associated with modest effectiveness against symptomatic infection with Omicron.

Another study including all ages eligible for vaccination (including young adults) that investigated the association between 3 doses of mRNA COVID-19 vaccines and symptomatic SARS-CoV-2 infection with Omicron and Delta variants using a test-negative case—control analysis. In an analysis that included age matched cases and controls a comparison of 3 doses versus 2 doses among Omicron cases and controls, the adjusted odds ratio (OR) versus 2 doses was 0.34 (95% CI: 0.32-0.36); among Delta cases and controls, the adjusted OR was 0.16 (95% CI: 0.14 0.14- < 0.001). When models were stratified by mRNA product, the adjusted ORs for Omicron were 0.35 (95% CI: 0.32-0.37) for 3 doses of BNT162b2 versus 2 doses and 0.31 (95% CI: 0.28-0.34) for 3 doses of mRNA-1273 versus 2 doses. For Delta, the adjusted ORs were 0.17 (95% CI: 0.16-0.19) for 3 doses of BNT162b2 versus 2 doses and 0.13 (95% CI: 0.110.15) for 3 doses of mRNA-1273 versus 2 doses. Q values for all comparisons (Omicron vs Delta) of product-specific ORs were less than 0.001 doses (vs 2 doses), with values closer to 0 representing a stronger magnitude of association.

Primary Series Adolescents (12 to <18 Years)

Vaccine effectiveness in adolescents aged ≥ 12 to < 18 years was inferred by demonstrating non-inferiority of both serum nAb GMTs and seroresponse rates (SRR) from adolescents compared with those from young adults enrolled in Study P301 (aged ≥ 18 to ≤ 25 years (Table 4). The GMR of adolescent (Study P203) to young adult (Study P301) nAb titers at Day 57 was 1.077 (95% CI: 0.939, 1.236), meeting the pre-specified 1.5-fold non-inferiority criterion (i.e., lower bound of the 95% CI for GMR is > 0.67). The difference in adolescent to young adult nAb SRRs at Day 57 was 0.2 (95% CI: -1.8, 2.4), meeting the pre-specified 10% non-inferiority criterion (lower bound of the 95% CI of the SRR difference is > -10%). Since both coprimary endpoints of Study P203 met the pre-specified success criteria for non-inferiority, the primary immunogenicity objective is considered to be met.

Table 4 **Analysis of Serum Antibody Level and Seroresponse at Day 57 by Pseudovirus Neutralization Assay (ID_{50}): ANCOVA Model (Per-Protocol Immunogenicity Subset for SARS-CoV-2-specific nAb)**

Serum antibody level pseudovirus neutralization (ID_{50})	**Study P203: ≥ 12 to < 18 Years GLSM 95% CI N=340**	**Study P301: ≥ 18 to ≤ 25 Years GLSM 95% CI N=305**	**GMR Study P203 vs. Study P301 95% CI**	**Met Success Criteria[a]?**
	1401.670 1276.300, 1539.355	1301.312 1176.979, 1438.780	1.077 0.939, 1.236	Yes
Seroresponse by pseudovirus neutralization (ID_{50})	**Study P203: ≥ 12 to < 18 Years n (%) 95% CI N=340**	**Study P301: ≥ 18 to ≤ 25 Years n (%) 95% CI N=305**	**Difference in Seroresponse Rate 95% CI**	**Met Success Criteria[b]?**
	336 (98.8) 97.0, 99.7	292 (98.6) 96.6, 99.6	0.2 -1.8, 2.4	Yes

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GMR = geometric mean ratio; ID50 = 50% inhibitory dilution or median infectious dose; LLOQ = lower limit of quantification; LS = least square; n = number of subjects with nonmissing data at the corresponding timepoint; nAb = neutralizing antibody; ULOQ = upper limit of quantification.

[a] The lower bound of the 95% CI of the GMR rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5, and the GMR point estimate > 0.8 (minimum threshold).

[b] The lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e. lower bound > -10%) using the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

Notes:

- The ULOQ for selected P301 participants tested previously was different.
- 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.
- The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (adolescents in P203 and young adults in Study P301) as fixed effect. The resultant LS means, difference of LS means, and 95% CI were back-transformed to the original scale for presentation.

Sources: Study P203 Report, Table 2.1.1.3.1 and Table 2.1.2.3.1.

Evidence from related previously completed regulatory procedures

Relevant data and regulatory assessments from the following previous procedures related to the indication definition of Spikevax were taken into consideration for decision making in the present procedure

- EMEA/H/C/005791/II/0021: Extension of indication for primary immunisation to adolescents 12 - < 18 years of age
- EMEA/H/C/005791/II/0042: Indication for heterologous boost in adults 18 years of age and older

3.2. Discussion on Immunogenicity and Efficacy

In support of the claimed booster indication for adolescents, the MAH has compiled evidence from several data sources as summarised below:

The MAH reports for pivotal study P301 that the final efficacy analysis of Part A (blinded phase) based on a database lock of 04 May 2021 demonstrated VE of 93.2%. Although no correlate of protection has been defined yet, the results of this huge study lay the basis to apply nAB titers as an immunological indicator of vaccine efficacy.

Regarding booster vaccination in study P201 Part B the MAH reports that potent serum neutralising titers were measured after the 50 µg booster vaccination, meeting pre-specified criteria for non-inferiority (NI) in terms of GMTs (relative to neutralising titers observed after a 2-dose primary series with 100 µg

mRNA-1273 in P301). These results are obtained in the overall study populations, i.e. adults ≥18 years of age. However, in a recent ad-hoc analysis focusing on the 18- to 25-year age group of study P201 Part B, although containing only a small number of participants (n=7), the 50 µg booster post 100 µg primary series led to an increase in baseline titers, with GMFR (28 days post booster to pre-dose 1) of 16.32 (95% CI: 4.53, 58.81). These data, although rather limited at this point in time, show that the 50 µg boost is working in principle in young adults.

For the purpose of immunobridging a comparison of peak PsVNA ID50 titers has been performed between P201 Part B (adults ≥18 years of age) and the pivotal study P301 (adults ≥18 years of age). When compared to the peak PsVNA ID_{50} titers in P301 Part A (Day 57 post primary vaccination with 2 vaccine doses), where clinical efficacy was demonstrated, the geometric mean ratio in relation to PsVNA ID50 titers of P201 Part B after a 50 µg booster dose (GMR; P201 Part B D29 vs P301 D57) was 1.71 (95% CI: 1.519, 1.929). The lower bound of the 95% CI was greater than 0.67 (corresponding to NIM=1.5) thus successfully meeting the pre-specified NIM criterion. These data indicate that applying a 50 µg booster dose is highly effective to increase post-primary vaccination nAB titers.

Study DMID 21-0012 is investigating efficacy and immunogenicity of a heterologous boost in adults ≥18 years of age. The MAH reports that GMT for nAB obtained 12 - 20 weeks after primary immunisation with 2 doses of 100 µg each mRNA-1273 compared to GMT obtained 14 days after a 100 µg booster dose (homologous boost using 100 µg mRNA-1273) are significantly lower. This demonstrates that the 100 µg boost lads to a significant increase in nAb titers with a GMFR of 10.17 (95%: 8.05, 12.85). GMFRs in response to booster vaccination were also specified in terms of the primary vaccination scheme applied: GMFRs comparing GMT prior to the 100 µg mRNA-1273 booster to the GMT 14 days after mRNA-1273 booster were 75.91 (prime with Janssen), 10.17 (prime with Moderna) and 31.69 (prime with Pfizer/BioNTech). These results emphasise that fold increase is influenced by baseline titers: 2 doses of mRNA-1273 achieved relatively high "baseline" titers (366.31) compared with "baseline" titers achieved by either the Janssen or Pfizer/BioNTech vaccines (36.81 and 102.44, respectively). These data show that a Spikevax booster dose increases pre-boost nAB irrespective of the primary vaccination scheme, underlining the basic applicability the heterologous boost approach.

Post-licensure analysis demonstrates 87.4% vaccine effectiveness against COVID-19 infection in individuals ≥18 years of age after receiving 2 doses of mRNA-1273. Vaccine efficacy against COVID-19 hospitalisation and hospital death was 95.8% and 97.9%, respectively.
A retrospective cohort study conducted in Qatar among over 2.2 million persons vaccinated with 2 doses was conducted to investigate the effectiveness of booster vaccination against symptomatic SARS-CoV-2. Booster effectiveness relative to primary series was 50.8% (95% CI: 43.4-57.3).
Another study including all ages eligible for vaccination (including young adults) that investigated the association between 3 doses of mRNA COVID-19 vaccines and symptomatic SARS-CoV-2 infection with Omicron and Delta variants using a test-negative case—control analysis. In an analysis that included age matched cases and controls a comparison of 3 doses versus 2 doses among Omicron cases and controls, the adjusted odds ratio (OR) versus 2 doses was 0.34 (95% CI: 0.32-0.36); among Delta cases and controls, the adjusted OR was 0.16 (95% CI: 0.14 0.14- < 0.001).

The MAH further reports an immunobridging as determined by nAB titers and seroresponse rates after primary vaccination from studies P203 (adolescent ≥12 years to <18 years) with young adults from study P301 (≥18 to <25 years of age). Vaccine effectiveness in adolescents aged ≥ 12 to < 18 years was inferred by demonstrating non-inferiority of both serum nAb GMTs and seroresponse rates (SRR) from adolescents compared with those from young adults enrolled in Study P301 (aged ≥ 18 to ≤ 25 years).

The GMR of adolescent (Study P203) to young adult (Study P301) nAb titers at Day 57 was 1.077 (95% CI: 0.939, 1.236), meeting the pre-specified 1.5-fold non-inferiority criterion (i.e., lower bound of the 95% CI for GMR is > 0.67). The difference in adolescent to young adult nAb SRRs at Day 57 was 0.2 (95% CI: -1.8, 2.4), meeting the pre-specified 10% non-inferiority criterion (lower bound of the 95% CI of the SRR difference is > -10%). Since both co-primary endpoints of Study P203 met the pre-specified success criteria for non-inferiority, the primary immunogenicity objective is met. These data indicate that the vaccine-induced immune response in terms of nAB titers after primary vaccination in adolescents is similar to that in young adults. These data are of crucial importance as they confirm the equivalence (non-inferiority) of the immune response in these two age groups, which is the scientific/regulatory basis for the extrapolation of the immune response after applying a booster dose from young adults to adolescents.

Assessor´s comment:
No specific data for efficacy, immunogenicity or effectiveness have been provided by the MAH for the claimed indication of a 50 µg booster dose in the adolescent age group. However, relevant evidence from various studies and data sources have been compiled in support of the claim for the adolescent boost. As a whole, these data are considered qualified to justify the claim for the extension of the current booster indication for Spikevax to adolescents. In particularly the comparison of vaccine-induced nAB titers after primary vaccination in young adults and adolescents confirm the equivalence of the measured immune responses in these two age groups. There is currently no scientifically justified reason to assume that booster immune responses in these two age groups should differ significantly while primary vaccination responses are highly comparable.

Therefore, extrapolation of immunogenicity data from the older age group ≥18 to <25 years to the younger age group ≥12 to <18 years is deemed acceptable.

Study P203 Part 1A was a Phase 2/3, randomised, observer-blind, placebo-controlled study that evaluates the safety, reactogenicity, and effectiveness of the mRNA-1273 vaccine in healthy adolescents. The goal of the study is to support an indication for use of mRNA-1273 (100 µg IM, given as 2 doses, 28 days apart) in the 12 to < 18 years of age group. The blinded placebo controlled portion of this study was submitted and approved under procedure EMEA/H/C/005791/II/0021.

A data snapshot for this submission was triggered (date: 08 May 2021) based on the availability of immunogenicity data from Study P203, with a median study follow-up duration of 53 days after dose 2, based on a total of 3732 participants (3726 participants randomised and receiving dose 1, with 1240 on placebo and 2486 on mRNA-1273).

The protocol for study P203 was amended to include Part C, which will evaluate the safety and immunogenicity of a booster dose of 50 µg of mRNA-1273. Part C is designed to offer homologous booster vaccine to active participants of the study and heterologous booster dose vaccine to non-Moderna primed eligible participants who will be enrolled into the study. A more recent amendment included a Part 2, which will evaluate safety and immunogenicity of a 50 µg dose of mRNA-1273 given as primary series and a booster dose.

The booster portion of the clinical trial (P203 Part C) is on-going (first subject dosed late December 2021) (Protocol Amendment #3). The generation of an interim analysis on at least the first 1000 subjects boosted with at least 2 months follow-up post booster, and corresponding regulatory submission package is currently planned for Q3 2022.

Assessor's comment:

The MAH was asked to provide additional information on the status of study P203 Part C regarding timelines and availability of interim or final study reports.

The MAH clarified that mRNA-1273 is being studied in adolescents 12 to < 18 years of age in the US in Study mRNA 1273-P203 (hereafter Study P203), a Phase 2/3, randomised, observer-blind, placebo controlled study that evaluates the safety, reactogenicity, and effectiveness of the mRNA-1273 vaccine in healthy adolescents. The goal of the study was to support an indication for use of mRNA-1273 (100 µg IM, given as 2 doses, 28 days apart) in the 12 to < 18 years of age group. The blinded placebo controlled portion of this study was submitted and approved under procedure EMEA/H/C/005791/II/0021. As per protocol upon FDA granting an EUA in the adolescent age group (for a SARS-CoV-2 mRNA vaccine other than mRNA-1273), subjects were unblinded and crossed over.
Recently, protocol Amendment #3 was implemented to provide a 50 µg booster dose (BD) of mRNA-1273 to all participants This change was prompted by the authorisation of a 50 ug booster dose for adults 18 years and older, supported by data from study P201B. The use of mRNA-1273 as a booster dose regimen in adolescents (12 - <18 years of age) is currently investigated in clinical study P203 Part C.

The booster portion of the clinical trial (P203 Part C) is on-going (first subject dosed late December 2021) (Protocol Amendment #3).

The generation of an interim analysis on at least the first 1000 subjects boosted with at least 2 months follow-up post booster, and corresponding regulatory submission package is currently planned for Q3 2022.

Conclusion:

The issue is partly resolved. The MAH provided information on the status as requested. Interim data for this study are expected in Q3. The MAH is requested to submit the interim and the final clinical study report from study P203 Part C as soon as it becomes available. The interim CSR is expected Q3 2022.

The MAH was requested to comment on the proposed boosting interval for adolescents, considering the slower rate decline of the immune response and the duration of protection in this population.

The MAH explained that the booster data on shortened intervals is being extrapolated from the NIH/DMID 21-0012 study, which included young adults (18-25yr), Study P201B, and post-authorisation safety data, in order to provide regulatory agency flexibility to best meet their local dosing interval recommendations. It is also important to note, that current post-authorisation safety data, does not distinguish the different dosing intervals that have been recommended for booster implementation in different countries, for example, France (3 months), Germany (3 months), UK (3 months), Canada - Ontario (3 months), Switzerland (4 months), and U.S. (5 months). By providing flexibility in the dosing interval, the decision when and for whom to implement a third dose of Spikevax can be made based on local recommending bodies needs and the evolution of the pandemic.

In summary the MAH's response is not satisfactory. The MAH justifies the booster interval of 3 months in adolescents with the extrapolation approach from young adults, without discussing the slower rate decline of immune response and the duration of protection in this population as requested. This should be done subsequently. The MAH is asked to submit and discuss:

•all available immunogenicity data comparing the decline of antibodies in adolescents and young adults 18-25 years of age beyond of the data from study P203
•all available data on the duration of protection in the 2 age cohorts
•to justify the identical booster interval for the 2 groups.

Conclusion
Issue not solved. The MAH is asked to submit and discuss:
•all available immunogenicity data comparing the decline of antibodies in adolescents and young adults 18-25 years of age beyond of the data from study P203
•all available data on the duration of protection in the 2 age cohorts
•to justify the identical booster interval for the 2 groups.

3.3. Population IS/ID Model

Methods and Model diagnostics

Besides exploratory analysis of nAB levels, a population Immunostimulation/Immunodynamic (IS/ID) model to characterise the dynamics of the neutralising antibody (nAB) responses following vaccination with different doses of mRNA-1273 has been developed. The model was used to evaluate a 50 µg booster for the adolescent population (12-18 years of age) after a 100 µg prime dose. No clinical efficacy data are available for this age group following a booster dose. As observed data across various dose levels in all age groups are not available from clinical studies, the IS/ID model developed using data pooled across different dose levels and age groups was intended to allow for interpolating nAB titers at dose levels not evaluated in clinical studies at specific dose and age group.

Software

The population IS/ID model was developed using non-linear mixed effects modelling (NLMEM) software Pumas (version 2.0.3; Pumas-AI Inc, Baltimore, MD, USA). Estimation was performed by first-order conditional estimation with interaction (FOCEI). Nonparametric bootstrap was used to quantify parameter uncertainty. Pumas (v2.0.3) and Julia language (version 1.6.2) used on JuliaHub (version 5.3; Julia Computing, Inc.), were used for data preparation, graphical analysis, model diagnostics, and statistical summaries.

Assessor's comment:

The use of non-linear mixed effects modelling for the population approach is endorsed. The MAH has used the Software PUMAS, that is not standard in this regard. The reporting of the used model and model outcome is not in line with the current EMA guideline on pop PK (CHMP/EWP/185990/06).

Data used for model building

The IS/ID analysis included a total of 2781 subjects pooled across P201 Part B, P203, P204 and P301 clinical studies, of which 63.5 (%) received the 100 µg dose [age groups: 6-12, 12-18 and >18 years of age], 30.92(%) received the 50 µg dose [age groups: 6-12 and 2-6] and 5.57 (%) received the 25 µg dose [age groups:2-6 and 6months – 2 years of age]. Log10 transformed nAB titers (LogPSVN50) data was obtained from clinical studies P201, P301, P203, P204. All per protocol subjects with available dosing history and at least 1 measurable titer were included in the analysis dataset.

Only per protocol subjects were included and only those observation with actual measurements, not imputed, after a vaccine dose of mRNA-1273 were included in the analysis. In the source datasets, if an nAB titer for a recorded sample was missing, the record was flagged and kept in the dataset with an imputed value of 9.26. In the modelling data sets these imputed values were removed since such imputed values at random would not contribute to the analysis and hence were removed. Similarly, if the dose amount was missing for a dose associated with a recorded nAB and the dose amount could not be imputed, the affected nAB titer was deleted.

nAB measurements reported as below the lower limit of quantification (LLOQ) were excluded from the analysis irrespective of whether these were pre-dose or post-dose nAB titers time points.

Outliers were identified by visual inspection of exploratory plots and by looking at conditional weighted residuals (CWRES) from the final base model. Observations with absolute value of CWRES greater than 6 were considered outliers. To determine whether these outliers would cause unnecessary bias in the parameter estimates, the outliers were excluded from the analysis dataset and the base model parameters were re-estimated. If the model's structural parameters estimated with the dataset in which the outliers had been removed did not differ by more than 15% from parameters estimated with the complete dataset, then the complete dataset was retained for all further model development steps.

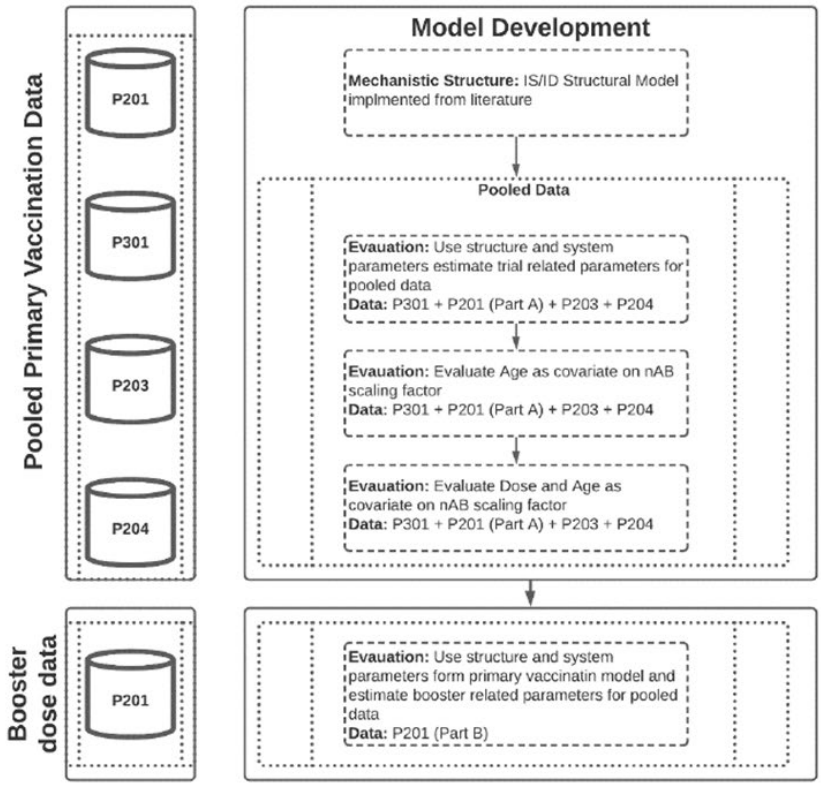

Figure 3-1 **Flow Chart of Major Model Development Steps**

A total of 2781 subjects pooled across P201 Part B, P203, P204 and P301 clinical studies, of which 63.5 (%) received the 100 µg dose [age groups: 6-12, 12-18 and >18 years of age], 30.92(%) received the 50 µg dose [age groups: 6-12 and 2-6] and 5.57 (%) received the 25 µg dose [age groups:2-6 and 6months – 2 years of age] were used for model-based nAB analysis. Data for primary vaccination comprised three doses and subjects ranged from 6 month of age to elderly. Data on booster dosing is only available from P201 Part B (adult subjects, 50 and 100 µg doses).

The MAH stated that BLQ values as well as those values classified as outliers and imputed values have been deleted from the nAB data set, however no % values or numbers of excluded values have been provided. The MAH is asked to provide the original data set and should indicate the excluded values per study and reason for exclusion. The MAH should further discuss the use of appropriate methods in order to justify the exclusion of observed values. (**OC**)

Model structure and Assumptions used for model building

The model structure to describe the nAB titer dynamics was developed by adapting the modelling framework used by Rhodes et al. entitled: Using vaccine Immunostimulation/Immunodynamic modelling methods to inform vaccine dose decision making. Ordinary differential equations were used to describe the mechanisms.

The antibody titer dynamics were attributed to several populations of B cells following vaccine administration. The B cell populations included active B cells, plasma cells (short-lived and long-lived) and memory B cells. The effect of mRNA-1273 dose was implemented on the rate at which B cells are activated (δ) and number of memory B cells that could be generated after vaccination using a linear function. δ was initiated at time of primary and re-vaccination and was assumed to be the same at all vaccination points.

$$\delta = a \cdot \left(e^{\frac{-(t-b)^2}{2c^2}} + e^{\frac{-(t-(b+revac\_time))^2}{2c^2}} \right) - (1)$$

Here a is a scalar that scales the shape of the activated B cell recruitment rate parameter, δ. An increase in a is expected to increase the magnitude of the Activated B cell population and therefore the response overall, a does not regulate the timings of the recruitment only the absolute number of activated B cells. b is the Gaussian equation mean and affects the activated B cell recruitment time. c is the variance in the Gaussian equation that describes the activated B cell recruitment rate parameter δ and acts on the overall magnitude of response. t is time, measured in days, and $revac\_time$ is revaccination time measured in days.

Different drug effect (effect of mRNA dose on δ) relationships were tested (linear, Emax) and it was concluded that the dose-response relationship was best described by a linear model. The Gaussian equation time of peak (b) was fixed to 5 days, based on observation of the available data.

The structural model included activation of B-cells following first vaccine dose which then entered the "Active B cells and Plasma cells (Short-lived) population", at rate δ. Equation 2 represents AB1, the pool of activated B cells. These cells then either died, at rate μ, or transitioned into memory B cells, at rate βAB, or differentiated to LLPCs, at rate βLL. This transition rate to LLPCs (βLL) was estimated to be different after each re-vaccination.

$$\frac{dAB1}{dt} = \delta_1 - \beta_{AB} \cdot AB1 \cdot 0.55 - \beta_{LL1} \cdot AB1 - \mu \cdot AB1 - (2)$$

Active B cells and SLPC lifespan are roughly equivalent and SLPCs are associated with early response with significantly less delay compared to LLPCs. Thus, SLPCs are not modelled as a separate compartment and are pooled in the activated B cell compartment (Active B cells Plasma cells (Short-lived)).

Equation 3 represents memory B cell formation on vaccination. During primary response/1st dose of vaccine the memory cells are formed from the activated B cell pool. Memory B cells were assumed to die, at rate μMB, and LLPCs were also assumed to die, at rate μLL. First vaccine dose has an impact on only the formation of memory B cells. The second vaccine dose has an impact on impact on both formation and proliferation (RMB) of memory B cells.

$$\frac{dMB1}{dt} = \beta_{AB} \cdot AB1 \cdot 0.55 - \beta_{MB} \cdot MB1 + R_{MB} \cdot MB1 \cdot \ln\left(\frac{MB_{max}}{MB(t)}\right) - \mu_{MB} \cdot MB1 - (3)$$

Upon re-vaccination due to the second dose, in addition to primary response a recall response driven by previously created memory B cells with high-affinity receptors is initiated. The primed memory B cells proliferate and differentiate (compartment (Memory B cells)) immediately to form LLPCs that secrete antibodies. A fraction of memory B cells move back into the germinal centre for further maturity affinity training. This is known as the anamnestic response. As the memory B cells are primed to the antigen during the 1st dose of vaccination, the response now is rapid as their activation threshold is lower. Thus, response is quicker as they quickly generate LLPCs of higher quality leading to greater amplitude of secreted antibodies.

Following re-vaccination, two process were initiated simultaneously in the model: First, memory B cells replicated at a rate RMB for τ days (equation 4). Following replication, memory B cells differentiated to LLPC. These cells enter the "AB2 pool of activated B cell" population (compartment (Active B cells and Plasma (Short-lived) cells), at rate βMB. The number of memory B cells that could be generated after vaccination was dependent on the vaccine dose and was limited to a maximum by controlling the proliferation rate of memory B cells (RMB) using the following equations:

$$\mathrm{R}_{MB}(\mathrm{t}) = R_{MB} \cdot \ln\left(\frac{MB_{max}}{MB(t)}\right) - (4)$$

$$MB_{max} = Dose \cdot SLOPE - (5)$$

where: RMB(t) is the proliferation rate of memory B cells at time=t, $MBmax$ is the maximum number of memory B cells, $MB(t)$ is the number of memory B cells at time t, $Dose$ is mRNA- 1273 dose, in mg, and $SLOPE$ is the number of memory B cells that are generated per each 1 μg dose of mRNA-1273.

As with primary vaccination, B cells were again activated and entered the Activated B cells compartment, at rate δ2 compartment (Active B cells Plasma (Short-lived) cells), then either died, at rate μ, or transitioned into memory B cells (MB) at rate βAB, or differentiated to LLPCs, at rate βLL2.

$$\frac{dAB2}{dt} = \delta_2 - \beta_{AB} \cdot AB2 \cdot 0.55 - \beta_{LL2} \cdot AB2 - \mu \cdot AB2 + \beta_{MB} \cdot MB1 - (6)$$

The production rate of LLPC is βLL1 and this production rate to LLPCs (βLL) was estimated to be different after re-vaccination βLL2, essentially at a faster rate. LLPCs were assumed to die, at rate μLL.

$$\frac{dLL1}{dt} = \beta_{LL1} \cdot AB1 - \mu_{LL} \cdot LL1 - (7)$$

$$\frac{dLL2}{dt} = \beta_{LL2} \cdot AB2 - \mu_{LL} \cdot LL2 - (8)$$

The observed antibody titer was assumed to be produced by SLPC and LLPC at rate $kMAB$. The rate of antibody titer production varies between the two types of plasma cells. LLPCs have a higher antibody secretion rate compared to SLPC. $kMAB$ is secretion rate of antibody by plasma cells and since SLPCs have a lower rate of antibody secretion we have reduced the secretion rate by multiplying it with a scalar 0.45 * $kMAB$, a value derived from our previous in-house work.

$$\frac{dAT}{dt} = k_{MAB} \cdot AB1 \cdot 0.45 + k_{MAB} \cdot LL1 + k_{MAB} \cdot AB2 \cdot 0.45 + k_{MAB} \cdot LL2 - k_{el} \cdot AT - (9)$$

The transition rate from active B cells to memory B cells (βAB), the death rate of long-lived plasma cells (μLL), the proliferation rate of memory B cells (RMB), the death rate of memory B cells (μMB), the

memory B cell replication time (τ), the secretion rate of antibody by plasma cells ($kMAB$) and the elimination rate for antibody (kel) were fixed to values found in literature (Chen et al, A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins: Part 1). All other parameters were free to be estimated.

For booster response, as with primary and secondary vaccination, B cells were again activated and entered the Activated B cells compartment, at rate δ3 (compartment (Active B cells Plasma (Short-lived) cells), then either died, at rate μ, or transitioned into memory B cells (MB) at rate βAB, or differentiated to LLPCs, at rate βLL3.

$$\frac{dAB3}{dt} = \delta_3 - \beta_{AB} \cdot AB3 \cdot 0.55 - \beta_{LL3} \cdot AB3 - \mu \cdot AB3 + \beta_{MB} \cdot MB2 \ (10)$$

Upon booster dose administration the pool of memory B cells formed after vaccination are replicated at a rate RMB for τ days (equation 4). Following replication, memory B cells differentiated to LLPC (LL3). These cells enter the "AB3 pool of activated B cell" population (compartment (Active B cells and Plasma (Short-lived) cells), at rate βMB. The number of memory B cells that could be generated after vaccination was governed by the same equation as for the first revaccination.

$$\frac{dMB2}{dt} = \beta_{AB} \cdot AB2 \cdot 0.55 - \beta_{MB} \cdot MB2 + R_{MB} \cdot MB2 \cdot \ln\left(\frac{MB_{max}}{MB(t)}\right) - \mu_{MB} \cdot MB2 \ (11)$$

The production rate of LLPC is βLL3 and this production rate to LLPCs (βLL) was estimated to be different compared to primary (βLL1) and secondary vaccination (βLL2), essentially at a faster rate. LLPCs were assumed to die, at rate μLL.

$$\frac{dLL3}{dt} = \beta_{LL3} \cdot AB3 - \mu_{LL} \cdot LL3 \ (12)$$

The observed antibody titer was assumed to be produced by SLPC and LLPC at rate $kMAB$. The rate of antibody titer production varies between the two types of plasma cells. LLPCs have a higher antibody secretion rate compared to SLPC. $kMAB$ is secretion rate of antibody by plasma cells and since SLPCs have a lower rate of antibody secretion we have reduced the secretion rate by multiplying it with a scalar 0.45 * $kMAB$, a value derived from our previous in-house work.

$$\begin{aligned}\frac{dAT}{dt} = {} & k_{MAB} \cdot AB1 \cdot 0.45 + k_{MAB} \cdot LL1 + \\ & k_{MAB} \cdot AB2 \cdot 0.45 + k_{MAB} \cdot LL2 + \\ & k_{MAB} \cdot AB3 \cdot 0.45 + k_{MAB} \cdot LL3 - k_{el} \cdot AT \ (13)\end{aligned}$$

Model development followed the steps outlined in flowchart above.

Initially only the primary vaccination data, i.e. levels after the first two doses were used.

The developed model for two doses was then extended to the booster assuming the revaccination response mechanism to be similar. So, in the second step, the parameters from the primary vaccination model were fixed and only the parameters relevant to booster dose were estimated.

Assessor's comment:

The model structure was adapted from Rhodes et al. There, the modelling framework was used to translate multi-dose tuberculosis vaccine immune responses from mice to predict most immunogenic

dose in humans. Only few pooled Phase I data in adult human (N=10 and N=8) were available for model validation.

Here, several parameters have been fixed based on different literature (Rhodes et al and Chen et al) and also based on sensitivity analyses that were not shown or provided for assessment, whether fixing to these values can be supported. In addition, some parameters that were fixed or estimated are not identical or in the range with corresponding values from literature. Parameter "death rate of short lived plasma cells" was estimated to 0.0653, the corresponding value from Chen et al. is 0.2310 and 0.2518 for activated B cells. Activation rate of memory B cells was estimated to 0.087 day-1, the corresponding value in Chen et al. is 3. Some other fixed parameters differ only slightly, Memory B cell replication time (days) of 5 could not be found in the list of parameters from Chen et al. and was set ad on internal data not (again not shown). Information on initial conditions is missing. Assumptions are overall poorly justified.

Taken together, parameter that are used in the modelling framework are indicated to be not plausible and not identifiable from the data. Predictability in particular outside the observation (that would be the case for prediction of nAB following a booster of different doses in the adolescent subgroup) is not deemed credible given the context of use.

Initially only the primary vaccination data, i.e. levels after the first two doses were used to estimate the non-fixed parameters. The developed model for two doses was then extended to the booster assuming the re-vaccination response mechanism to be similar. The parameter from the primary vaccination model were fixed and only the parameters relevant to booster dose were estimated. Although, no supporting data for the assumption of similarity has been provided, the two-step process for parameter estimation is in general endorsed.

The elimination rate for antibody (kel) was also fixed to a value in the range of that found in literature (Chen et al, A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins: Part 1). Elimination of mabs is however indicated to be dependent on weight. Weight was stated to be intended to be investigated during covariate selection, however, no information in this regard has been provided in the modelling and simulation report. In addition, the included AGE effect was only tested and introduced on a scaling factor V (volume), but one is not informed about the meaning/function of V in the mechanistic modelling framework. In particular, AGE does not reflect any degree of maturation that should be included in the model, as data from age group 6 month to two years of age were used for model building. See section Covariates in this regard.

It was stated in the modelling report that different drug effect (effect of mRNA dose on δ) relationships have been tested (linear, Emax) by the MAH, and it was concluded that the dose-response relationship was best described by a linear model. However, no supporting documents could be found. Dose response is informed by two different doses tested in each age group, however this (potentially linear) relationship is expected to be different per age groups.

The MAH is asked to justify the assumption that a linear function would be appropriate to characterise the drug effect **(OC)**

The observed antibody titer was assumed to be produced by SLPC and LLPC at rate $kMAB$, a value derived from our previous in-house work by the MAH. No further information on the derivation of this parameter was provided with regards to this parameter. The MAH is asked to provide further information on the selection of kMAB, that seems to be a sensitive parameter for both, primary and booster response **(OC).**

It is indicated that the rate of antibody titer production varies between the two types of plasma cells SLPC and LLPC. LLPCs have a higher antibody secretion rate compared to SLPC. $kMAB$ is secretion rate of antibody by plasma cells and since SLPCs have a lower rate of antibody secretion we have reduced

the secretion rate by multiplying it with a scalar 0.45 * $kMAB$. Again, no further data to support the setting of this scaling factor to 0.45 could be found in the modelling report and should be provided. Of note, this parameter is reflected with 0.44 in the table listing the final parameter estimates. **(OC)**

Covariate selection

Inter-individual variability was estimated for the scaling factor, representing volume, only. Covariates evaluated included age, bodyweight and revaccination time. Demographic characteristics (age, sex, body weight) were available in clinical studies that were added to the analysis dataset. Two covariates were assessed on the scaling factor, Volume of the IS/ID model, namely age of the subject and the dose received.

Assessor's comment:

Inter-individual variability was estimated for the scaling factor, representing volume, only. Volume was estimated to 1.21e11 without statement of any unit and statement of plausibility. In the Methods part, it was stated that potentially relevant covariates evaluated included age, bodyweight and revaccination time, these demographic characteristics (age, sex, body weight) were available in clinical studies. However, only two covariates were assessed on the scaling factor, Volume of the IS/ID model, namely Age of the subject and the Dose received, which is not supported. Moreover, it was informed that dose played an important factor in the non-linear production of activated B cells and in a non-linear dose-dependent production of memory-B cells, however seems not to be tested whether a covariate on these parameters would have been of statistical relevance. Other parameters such as kel (elimination of the antibody) or potentially relevant covariates including weight, and maturation (nAB data collected from very young subjects aged from 6 month to 2 years of age) have not been addressed. The covariate selection process could not be followed given the details in the Modelling report. It seems that it was not following a definite method, rather than just opposing the decrease in the objective function value by adding AGE and AGE+DOSE effects on V. No significance criterion was provided that would justify the selection of these covariates, that in addition seem to be correlated (Figure 4-3). In addition, no formula could be find that reflects how AGE and DOSE were implemented as covariate on V, and how V is connected to the modelled mechanistic dynamic. The proper integration of AGE and WEIGHT effects in this regard is however deemed pivotal, given the age range of subjects included in the population analysis. To circumvent these issues and to render the modelling more predictive – in particular concerning transferability to adolescents – exclusion of data from young children <2 years of age from model building is recommended. Overall, the details in terms of pre-specified analysis planned and documentation of modelling exercises are deemed incomplete, and not fully in line with the guideline on pop PK analysis.

The MAH is asked to discuss the role of volume V in the modelling framework, including this would represent a physiological systems variable or just needed to describe the data. In this regard, a re-discussion of covariate selection is to be provided by the MAH taking other potentially clinically relevant covariates such as weight into account. V as the single parameter for testing covariate effects should be further justified. As long as no maturation is included in the model, and AGE and weight effects are not clearly reflected, the inclusion of data from very young subjects for model building is not supported **(OC).**

Model diagnostics

The following criteria were considered in performing model selection:

- Goodness-of-fit diagnostic plots and other graphical assessments
- Minimum value of the objective function (MVOF)
- Shrinkage of the deviation of an individual-specific parameter estimate from the population typical value
- Graphical Assessment

Standard goodness-of-fit diagnostic plots were generated including:

- Observed concentrations versus population predictions
- Observed concentrations versus individual predictions
- Individual subject fits
- Visual predictive checks

For the final combined post-booster model, a basic goodness of fit plots is shown below

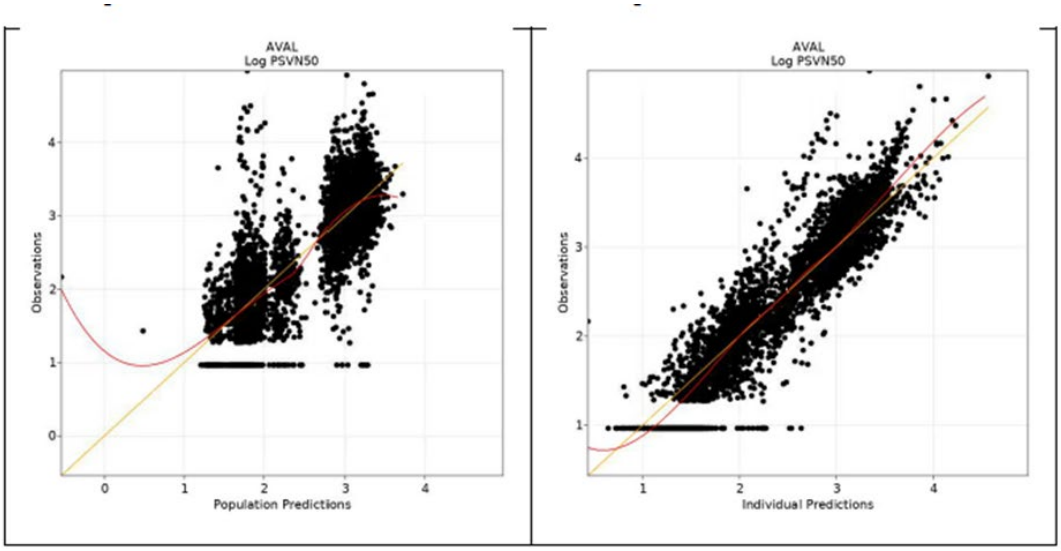

Figure 4-4: Diagnostic Plots for the Final IS/ID Model of mRNA-1273
Note: Circles represent observed data; the orange line is the line of identity; the red line represents a LOESS smoother.

Adolescent individual fits for nAB titer following mRNA-1273 administration are shown in Figure 4-5 (Study P203).

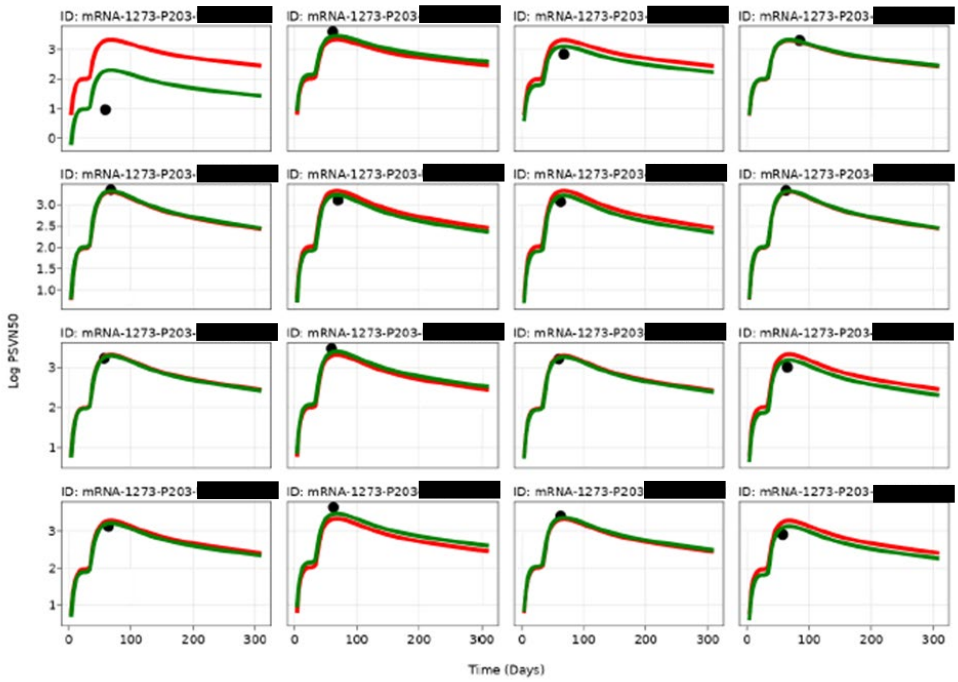

Figure 4-5: Representative individual fits for P203 at 100µg Dose Administered 28 days apart
Green line: individual predictions, red line: population predictions, black dots: observed data

Figure 4-8 on the other hand shows the individual fits from representative post-booster dose fits.

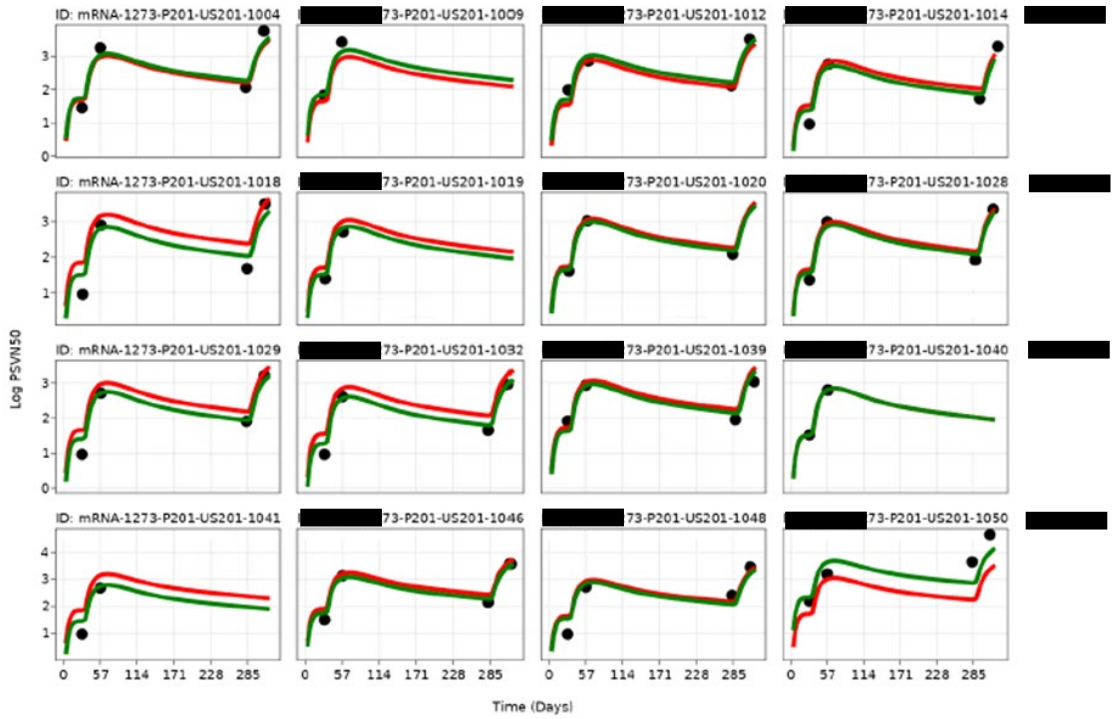

Figure 4-8: Representative individual fits for P201 Part A 50µg
Green line: individual predictions, red line: population predictions, black dots: observed data

The predictive performance of the final models was assessed using visual predictive checks (VPC) and by comparing the mean GMT nAB titer of the model grouped by age and dose group compared to the

observed mean GMT in these groups. In addition, the % difference between the observed and predicted was computed (see table below).

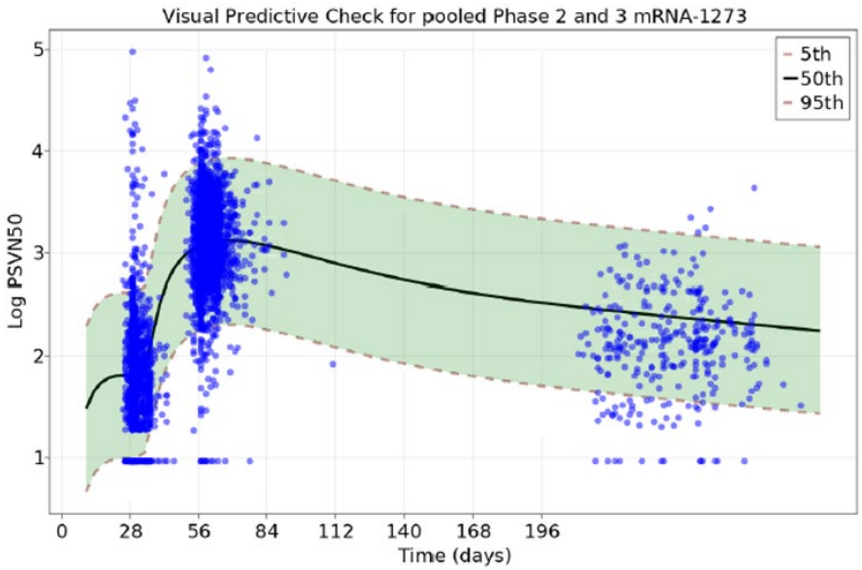

Figure 4-9: Visual predictive checks of the final booster model.
The green shaded area represents the 90% prediction interval, and the lines represent the quantiles.

Table 4-4: Comparison of Observed and Model predicted Day 57 nAB GMT Across Age and Dose Groups

Study	Dose	Age Group	N	Observed nAb GMT (95%CI)	Predicted nAb GMT (95%CI)	%Difference Between (Observed vs Predicted GMT)
301	100µg	≥18	1055	**1081** (1020, 1146)	1291 (1188, 1393)	19.4
301	100µg	≥18 to <25	295	**1299** (1181,1429)	1227 (1007, 1448)	5.8
301	100µg	≥18 to <65	700	**1207** (1126,1293)	1366 (1254, 1479)	13.1
201	50µg	≥18y	185	**643** (569, 726)	709 (659,709)	10.2
203	100µg	≥12y to <18y	340	**1402** (1280, 1535)	1734 (1671, 1798)	23.6
204	100µg	≥6y to <12y	57	**1888** (1520, 2344)	2483 (2374, 2591)	31.5
	50µg		521	**1610** (1456, 1780) [Arm8, N=320]	1827 (1747, 1907)	13.4
	25µg	≥2y to <6y	50	**1014** (846, 1215)	1290 (1224, 1355)	27.2
	50µg		68	**1847** (1602, 2130)	1767 (1678, 1857)	-4.3
	25µg	≥6m to <2y	97	**1783** (1542, 2061)	1718 (1584.0, 1852.0)	-3.6

Individual random effects were plotted versus covariates such as study, age, dose. Individual random effects versus covariates included in the final model were compared in the base and final models to assess whether trends have been removed through the addition of covariate effects and whether any residual trends remain. Correlation plot matrices of individual random effects were explored to assess possible correlations between parameters. Individual fitted plots overlaid on observed data were examined for the final model to see if the model was able to capture the trends in the observed data on an individual level and to identify any unexplained or potentially erroneous data.

Covariate of age or dose related to the empirical Bayes estimates are depicted below.

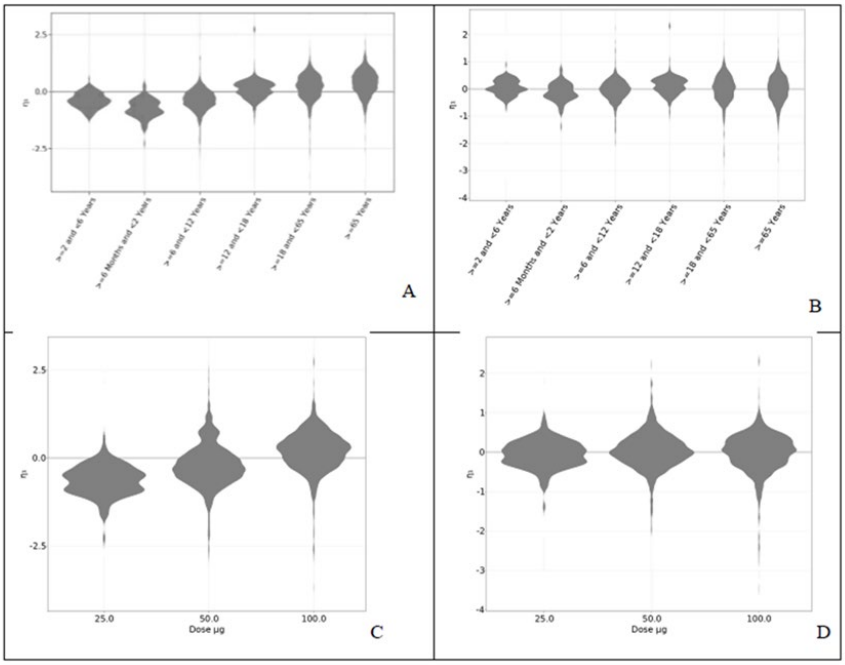

Figure 4-3: Pre-booster dose model's covariate vs empirical Bayes plots for the base (left panels A & C) and final (right panels B & D) against Age Group (top panels A & B) and Dose (bottom panels C & D)

Assessor's comment

Observed vs predicted plots indicate a large variability in the data and a certain degree of shrinkage. In addition, there appear to be some subpopulations where nAB levels have the trend to be under-estimated and deviate from the line of identity. These might be AGE or Dose-groups, or trends driven other effects not reflected in the model.

Adolescent individual fits for nAB titer following mRNA-1273 administration (Study P203) and from representative post-booster dose fits (mean or median) indicate an overall acceptable description of data, however without a measure of variability with regards to the observation and prediction.

The VPC plot indicate the model does not fully capture the variability in the data with respect to all measured time points (pooled Phase 2 and 3 data), with a certain percentage of observation with value 1 on log scale. A trend in over-estimation of observation post day 150 is indicated.

Thus, the MAH is asked to provide VPC plots stratified by age groups, study, and dose. **(OC)**

In the Modelling Report it was stated that individual random effects were plotted versus covariates such as study, age, dose. This was only shown for age groups and doses. Individual random effects versus covariates included in the final model were compared in the base and final models to assess whether trends have been removed through the addition of covariate effects and whether any residual trends remain.

Correlation plot matrices of individual random effects were stated to be explored to assess possible correlations between parameters. No correlation matrices were found and should be provided. It is indicated (Fig 4-3) that dose and age groups indeed are correlated. **(OC)**

Comparison (Table 4-4):

The % difference between the observed and predicted geometric mean titer (Day57) was computed per dose and age groups per study. Observed and predicted GMT were characterised by the respective 95% confidence interval. The percentage difference was greatest (31%) for the response following 100 µg dose in study 204 (age group 6-12 years of age), for the adolescent subpopulation in study 203

(100 µg dose) the % difference was calculated to 23.6%. Of note, 95% CI are completely disjunct. Predicted GMT exceeds the observed GMT for most presented scenarios, including all adult and adolescent subgroups but young adults (18-25 years of age).

Overall, from model evaluation and diagnostic plots some issues were identified concerning the predictive performance of the final model for primary and booster vaccination response.

Results

Data used for analysis and subject characteristics

The distribution of subjects used in this IS/ID analysis and observed log PSVN50 versus time by AGE and DOSE are shown below.

Table 4-1: Distribution of subjects, across studies, dose and age groups used in IS/ID analysis

		Study							
		P203	P204			P301		P201 Part A & B	
		Age Group	Age Group			Age Group		Age Group	
	Overall	>=12 and <18 Years	>=6 Months and <2 Years	>=2 and <6 Years	>=6 and <12 Years	>=18 and <65 Years	>=65 Years	>=18 and <65 Years	>=65 Years
N									
	2781	379	102	125	652	758	368	304	93
Dose, n (%)									
25.0	155 (5.57)	0 (0.0)	102 (100.0)	53 (42.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
50.0	860 (30.92)	0 (0.0)	0 (0.0)	72 (57.6)	590 (90.49)	0 (0.0)	0 (0.0)	148 (48.68)	50 (53.76)
100.0	1766 (63.5)	379 (100.0)	0 (0.0)	0 (0.0)	62 (9.51)	758 (100.0)	368 (100.0)	156 (51.32)	43 (46.24)
AGE, median [Q1, Q3]									
	29.0 [10.0,58.0]	14.0 [13.0,16.0]	1.0 [0.85,1.0]	4.0 [3.0,5.0]	9.0 [7.0,10.0]	48.0 [38.0,57.0]	69.0 [67.0,73.0]	46.0 [34.75,57.0]	68.0 [66.0,72.0]

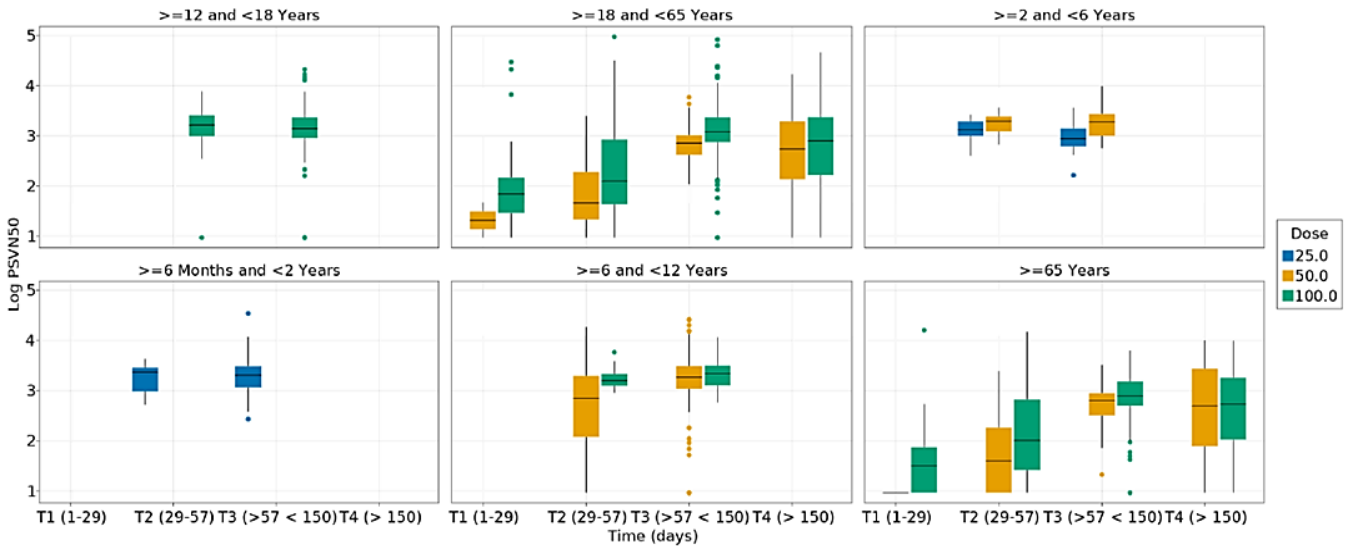

Figure 4-1 Distribution Plots of Observed Log PSVN50 Versus Time by Age Group and Dose.

Exploratory Data Analysis

Distribution plots of GMT of nAB grouped by dose and age group against time are presented in

Table 4-1: Distribution of subjects, across studies, dose and age groups used in IS/ID analysis

	Study								
		P203	P204			P301		P201 Part A & B	
		Age Group	Age Group			Age Group		Age Group	
	Overall	>=12 and <18 Years	>=6 Months and <2 Years	>=2 and <6 Years	>=6 and <12 Years	>=18 and <65 Years	>=65 Years	>=18 and <65 Years	>=65 Years
N									
	2781	379	102	125	652	758	368	304	93
Dose, n (%)									
25.0	155 (5.57)	0 (0.0)	102 (100.0)	53 (42.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
50.0	860 (30.92)	0 (0.0)	0 (0.0)	72 (57.6)	590 (90.49)	0 (0.0)	0 (0.0)	148 (48.68)	50 (53.76)
100.0	1766 (63.5)	379 (100.0)	0 (0.0)	0 (0.0)	62 (9.51)	758 (100.0)	368 (100.0)	156 (51.32)	43 (46.24)
AGE, median [Q1, Q3]									
	29.0 [10.0,58.0]	14.0 [13.0,16.0]	1.0 [0.85,1.0]	4.0 [3.0,5.0]	9.0 [7.0,10.0]	48.0 [38.0,57.0]	69.0 [67.0,73.0]	46.0 [34.75,57.0]	68.0 [66.0,72.0]

Except study P201 and P301 that represent the > 18-year age group, all other studies and age groups had only one time point collected per subject (as per protocol).

In the > 18-year-old subjects, the nAB titer increases with time and the values collected at Day 57 on an average match the Day 57 titers observed with lower doses in other age groups.

GMTs in the T4 group indicate levels after a booster dose collected from 201 Part B. The booster dose in this arm was given anywhere between 180 days to 275 days after the second vaccine dose.

Final IS/ID Model and population IS/ID Analysis

The IS/ID model was used to evaluate a 50 µg booster for the adolescent after a 100 µg prime dose. The schematic of the final population IS/ID model structure and parameter definitions and estimates are shown below:

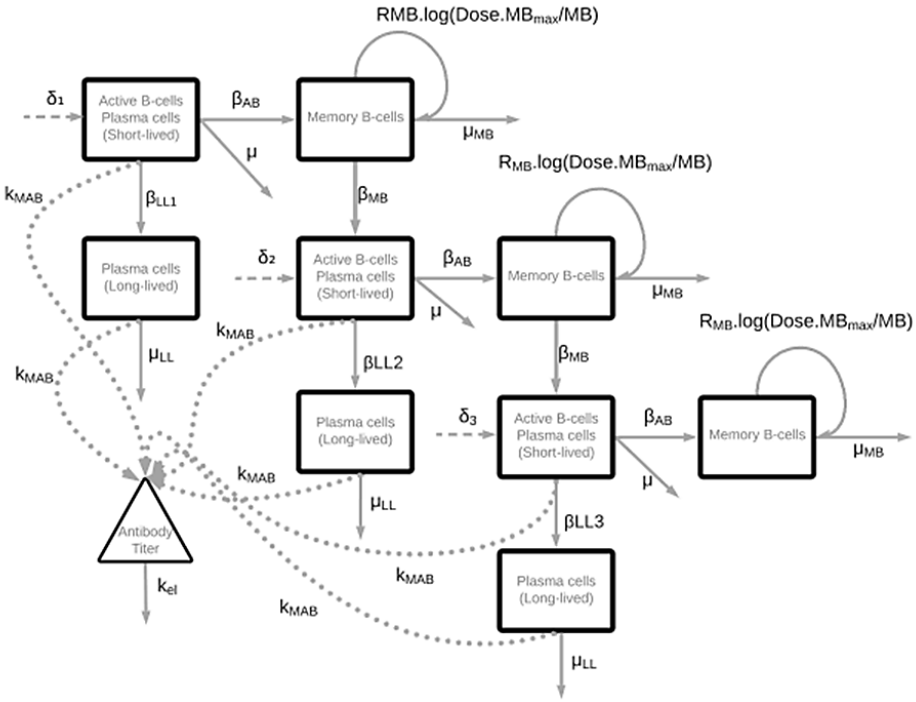

Figure 4-2: Structure Diagram of the IS/ID model

δ_1 = B cell activation rate on 1st vaccination; β_{AB} = Transition rate to memory cells; μ = Death rate of activated B cells and short-lived plasma cells; β_{LL1} =Transition rate to long-lived plasma cells after 1st vaccination; k_{MAB}= Secretion rate of antibody by plasma cells; μLL = Death rate of long-lived plasma cells; μ_{MB} = Death rate of memory B cells; k_{el} = Elimination rate for antibody; δ_2 = B cell activation rate on 2nd vaccination; β_{MB} = Activation rate of memory B cells on 2nd or 3rd vaccination; RMB = proliferation rate of memory B cells; MB_{max} = maximum number of memory B cells; MB = Number of memory B cells; β_{LL2} = Transition rate to long-lived plasma cells after 2nd vaccination; δ_3 = B cell activation rate on 3rd vaccination; β_{LL3} = Transition rate to long-lived plasma cells after 3rd vaccination.

For the pre-booster dose, δ3 , the booster dose component was not active. The final booster model was selected a two consecutive steps:

First step: Analysing Pooled Pre-Booster P301, P201, P204 and P203 data

The structure of the model developed established earlier was used to estimate model parameters. In addition to some system related parameters being fixed, a sensitivity analysis was performed to empirically stabilise a few parameters. At this stage of the analysis, using only data from primary vaccination series, i.e., 2 doses, three models were evaluated,

1. Base model

2. Age as a covariate on scaling factor, volume (V)

3. Dose and age as a covariate on the scaling factor, volume (V)

with results shown below:

Table 4-2: Model metrics for the models tests on the Base and Covariate Models

Metric	Base model	Age as covariate on V	Dose and age as covariate on V
-2 * LogLikelihood	6467.63	5672.58	5606.21
AIC	6481.63	5688.58	5624.21
BIC	6526.6	5739.97	5682.02
(η-shrinkage) η_1	0.199	0.258	0.259
(ϵ-shrinkage) AVAL	0.213	0.179	0.179

Shrinkage on inter-individual variability random effects (η -shrinkage) was estimated to up to 26 % (Table 4-2).

Assessor's comment:

As indicates above, covariate selection does not seem to follow a pre-specified analysis plan. Sensitivity analyses that lead to parameter fixing were not provided. The need for inclusion of Dose effect in addition to AGE-effect on V has not been justified based on any statistical pre-specified criterion.

The decrease in objective function value by introducing additional degrees of freedom is expected.

Second Step: Analysing Post-Booster P201-Part B data

The booster data from P201-partB was then added to the analysis dataset and the third dose, $\delta 3$ was activated to fit the data. The system parameters were fixed to those used or estimated in the pre-booster model.

The full parameter table for the final population IS/ID model for pre- and post-booster analysis fits is presented in Table 4-3. The bootstrap medians were close to the final estimates for both models, and were relatively well centred within the bootstrap 95% CI, except for the transition rate to memory cells (day-1) and number of memory B cells that are generated per each 1 µg dose of mRNA-1273 (cells/µg).

Table 4-3: Population IS/ID model parameters

PARAMETER	DESCRIPTION	PRE-BOOSTER ESTIMATE (95 % CI)	PRE & POST-BOOSTER ESTIMATE (95 % CI)
tva#	Gaussian equation curve multiplier (number of cells)	12.64	12.64
tvb#	Gaussian equation time of peak (days)	5.0	5.0
tvc#	Gaussian equation variance (days)	3.9045	3.9045
tvβAB	Transition rate to memory cells (day^{-1})	0.0392 (0.0001, 0.04)	0.0392
tvμ	Death rate of activated B cells and short-lived plasma cells (day^{-1})	0.0653 (0.05, 0.08)	0.0653
tvβMB	Activation rate of memory B cells (day^{-1})	0.087 (0.07, 0.09)	0.087
tvRem*	Proliferation rate of memory B cells (day^{-1})	0.723	0.723
tvμMB*	Death rate of memory B cells (day^{-1})	7.83e-5	7.83e-5
tvτ*	Memory B cell replication time (days)	5.0	5.0
tvKmab*	Secretion rate of antibody by plasma cells (day^{-1})	8.64e8	8.64e8
tvKel*	Elimination rate for antibody (day^{-1})	0.033	0.033
tvV	Scaling factor	1.1145e11 (9.61e10, 1.27e11)	1.2142e11 (1.11e11, 1.35e11)

tvSLOPE	Number of memory B cells that are generated per each 1 µg dose of mRNA-1273 (cells/µg)	2465.7 (2287.7, 9984.8)	2617.1 (2475.6, 2807.4)
tvβLL1#	Transition rate to long-lived plasma cells after 1st vaccination (day^{-1})	0.00044661	0.00044661
tvβLL2#	Transition rate to long-lived plasma cells after 2nd vaccination (day^{-1})	0.0031606	0.0031606
tvβLL3	Transition rate to long-lived plasma cells after 2nd vaccination (day^{-1})	-	0.00685§ (0.0017, 0.0130)
tvµLL*	Death rate of long-lived plasma cells (day^{-1})	0.005	0.005
tvAGEonV	Age factor on V	4.48e9 (3.75e9, 5.43e9)	4.17e9§ (3.56e9, 4.83e9)
tvDoseonV	Dose factor on V	0.5599 (0.45, 0.69)	0.615§ (0.506, 0.755)
$\Omega_{1,1}$	Between subject variability on scaling factor	0.51 (0.45, 0.58)	0.50§ (0.44, 0.55)
σ_1	Additive error on log scale	0.35 (0.33, 0.36)	0.35§ (0.34, 0.37)
$tv\theta_1$#	Proportion of antibody secretion from SLPC	0.55	0.55
$tv\theta_2$#	Proportion of antibody secretion from LLPC	0.44	0.44

* System parameters fixed to literature values[2]
# System parameters fixed based on sensitivity analysis
§ Parameters estimated for post-booster analysis

Assessor's comment

In total, 6 of the system parameters were fixed to literature values, 7 were fixed based on sensitivity analyses (not shown for assessment). From the remaining parameters, 6 were again estimated based on data only, where the additive error, IIV on V, Age and Dose factor on V and the number of memory B cells that are generated per each 1 µg dose of mRNA1273 (cells/µg) remained at comparative size. For the latter, the 95% CI was found to be smaller for the combined pre- and post-booster estimate. Transition rate to long-lived plasma cells after 3rd vaccination was found to be about twice the one for the second vaccination, however estimated with a wide 95% confidence interval (0.0017, 0.0130). It is unclear how sensitive the nAB dymics would react with changes in fixed and estimated parameters, especially in those with balanced 95% CI (tvSLOPE, tvβAB).

Further comments on chose parameters could be found in the Assessor's comment on the model structure.

Adolescent booster dose predictions

The final IS/ID model with the booster dose included was used to simulated nAB titers on 28 days after a booster dose that was given 6 months after the second dose (100 µg primary vaccine dose).

Specifically, the empirical Bayes estimates from the IS/ID model fits were used to simulate booster dosing in study P203 adolescent subjects (N=379). The ratio of the 28-day post-booster nAB GMT to the pre-booster nAB GMT was taken to compute a geometric mean fold ratio (GMFR) and the confidence interval around that estimate. The model predicted GMFR and its confidence interval were compared to the observed GMFR and confidence interval from the 18-25 year or the 18-55 year age group.

Table 5-1: Comparison of Observed and Model predicted (12-18 years) GMFR for 6-month 50µg booster after 100µg primary dose

Age Group (years)	GMFR (95% CI)	N	Study
18-25	16.32 (4.53, 58.81)	7	P201 Part B
18-55	11.88 (9.38, 15.06)	68	P201 Part B
12-18*	9.04 (8.57, 9.53)	379	P203

** ISID model predicted*

Age Group (years)	Day	GMT (95% CI)
12-18	57	1402 (1280, 1535)
	207	349 (337, 361)*
	236	3159 (3049, 3268)*

** ISID model predicted*

In the actual P201 Part B study, the timing of booster ranged from 180-275 days (6-9 months) after the second dose. The observed GMFR is reflective of this distribution.

In the adolescent predictions, all subjects received the 50 µg booster exactly 6 months after the second primary dose, i.e., at day 208 and the 28-day post booster was at day 236. As a result of the two points above, it is expected that the mean predicted GMFR is lower than the observed across the age groups.

There were only N=7 subjects in 18–25-year age group in 201 Part B and hence the wide observed GMFR and confidence interval.

The model predicted CI for the GMFR for the 12–18-year subjects (9.04 (8.57, 9.53)) lays within the range of the observed CI's for the other age groups, i.e., 16.32 (4.53, 58.81) in 18-25-year (N=7) and 11.88 (9.38, 15.06) in the 18-55-year subjects (N=68).

Assessor's comment:

The model predicted GMFR in adolescents following a 50 µg booster dose 6 month after the second dose, and its confidence interval were compared to the observed GMFR and confidence interval from the 18-25 year or the 18-55 year age group. Comparison is however hampered due to the imprecise timing of the booster dose in age group 18-55 years of age (booster: 6-9 months) and very few subjects (N=7) available in age group 18-25 years of age.

In order to improve the comparability between age groups and to meet the claimed EOI, the MAH is asked to simulate the following scenarios:

- Adolescents receiving 50 µg booster dose 3 months and 9 months after second dose

- Adolescents receiving 25 µg booster dose 3, 6 and 9 months after second dose

- Adult age groups (18-25 and 18-65) receiving 50 µg booster dose 3, 6 and 9 months after second dose.

GMT (+ 95% CI) should be provided post second dose, pre-booster and post-booster and GMFR (+95% CI) should be calculated and compared**. (OC)**

Discussion and conclusion

The model structure was adapted from Rhodes et al. There, the modelling framework was used to translate multi-dose tuberculosis vaccine immune responses from mice to predict most immunogenic dose in humans. Only few pooled Phase I data in adult human (N=10 and N=8) were available for model validation.

Here, several parameters have been fix based on different literature (Rhodes et al and Chen et al) and also based on sensitivity analyses that were not shown or provided for assessment or following the request for supplementary information. In addition, some parameters that were fixed or estimated are not identical or in the range with corresponding values from literature. Overall, parameter that are used in the modelling framework are indicated to be not plausible and not identifiable from the data. This is not acceptable in the context of use.

The MAH requests an amendment to extend the use of a 50 µg booster dose of Spikevax to adolescents (12 to < 18 years) at a dosing interval of at least 3 months after completion of the primary series to prevent COVID-19. Modelling exercises have been conducted to support the submission being based on the extrapolation of safety, immunogenicity and efficacy data from young adults (18 to 25 years of age).

The IS/ID analysis included a total of 2781 subjects pooled across P201 Part B, P203, P204 and P301 clinical studies, of which 63.5 (%) received the 100 µg dose [age groups: 6-12, 12-18 and >18 years of age], 30.92(%) received the 50 µg dose [age groups: 6-12 and 2-6] and 5.57 (%) received the 25 µg dose [age groups:2-6 and 6months – 2 years of age]. Log10 transformed nAB titers (LogPSVN50) data was obtained from clinical studies P201, P301, P203, P204. Clinical and nAB data from young adults however was sparse. Only N=7 subjects in 18–25-year age group in 201 Part B leading to observed GMFR with wide confidence interval. To improve the comparability in nAB response between adolescent and adult subpopulations, respective simulations were asked and have been provided. Requested simulations showed that indeed, no distinct selection of dose and timing of the booster dose could be made while comparing adolescents with adult subpopulations. Given that no regulatory decision is based on modelling and simulation, this is acceptable.

There remains uncertainty concerning the predictive performance of the pop IS/ID model. Several concerns could be identified with respect to the model structure/parameters used and covariate selection and analysis, assumptions were poorly justified, and reporting was not in line with the current guidance for pop PK modelling. Although data from very young children were used for model building, no maturation effect has been included in the model, and AGE and weight effects are not clearly reflected. Model evaluation indicates that the model serves for description of the data only. Justification for assuming a linear function to appropriately characterise the drug effect is still considered poor and there were inconsistencies with statements made in the IS/ID modelling report It was admitted that no further functions were tested and this will be addressed in updated version of the model. Justification of the timing and setting the dose strength of a booster dose for adolescents is however not acceptable based on modelling exercises (medium to high impact), given that no confirmatory efficacy data/nAB data in adolescents from clinical studies following booster vaccination are available.

In total, the modelling and simulation approach for informing paediatric vaccination is acknowledged. Modelling exercises provided and data used for exploratory analyses indicate that the expected nAB response following a 50 µg booster vaccination would be at least in the range of that observed in the adult population. Model-based conclusion and simulation are in support, however should be considered with caution regarding definite decision on timing and dose strength of a booster vaccination in adolescents in the context of this variation procedure.

4. Clinical Safety aspects

4.1. Safety Methods – analysis of data submitted

The safety profile of Spikevax has been characterised within the previously approved indication extension from adults to adolescents 12-<18 years of age (EMA Procedure Number EMEA/H/C/005791/II/0021). The safety database for the indication extension included data from the 08 May 2021 data snapshot. As of this cut-off date 2,486 adolescent received at least one dose of mRNA-1273 vaccine and 2,480 received 2 doses. The median follow-up duration post dose 2 was 53 days for mRNA-1273 recipients. Within this procedure, the reactogenicity of Spikevax in adolescent has been compared to young adults 18-25 years of age. In this submission, the safety database for the use of Spikevax in adolescent is extended by global post-authorisation data from over 7.4 million adolescents completing the full 2-dose regimen.

The present claim for approval of a booster dose of 50 µg of Spikevax in adolescents 12-<17 years of age given at least 3 months after completion of the primary vaccination schedule (2nd dose of Spikevax) is based on extrapolation of safety, immunogenicity, and efficacy data from young adults (18 to 25 years of age) to adolescents (12-<18 years of age).

The following studies are the base to support the extrapolation of the safety of Spikevax when given as booster of 50 µg to adolescent.

Initial marketing authorisation and indication for adults:

P301: Ongoing pivotal randomised, initially observer-blind, placebo-controlled study conducted in more than 30,000 participants, that supported the indication of COVID-19 Vaccine Moderna in adults ≥ 18 years of age (EMA Procedure Number EMEA/H/C/005791/0000)

Booster and heterologous booster after full primary vaccination:

P201: Part B of trial P201 is an open-label part 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). The interval between the prime series in Part A and the booster ranged from 5.8-8.8 months, with a mean of approximately 7.1 months. This study has been assessed within EMA procedure EMEA/H/C/005791/II/0034 to support the approval of a 50 µg booster dose of Spikevax in adults.

Within EMA procedure EMEA/H/C/005791/II/0042 a heterologous booster of 50 µg of Spikevax was approved in adults. The approval was based on the NIH DMID 21-0012 study. The interval between primary series and booster injection was shorter in the DMID trial compared to the P201 trial with approximately 12-20 weeks after full primary vaccination. Based on this study and on the Com-COV2, and the COV-BOOST studies, the booster interval was shortened to 3 months after primary vaccination.

Indication extension to adolescent:

P203: Ongoing, two-part (Part A and Part B), Phase 2/3, randomised, observer-blind, placebo-controlled study that evaluates the safety, reactogenicity, and efficacy of Spikevax in healthy adolescents aged 12 - < 18 years. This study was evaluated in EMA procedure EMEA/H/C/005791/II/0021 to approve the licensure for adolescent 12-<18 years of age.

The present submission to support the use of Spikevax for a booster dose in adolescent is completed by global post-authorisation data from an estimated number of over 20 million booster doses (either 50 µg or 100 µg) administered to 18- to 25-year-old young adults. A 3rd 100 µg dose 28 days post dose 2 is licensed and recommended for severely immunocompromised individuals 12 years of age and older (100 micrograms) and children 6 - 11 years (50 micrograms).

4.2. Safety Results

Analysis of Solicited Adverse Reactions in Participants 12 to < 18 Years of Age Compared With 18 to 25 Years of Age

Within procedure EMEA/H/C/005791/II/0021 that led to approval of the extension of indication for primary immunisation to adolescent, the reactogenicity of 2 doses of 100 µg of Spikevax has already been compared to adults 18-25 years of age. Solicited ARs from 12- to < 18-year-old participants in the mRNA-1273 group (100 µg) of Study P203 were compared with solicited ARs reported from 18- to 25-year-old participants in the mRNA-1273 group (100 µg) in Part A of Study P301. The 08 May 2021 data snapshot relevant for the approval included a median study follow-up duration of 53 days (approximately 2 months) after dose 2. As of 08 May 2021 (data snapshot date), 2,486 of 2,489 randomised adolescent participants (99.9%) in the mRNA-1273 group and 1,240 of 1,243 randomised participants (99.8%) in the placebo group had received dose 1. 2,480 (99.6%) and 1,222 (98.3%) in the two groups had received dose 2, respectively (information is taken from the AR for procedure II/021).

The main reactogenicity results were summarised within the clinical overview of the present submission and are shown below.

Table 1 and Table 2 present local and systemic solicited ARs by dose and severity, respectively.

Table 1: Frequency of Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 12 to 17 Years of Age (Study P203) and Participants 18 to 25 Years of Age (Study P301) (Solicited Safety Analysis Set)

	Dose 1[a]		Dose 2[a]	
	Study P203 ≥ 12 to 17 Years	Study P301 ≥ 18 to 25 Years	Study P203 ≥ 12 to 17 Years	Study P301 ≥ 18 to 25 Years
Event	mRNA-1273 N = 2482 n (%)	mRNA-1273 N = 878 n (%)	mRNA-1273 N = 2478 n (%)	mRNA-1273 N = 819 n (%)
Any local adverse reaction				
Any	2339 (94.2)	793 (90.3)	2314 (93.4)	739 (90.2)
Grade 3	170 (6.8)	52 (5.9)	220 (8.9)	63 (7.7)
Pain				
Any	2310 (93.1)	785 (89.4)	2290 (92.4)	732 (89.4)
Grade 3	133 (5.4)	47 (5.4)	126 (5.1)	53 (6.5)
Erythema (redness)				
Any	334 (13.5)	33 (3.8)	484 (19.5)	60 (7.3)
Grade 3	21 (0.8)	2 (0.2)	72 (2.9)	7 (0.9)
Swelling (hardness)				
Any	403 (16.2)	71 (8.1)	509 (20.5)	83 (10.1)
Grade 3	27 (1.1)	5 (0.6)	56 (2.3)	8 (1.0)
Axillary swelling or tenderness				
Any	578 (23.3)	160 (18.2)	519 (21.0)	153 (18.7)
Grade 3	10 (0.4)	2 (0.2)	7 (0.3)	3 (0.4)

Abbreviations: Any = grade 1 or higher; AR = adverse reaction; eDiary = electronic diary; N = number of exposed participants who submitted any data for the event; SAR = solicited adverse reaction.

Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any SAR data from the time of the first (second) study injection through the following 6 days.

[a] The First and Second Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first or second dose and contributed any SAR data (eDiary) from the time of first or second dose through the following 6 days.

[b] Pain Grade 3: any use of prescription pain reliever/prevents daily activity;

[c] Erythema (redness) and swelling (hardness) Grade 3: > 100 mm/> 10 cm;

[d] Axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity;

Source: Study P203, Table 3.1.1.1; Table 3.1.1.2 and Study P301, Table 14.3.1.1.14.1; Table 14.3.1.1.14.2.

Table 2: Frequency of Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 12 to 17 Years of Age in Study P203 and Participants 18 to 25 Years of Age in Study P301 (Solicited Safety Analysis Set)

Event	Dose 1[a]		Dose 2[a]	
	Study P203 ≥ 12 to 17 Years	Study P301 ≥ 18 to 25 Years	Study P203 ≥ 12 to 17 Years	Study P301 ≥ 18 to 25 Years
	mRNA-1273 N = 2482 n (%)	mRNA-1273 N = 878 n (%)	mRNA-1273 N = 2478 n (%)	mRNA-1273 N = 819 n (%)
Any systemic AR				
Any	1701 (68.5)	578 (65.8)	2134 (86.1)	702 (85.7)
Grade 3	108 (4.4)	46 (5.2)	340 (13.7)	177 (21.6)
Grade 4	0	0	3 (0.1)	0
Fever				
Any	63 (2.5)	15 (1.7)	302 (12.2)	149 (18.2)
Grade 3[b]	9 (0.4)	0	46 (1.9)	10 (1.2)
Grade 4[b]	0	0	1 (< 0.1)	0
Headache				
Any	1106 (44.6)	376 (42.8)	1739 (70.2)	574 (70.1)
Grade 3[c]	56 (2.3)	28 (3.2)	112 (4.5)	52 (6.3)
Grade 4[c]	0	0	1 (< 0.1)	0
Fatigue				
Any	1188 (47.9)	403 (45.9)	1679 (67.8)	567 (69.2)
Grade 3[d]	33 (1.3)	13 (1.5)	188 (7.6)	96 (11.7)
Grade 4[d]	0	0	0	0
Myalgia				
Any	668 (26.9)	249 (28.4)	1154 (46.6)	490 (59.8)
Grade 3[d]	24 (1.0)	12 (1.4)	129 (5.2)	92 (11.2)
Grade 4[d]	0	0	0	0
Arthralgia				
Any	371 (15.0)	154 (17.5)	716 (28.9)	340 (41.5)
Grade 3[d]	15 (0.6)	5 (0.6)	57 (2.3)	47 (5.7)
Grade 4[d]	0	0	0	0

Event	Dose 1[a]		Dose 2[a]	
	Study P203 ≥ 12 to 17 Years	Study P301 ≥ 18 to 25 Years	Study P203 ≥ 12 to 17 Years	Study P301 ≥ 18 to 25 Years
	mRNA-1273 N = 2482 n (%)	mRNA-1273 N = 878 n (%)	mRNA-1273 N = 2478 n (%)	mRNA-1273 N = 819 n (%)
Nausea/vomiting				
Any	281 (11.3)	113 (12.9)	591 (23.9)	231 (28.2)
Grade 3[e]	2 (< 0.1)	0	2 (< 0.1)	0
Grade 4[e]	0	0	1 (< 0.1)	0
Chills				
Any	456 (18.4)	126 (14.4)	1066 (43.0)	431 (52.6)
Grade 3[f]	4 (0.2)	0	11 (0.4)	11 (1.3)
Grade 4[f]	0	0	0	0

Abbreviations: Any = grade 1 or higher; AR = adverse reaction; eDiary = electronic diary; IP = investigational product; N = number of exposed participants who submitted any data for the event; SAR = solicited adverse reaction.

Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received at least 1 dose of IP and contributed any solicited AR data (ie, had at least 1 postbaseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) dose and contributed any solicited AR data from the time of the first (second) dose through the following 6 days. Medications were collected on the eDiary.

[a] The First and Second Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received dose 1 or dose 2 and contributed any SAR data (eDiary) from the time of dose 1 or dose 2 through the following 6 days.

[b] Fever is defined as: Grade 3 = 39°C to 40°C; Grade 4 = greater than 40°C.

[c] Headache: Grade 3 significant, any use of prescription pain reliever or prevents daily activity; Grade 4 requires emergency room visit or hospitalization.

[d] Fatigue, myalgia, arthralgia: Grade 3 significant, prevents daily activity; Grade 4 requires emergency room visit or hospitalization.

[e] Nausea/vomiting: Grade 3 prevents daily activity, requires outpatient intravenous hydration; Grade 4 requires emergency room visit or hospitalization for hypotensive shock.

[f] Chills: Grade 3 prevents daily activity and requires medical intervention; Grade 4 requires emergency room visit or hospitalization.

Source: Study P203, Table 3.1.1.1; Table 3.1.1.2; Table 1.7.1; Table 1.7.2 and Study P301, Table 14.3.1.1.14.1; Table 14.3.1.1.14.

In both age groups the reactogenicity was higher post dose 2 compared with post dose 1. The comparison of local and systemic reactogenicity indicates that the overall incidence of solicited local ARs including grade 3 ARs is slightly higher in the age cohort 12 to <18 years compared with the age cohort 18 to 25 years of age. The highest difference in local reactogenicity has been observed for injection site erythema and swelling, almost no difference for injection site pain. No meaningful difference could be observed for solicited systemic ARs including grade 3 ARs. The incidence of systemic solicited ARs tended to be comparable or slightly higher in young adults 18 to 25 years of age compared with adolescent 12 to <18 years of age. The incidence of severe (grade 3) systemic ARs in adolescent is lower post dose 2, compared to young adults (13.7 versus 21.6). The reactogenicity post dose 2 is higher in both age groups. The persistence of solicited ARs is comparable between the two age groups. Results must be interpreted with caution since the sample size in the age cohort 12 to <18 years was 3 fold higher than in the age cohort 18 to 25 years of age and it is a historical control group. Overall, no clinically meaningful difference in safety and reactogenicity could be observed in adolescents compared to young adults.

Analysis of Unsolicited Adverse Events in Participants 12 to < 18 Years of Age Compared With 18 to 25 Years of Age

As previously demonstrated in EMA Procedure Number EMEA/H/C/005791/II/0021, a comparison of unsolicited AE revealed similar results in adolescents and young adults. The incidence of unsolicited AEs was similar between age groups, with rates of 21% in adolescents and 26% in young adults within 28 days after any injection. Most events were considered to be not vaccine-related and not severe. Within 28 days after vaccination, there were 2 SAEs occurring in the adolescent group (< 0.1%) and no SAEs were reported in young adults. At the time of data snapshot, SAEs were reported by 0.2% of adolescent subjects in the MRNA-1273 vaccine group (6 subjects). SAEs in the mRNA-1273 vaccine group beside the 2 events that occurred through day 28 (drug-induced liver injury and appendicitis together with diarrhoea, vomiting, and post-procedural fever) were pectus excavatum, suicidal ideation (2 subjects), and depression suicidal (1 subject). None of the SAEs was considered vaccine related. No cases of MIS-C were reported in adolescents, but the sample number is insufficient to detect this or other rare or very rare events. Results are summarised in Table 3.

Table 3: Summary of Unsolicited Adverse Events in Participants 12 to < 18 Years of Age Compared With 18 to 25 Years of Age

	mRNA-1273 Adolescents N=2486	Young Adults N=878
Unsolicited adverse events	**n (%)**	**n (%)**
Unsolicited adverse event up to 28 days after any injection	510 (20.5)	227 (25.9)
Non-serious unsolicited adverse event	509 (20.5)	227 (25.9)
Related non-serious unsolicited AE	312 (12.6)	103 (11.7)
Severe non-serious unsolicited AE	2 (< 0.1)	9 (1.0)
Related severe non-serious unsolicited AE	0	3 (0.3)
Medically attended adverse event up to 28 days after any injection	156 (6.3)	85 (9.7)
Related MAAE	19 (0.8)	15 (1.7)
SAE up to 28 days after any injection	2 (< 0.1)	0
Related SAE	0	0
Deaths up to data cutoff	0	0
AE leading to discontinuation of the vaccine up to 28 days after any injection	0	3 (0.3)

Abbreviations: AE=adverse events; MAAE=medically attended adverse events; SAE=serious adverse events

Source: Study P203, Table 14.3.1.7.15; and Table3.2.1.1.

As stated in the clinical overview there were no SAEs assessed by the investigator as related to study vaccine, no deaths, and no cases of MIS-C reported during the entire study period of trial P203. As of 01 Feb 2022 in the live database of the ongoing trial P203 (Open-label Phase now), there were 31 SAEs reported, and none were assessed as related to the study vaccine. There were no deaths and no cases of MIS-C reported.

Assessor´s comment:

Based on the safety data submitted within procedure EMEA/H/C/005791/II/0021 to approve the indication extension to adults, the following has been concluded:

A comparison with reactogenicity data from study P301 indicated a slightly higher local reactogenicity for all solicited local ARs except for pain in the age cohort 12 to <18 years compared with the age cohort 18 to 25 years of age. No clinical meaningful difference could be observed for solicited systemic ARs. The incidence tended to be comparable or slightly higher in the age cohort 18 to 25 years of age compared with the age cohort 12 to <18 years of age. A comparison between adolescents and young adults suggests that the incidence of severe (grade 3) systemic ARs is somewhat lower for adolescents (4.4% dose 1, 13.7% dose 2), compared to young adults (5.2% dose 1, 21.6% dose 2). Results must be interpreted with caution since the sample size in the age cohort 12 to <18 years was 3 fold higher than in the age cohort 18 to 25 years of age and it is a historical control group.

A high level overview of the ongoing trial P203 has been provided in the clinical overview. This includes information, that no SAEs assessed by the investigator as related to study vaccine, no deaths, and no cases of MIS-C were reported during the entire study period. As of 1st February 2022, there were 31 SAEs reported in the live database of this ongoing study. This trial is now ongoing in an open-label design. Reference to corresponding listings are included in the overview, but were not submitted. As the scope of this submission is the approval of a booster dose of Spikevax for adolescent based on the extrapolation of reactogenicity to young adults, the update listings and safety data for trial P203 were not subsequently requested or assessed. The assessment of the ongoing trial P203 is not the scope of this submission.

Due to the comparable reactogenicity profile observed for adolescents and young adults 18-25 years of age after mRNA-1273 primary vaccination and taking into consideration results from the ongoing safety monitoring in study P203 extrapolation of reactogenicity profile after the booster dose from young adults to adolescents maybe taken into consideration. However, the PDCO has recently concluded that the reactogenicity profile for the booster dose in adolescents shall be characterised as it could provide some insight into the general safety profile as well. Therefore, the MAH is requested to elaborate on existing data allowing for an estimation of reactogenicity after the third dose in adolescents.

In addition to support the approval of a Spikevax booster dose in adolescents, the MAH submitted a clinical overview, the only document that has been submitted for the assessment of safety data. The clinical overview includes a high level summary of post authorisation pharmacovigilance data of the Safety Summary Report (SSR) #11. The SSRs are under PRAC surveillance. The assessment of the post-approval safety data from the SSR #11 can be found in the following sections below.

Post-Authorisation Safety Data

Overall exposure and exposure by dose

To further support the approval of the booster dose of Spikevax for adolescent, the MAH submitted a cumulative overview and high level analysis of post-authorisation safety data, extrapolating from the proportion of US vaccine recipients to the estimated global use. The reporting period for the booster dose/ 3rd dose is 18 Dec 2020 to 31 Dec 2021, as stated in the title of section 2.5.6.2.1.1 "Summary After a Third Dose or Booster Dose of SPIKEVAX Cumulative (18 Dec 2020 to 31 Dec 2021)". The full Safety Summary Report has not been submitted but has been previously assessed by the PRAC (PRAC Assessment Report for the 11th summary safety update - Post-Opinion Measure 011.10).

The collected safety data do not fully distinguish between individuals who received a third 100 µg dose, indicated for immunocompromised patients in some settings, and a 50 µg booster dose. Current data also do not distinguish the different dosing intervals that have been recommended for booster implementation in different countries. The recommended intervals range from 3 to 5 months, i.e. for example, France (3 months), Germany (3 months), United Kingdom (3 months), Canada - Ontario (3 months), Switzerland (4 months), and US (5 months).

It should be noted, that the initially estimated exposure stated in the overview was inconsistent. A corresponding clarification was requested from the MAH. Within the response, the company clarified that in the Bi-Monthly Safety Summary Report # 1 (BSSR 1) it was stated, that the prior safety summary report (Data Lock Point: 31 December 2021) had a systematic error that overestimated the governmental donation doses by approximately 93 million doses. The error was clerical in nature: all estimated bilateral donations (124,091,211 doses) were included as administered rather than the stated assumption of 25% of estimated bilateral donation (31,022,803 doses). At the same time estimation of individuals receiving each dose number was also over estimated.

To estimate global use, the MAH extrapolates from the proportion of US vaccine recipients. In the response, the MAH estimates that as of 31 December 2021 a total of 827,274,740 doses have been distributed and 466,804,529 doses have been administered.

As stated in the response, the correct number of estimated global use of Spikevax as of 31st Dec 2021 was 216,113,851 individuals receiving a first dose, 176,800,748 receiving a second dose, and 73,889,930 receiving a third dose.

The MAH stated that the review of revised observed to expected analyses for the affected data did not materially change interpretation of safety assessment for any topic evaluated.

Exposure per dose and age

The exposure by age and dose as initially submitted by the MAH is shown in Table 4 below. In this table the 3rd dose exposure for young adults 18 to 24 years of age (8,128,797 estimated 3rd doses) is approximately 3 times higher than for adolescent (2,574,119 estimated 3rd doses). The 3rd dose exposure of approximately 3 million doses appeared unexpectedly high considering that Spikevax is not licensed in the US for individuals below 18 years of age for primary vaccination, and in the EU not yet for booster vaccination. The MAH was therefore asked to confirm the 3rd dose exposure of adolescents. The MAH response with regards to 3rd dose exposure revealed that the exposure number is rather based on assumptions than on reported information. Of note, this is due to the reporting system and the sources used by the company to estimate dose distribution and administration. Supply chain estimates are used to define the number of SPIKEVAX doses distributed by country, administration data are tracked by health officials within countries receiving the vaccine. Knowledge of demographics for administration data is limited to the information tracked and published by health officials within countries receiving the vaccine. Not all health authorities provide the same age strata when sharing this information, and none provide demographic data that are specific by brand and dose number. In fact, the previously reported 3rd dose exposure of 3 million doses is far too high, and has been corrected to 120,000 3rd doses administered to individuals below 18 years of age. It should be noted, that this exposure estimation is not restricted to adolescents but includes also individuals below 12 years of age).

It should be noted, that the total numbers of administered doses 1 (216,113,851), 2 (176,800,748), and 3 (73,889,930) in the top line of the table summarise the doses administered to the overall population. The table shows, that 2.8% of all 3rd doses were administered to adolescent and 9.0% to young adults.

Adding the doses for each age group, the total exposure by dose for individuals up to 24 years of age would be the follows.

For dose 1: 25, 933, 663 for dose 2: 21,215,811 and for dose 3: 10,838,396. The total number of 3rd doses in the top line of table 3 (90,319,965) still appears to be inconsistent too what was stated in the text (73,889,930).

Table 4: Spikevax Estimated Vaccine Recipients by Dose Number and Age Groups – Cumulative to 31st Dec 2021, source: table 3, ITEM 2, clinical questions

Age Group	Dose 1 (216,113,851)		Dose 2 (176,798,419)		Dose 3 (90,319,965)	
	N	%	N	%	N	%
<12 years	324,171	0.2	265,198	0.2	135,480	0.2
12 to 17 years	6,159,245	2.9	5,038,755	2.9	2,574,119	2.8
18 to 24 years	19,450,247	9.0	15,911,858	9.0	8,128,797	9.0

Assessor´s comment:

The summary of distributed and administered doses overall, and by age has been inconsistently presented in the clinical overview. The MAH was asked to clarify. The presentation within the MAH's response is still confusing. According to the MAH as of 31 December 2021 cumulative 827,274,740 doses have been distributed and 466,804,529 doses have been administered. As stated in the response, the correct number of estimated global use of Spikevax as of 31st Dec 2021 was 216,113,851 individuals receiving a first dose, 176,800,748 receiving a second dose, and 73,889,930 receiving a third dose. According to the submitted data, the exposure to dose 3 is 3 times higher in young adults 18-24 years of age (8,128,797 estimated 3rd doses) than in adolescent (2,574,119 estimated 3rd doses).

Considering that Spikevax is not licensed in the US for individuals below 18 years of age for primary vaccination, and in the EU not yet for booster vaccination in children and adolescent, the claimed 3rd dose exposure of more than 3 million doses in adolescents appears unexpectedly high. It was not clear how the estimates for doses received and for the different age categories – in particular adolescents - were derived and further clarification was requested. The MAH' response with regards to 3rd dose exposure revealed that the exposure number is rather based on assumptions than on reported information. Of note, this is due to the reporting system and the sources used by the company to estimate dose distribution and administration. Supply chain estimates are used to define the number of SPIKEVAX doses distributed by country, administration data are tracked by health officials within countries receiving the vaccine. Knowledge of demographics for administration data is limited to the information tracked and published by health officials within countries receiving the vaccine. Not all health authorities provide the same age strata when sharing this information, and none provide demographic data that are specific by brand and dose number. In fact, the previously reported 3rd dose exposure of 3 million doses is far too high, and has been corrected to 120,000 3rd doses administered to individuals below 18 years of age. It should be noted, that this exposure estimation is not restricted to adolescents but includes also individuals below 12 years of age.

The MAH was requested to describe in detail the methodology and data sources (Countries/jurisdiction for use) that lead to the estimated exposure in the different age categories as well as estimates according to age and numbers of doses received.

The MAH's response contains uncertainties with regard to the methodology of spontaneous reporting for the assessment of age and dose related safety evaluations in mind the submitted data from spontaneous reporting to the MAH is not considered adequate to support the extrapolation approach.

To support the extrapolation approach on a larger safety database the MAH is asked to submit:

- Information on the proportion of adolescents 12-<18 years of age and young adults 18-25 years of age enrolled in ongoing PASSs.
- A comprehensive comparison of the reactogenicity and safety profile of adolescents versus young adults based on the data available in the PASSs in the 2 populations
- A comprehensive comparison of the reactogenicity and safety profile post dose 2 versus post dose 3 in young adults based on available safety data from PASSs (OC).

Summary of data after a Third Dose or Booster Dose of SPIKEVAX, Cumulative (18 Dec 2020 to 31 Dec 2021)

Upon request the MAH confirmed, that by the time of the submission of the present indication extension there was no back log of event recording. The covered surveillance period for cumulative reporting is 18 Dec 2020 to 31 Dec 2021.

With regard to a booster dose of 50 µg or a 3rd dose of 100 µg, cumulatively, the MAH has received 17,511 cases with 52,354 events - of which 29,181 events were serious - for recipients after an estimated 88.6 million third dose or booster dose of Spikevax. Of these, 5,171 cases were medically confirmed, 8346 cases were serious, and 142 cases had fatal outcomes. The majority of cases were reported in females (11,673; 66.7%) compared to males (4,896; 28.0%) with the mean age of 52.8 years (SD: 16.6; median: 53.0 years). Age and gender distribution of cases after a third dose is shown in Table 5. Table 5 indicates a low absolute number of reported cases in individuals below 18 years of age post dose 3.

Table 5: Distribution of Cases After a Third Dose or Booster Dose of SPIKEVAX by Age Group and Gender Cumulative, source: clinical overview, Table 9

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
< 2	12	0.1	4	0.02	1	0.01	17	0.1
02-11	0	0.0	6	0.03	0	0.00	6	0.03
12-15	6	0.03	1	0.01	0	0.00	7	0.04
16-17	9	0.1	5	0.03	1	0.01	15	0.1
18-29	969	5.5	355	2.0	37	0.2	1361	7.8
30-39	1686	9.6	536	3.1	50	0.3	2272	13.0
40-49	2050	11.7	709	4.0	78	0.4	2837	16.2
50-64	3484	19.9	1460	8.3	137	0.8	5081	29.0
65-74	1462	8.3	847	4.8	86	0.5	2395	13.7
75+	883	5.0	611	3.5	47	0.3	1541	8.8
Missing	1112	6.4	362	2.1	505	2.9	1979	11.3
Grand total	11,673	66.7	4896	28.0	942	5.4	17,511	100.0

Source: Safety Summary Report #11

Out of the 45 cases of children under 18 years of age that reported receiving a 3rd dose, 21 cases were reported as a medication error under the PT of "Product administered to patient of inappropriate age" and 4 cases co-reported "Product administered to patient of inappropriate age" and "Inappropriate schedule of product administration". The 17 cases reported in children <2 years of age were either pregnancy related or exposure through breast milk cases. Information about the remaining 3 cases with events different from Product administered to patient of inappropriate age" and "Inappropriate schedule of product administration" were submitted upon request from the assessor and included the following events.

1. A 12-15 years old subject with unknown medical history received a heterologous booster with Spikevax after full primary vaccination with Comirnaty. 2 doses of Comirnaty were administered within 22 days. The subject did not experience any ARs after primary vaccination. Approximately 3 months later, the subject received a heterologous booster with one dose of Spikevax. A day after vaccination the subject experienced several severe ARs including muscle weakness, injection site pain, myalgia, fever, flu like symptoms asthenia, pain (described as body aches), flushing, and chills. Events were resolving on day 3 after vaccination. It can be agreed with the MAH, that the events are considered possible related and considered an expression of reactogenicity events currently labelled for Spikevax.
2. A 16-17 years old subject with unknown medical history experienced on the next day after the 3rd dose with Spikevax several reactogenicity events including pyrexia, myalgia, and pain in extremity (described as sore arm, probable the vaccinated arm). Information on severity of events was not provided Patient was treated with ibuprofen and the next day events resolved. No other information was provided. Based on the description of the symptoms and the temporal

relationship it can be agreed, that the events are possibly related and sign of expected reactogenicity labelled for Spikevax.

3. This case describes occurrence of myasthenia gravis crisis in a 16-17-year-old subject with medical history of COVID-19 and myasthenia gravis developed after COVID-19. The time point of COVID-19 and Spikevax with the 3 Spikevax doses is not provided. The subject had received a 3rd dose of Spikevax. The first two doses were given one month apart, the third dose was given 175 days after the second dose. The provided report is however inconsistent with the dosing dates, but the mentioned periods in between doses are deemed the correct dates. Symptom onset for myasthenia gravis crisis was 1 week after vaccination, with inability to move, trouble talking, moving and swallowing over a couple of Weeks until it reached a peak which lasted for months. Since the third dose IVIGs side effects have also been really bad for multiple days afterwards which was not the case before. The subject is still not where they was before the additional dose of Spikevax. The subject did not report AEs after the 2 previous doses of Spikevax. The additional dose of Spikevax was considered as 3rd dose because of the subject being immunocompromised. Information on the administered dose (50 µg or 100 µg) is not provided. Recorded medication includes Mestinon, Prostigmin, Prednisone, Vit D, Omeprazole.

The case number of 45 cases in individuals below 18 years of age was confirmed by the MAH within the responses to RSI, but is now as said above related to approximately 120,000 3rd dose administrations, the number after the re estimation of 3rd dose exposure that was performed by the MAH.

Assessor´s comment:

It appears that cumulative only few cases post dose 3 (i.e. either a 50 µg booster or a 100 µg 3rd dose in case of immunosuppressed condition) are recorded for adolescents. Table 9 confirms the low absolute number of cases in individuals below 18 years of age. Only for 42 of 45 reported cases information is available in the overview. The reported AEs were due to medication error under the PT of "Product administered to patient of inappropriate age" and "Inappropriate schedule of product administration". The MAH was asked to submit information with regard to the nature and severity of the remaining cases and events in children below 18 years of age including a causality assessment. The clinical information for the remaining 3 cases has been submitted by the MAH as has been described above. Two of the cases represent expected reactogenicity events that are labelled for Spikevax. One of these 2 cases occurred after heterologous booster administration (Comirnaty primary vaccination without ARs, booster with Spikevax 3 month after primary vaccination). The third case describes a myasthenia gravis crisis in a 16-17 year old subject with known myasthenia gravis that the subject acquired after COVID-19. The time frames of COVID-19 and the vaccination with 3 doses of Spikevax is not provided. A causal relationship cannot be excluded.

Due to a clerical error (details are discussed below), the reported cases after dose 3 were unclear. The MAH was asked to clarify the case number after dose 3 in individuals below 18 years of age. The MAH submitted a corresponding table within the response document (Table 2, ITEM 2). The table confirmed the low case number.

Table 2 Distribution of Cases After a Third Dose or Booster Dose of SPIKEVAX by Age Groups Cumulative

Age Group	Total # Cases	Total % Cases
<2	17	37.8
02-11	6	13.3
12-15	7	15.6
16-17	15	33.3
Grand total	**45**	**100.0**

For the sake of absolute clarity/certainty regarding this important aspect, the MAH is requested to confirm that the number of 45 cases in children and adolescent below 18 years of only refers to cases observed in the period from 18 December 2020 to 31 December 2021. In the MAH's response the case number of 45 cases in individuals below 18 years of age was confirmed within the responses to RSI, but is now as said above related to approximately 120.000 3rd dose administrations, the number after the re-estimation of 3rd dose exposure that was performed by the MAH.

Events of Clinical Interest Based on MedDRA System Organ Class

Cumulative, 52,354 events for recipients after a third dose or booster dose of Spikevax were reported of which 29,181 were serious from an estimated 88.6 million 3rd doses. The top 3 system organ classes, higher level terms, and PTs for all events for recipients after a third dose or booster dose of Spikevax in the cumulative reporting period are presented in Table 6.

Table 6: Top 3 **Events** After a **Third Dose or Booster Dose** of Spikevax by SOC, HLT, and PT, Cumulative (source: Table 11, clinical overview)

Classification	Event	Events (N)	Events (%)
SOC	General disorders and administration site conditions	15,069	28.8
	Nervous system disorders	7554	14.4
	Musculoskeletal and connective tissue disorders	5913	11.3
HLT	Headaches NEC	3319	6.3
	Asthenic conditions	3053	5.8
	Febrile disorders	2866	5.5
PT	Headache	3183	6.1
	Pyrexia	2861	5.5
	Fatigue	2201	4.2

Abbreviations: HLT = higher level term; NEC = not elsewhere classified; PT = preferred term; SOC = system organ class.
Source: Safety Summary Report #11

The Top 3 Serious Events **After a Third Dose or Booster Dose** of Spikevax by SOC, HLT, and PT during the 2 reporting periods 01 Dec 2021 to 31 Dec 2021 and 01 Nov 2021 to 30 Nov 2021 are presented in Table 7 and Table 8.

Table 7: Top 3 **Serious Events** After a **Third Dose or Booster Dose** of SPIKEVAX by SOC, HLT, and PT During the Reporting Period (**01 Dec 2021 to 31 Dec 2021**), source: Table 6-47 SSR 11, section 6.4.1.1

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

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

Table 8: Top 3 **Serious Events** After a **Third Dose or Booster Dose** of SPIKEVAX by SOC, HLT, and PT During the Reporting Period (**01 Nov 2021 to 30 Nov 2021**), source: Table 6-49, SSR 11, section 6.4.1.1

Classification	Event	Total Events (N)	Total Events (%)
SOC	General disorders and administration site conditions	1,644	23.6
	Investigations	1,093	15.7
	Nervous system disorders	1,090	15.6
HLT	Headaches NEC	468	6.7
	Nausea and vomiting symptoms	409	5.9
	Asthenic conditions	373	5.4
PT	Headache	448	6.4
	Pyrexia	358	5.1
	Fatigue	278	4.0

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

Assessor´s comment:

The tables showing Top 3 Serious AEs after a 3rd dose were not inserted in the overview. The entire SSR #11 has also not been submitted but the document is available from the corresponding PRAC procedure. Cumulative events, but not cumulative SAEs by SOC/HLT/PT after a 3rd or a booster dose can be found in the SSR 11. SAEs are provided only for 2 different reporting periods (01 Dec 2021 to 31 Dec 2021 and 01 Nov 2021 to 30 Nov 2021). The top 3 events and top 3 SAEs are however the same by PT, i.e. headache, pyrexia and fatigue. All events are already known and documented AEs for Spikevax.

Overview of Reported Cases for Adolescents (12 to 17 Years Old) regardless of dose number

This AR paragraph relates to information given in section 2.5.6.2.1.4, which contains number of cases reported in adolescent **regardless of the dose number**. The headline section has a clerical mistake by stating, that reports were received after 3rdor booster dose.

Cumulatively, the MAH has received 5808 cases (9981 events, of which 1081 events were serious) for adolescents (12 to 17 years old) from an estimated 3,087,330 third or booster dose. Of these, 4936 cases were medically confirmed, 443 cases were serious, and 7 cases had fatal outcomes.

Age and sex distribution of events, absolute case numbers of events after each dose, the time to onset (TTO), and the Top 10 preferred terms (PTs) are shown in Table 9 to10. The majority of cases were reported in females (54.3%, 3153) compared to males (41.6%, 2415) with the mean age of 15.9 years (SD: 1.5; median: 16.0 years). More cases were reported for females (3153) than for males (2415), and more cases in the older age range 16-17 years of age (4433), than in the younger age range 12-15 (1375). The majority of the events reported for adolescents were after dose 1 (5791; 58%) and with a TTO of 0 to 2 days (5186; 52%). The 10 most commonly reported events for adolescent excluding product administered to patients of inappropriate age were events related to reactogenicity. The comparison between age groups and gender is limited, since only absolute numbers and not reporting rates/incidences are provided.

Table 9: Distribution of Reported Cases for Adolescents (12 to 17 Years Old) by Age Group and Gender, source: Table 13, clinical summary

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
12-15	720	12.4	615	10.6	40	0.7	1375	23.7
16-17	2433	41.9	1800	31.0	200	3.4	4433	76.3
Grand total	3153	54.3	2415	41.6	240	4.1	5808	100.0

Source: Safety Summary Report #11

Table 10: Distribution of Reported Events for Adolescents (12 to 17 Years Old) By Dose Number and Time to Onset (TTO) (Cumulative), source: Table 14, clinical summary

Dose Number	TTO (days)	Events (N)	Events (%)
Dose 1	*Subtotal*	*5791*	*58.0*
	0 days	4640	46.5
	01-02	546	5.5
	03-04	83	0.8
	05-06	75	0.8
	07-13	242	2.4
	14-29	149	1.5
	30+	56	0.6
Dose 2	*Subtotal*	*1369*	*13.7*
	0 days	895	9.0
	01-02	309	3.1
	03-04	47	0.5
	05-06	31	0.3
	07-13	27	0.3
	14-29	38	0.4
	30+	22	0.2
Dose 3	*Subtotal*	*52*	*0.5*
	0 days	42	0.4
	01-02	4	0.0
	07-13	6	0.1
Unknown	*Subtotal*	*2769*	*27.7*
	Missing	2769	27.7
Grand Total		**9981**	**100.0**

Source: Safety Summary Report #11

Table 11: Top 10 Preferred Terms (PT) for Adolescents (12 to 17 Years Old) Cumulative, source: Table 15, clinical summary

PT	# Events	% Total Events
Pyrexia	480	4.8%
Headache	338	3.4%
Vaccination site pain	202	2.0%
Pain in extremity	198	2.0%
Fatigue	175	1.8%
Nausea	137	1.4%
Dizziness	120	1.2%
Myalgia	118	1.2%
Malaise	101	1.0%
Vomiting	101	1.0%

Source: Safety Summary Report #11

SAEs after any dose

Upon request the MAH provided a table (Table 5 in response to ITEM 4, not presented in this AR) showing all SAEs by SOC and preferred term. In summary the vast majority of SAEs is related to expected and labelled symptoms of reactogenicity, e.g. pyrexia (21.4%), fatigue (6.8%), nausea (6.8%), vomiting (6.1%), and fatigue (6.8%), malaise (5.0%). However, 22.3% of SAEs were due to myocarditis and 4.5% due to pericarditis. Altogether 61 PTs (13.7%) were related to cardiac events other than myocarditis and pericarditis (e.g. arrhythmia, atrial tachycardia, bradycardia, cardiac flutter, palpitations, sinus tachycardia, tachycardia, sinus tachycardia, SVT, and VT). From the table it cannot be concluded if and to what extent the cardiac events are associated with cases of myo-or pericarditis. Other PTs with high proportion was dyspnoea (8.4%), chest pain and chest discomfort (15.1% together), syncope (10.6%), and loss of consciousness (5.2%).

Not in the clinical overview, but available in SSR #11, the top 10 most frequently reported PTs in serious cases in adolescent with >2% reporting rate (after any dose) are shown and are tabled below in Table 12. The TOP 3 SAEs for adolescent after any dose for the reporting period 01 Dec 2021 to 31 Dec 2021 are myocarditis, pyrexia, and chest pain. Of the 9 cases of chest pain, five were in association with Myocarditis, and one case is in association with Pericarditis.

Table 12: Most Frequently Reported PTs in Serious Cases in Children Age 12 – 17 Years >2%During the Reporting Period (01 Dec 2021 to 31 Dec 2021), source: Table 7-4 SSR 11

PT	Serious	
	# Events	% of Total Events
Myocarditis	19	11.2
Pyrexia	15	8.8
Chest pain	9	5.3
Headache	9	5.3
Syncope	8	4.7
Loss of consciousness	6	3.5
Dyspnoea	5	2.9
Pericarditis	5	2.9
Seizure	4	2.4
Vomiting	4	2.4

Assessor`s comment:

The SAEs reported after any dose are more relevant for the assessment of the general safety of Spikevax including the primary vaccination, rather than the booster dose. The assessment of the primary vaccination is not scope of this procedure. The submitted data however cannot be ignored. Within the previous EMA procedures, extending the indication to adolescent and later to children below 12 years of age, causality of the events of cardiac rhythm disorders, chest pain, and dyspnoea could not finally be estimated, therefore reassessment with another data base assessment seems needed. The MAH is asked to reassess the events shown in Table 5, that was submitted within the response to ITEM 4 as follows:

a. to investigate potential causality of the SAEs of cardiac rhythm disorders and cardiac events other than myo-or pericarditis, chest pain, and dyspnoea. From the table it cannot be concluded to what extent these cardiac events were associated with cases of myocarditis or pericarditis. This should also be clarified. Depending on the assessment, the events should be included in the SmPC specifically for the paediatric population.

It should be noted, that this question has been removed during ETF discussion to transfer this issue to PRAC.

Sections 2.5.6.2.1.1 and 2.5.6.2.1.4 of the overview appeared to be inconsistent or at least misleading with regard to recorded cases. In section 2.5.6.2.1.4 of the overview it is stated, that cumulatively, Moderna has received 5808 cases (9981 events, of which 1081 events were serious) for adolescents (12 to 17 years old) from an estimated 3,087,330 **third or booster dose**. Of these, 4936 cases were medically confirmed, 443 cases were serious, and 7 cases had fatal outcomes. This appeared to be inconsistent with the numbers mentioned in section 2.5.6.2.1.1 stating that 45 cases in children under 18 years of age who had received a 3rd dose were reported cumulative (18 Dec 2020 to 31 Dec 2021) after an estimated 88.6 million third dose or booster dose of Spikevax. The MAH was asked to clarify (ITEM 2a.) Within the response the MAH clarified that the inconsistency is due to clerical mistake. In section **2.5.6.2.1.4** the information provided referred to the number of cases that the MAH had received for 12 to 17 years old cumulative as of 31st December 2021 (5808 cases (9981 events, of which 1081 events were serious)), **regardless of dose number**. The clerical mistake was adding in the section headline, that those reports were after a **3rd or booster dose**. All the information provided in section 2.5.6.2.1.4 pertains to the cumulative number of cases reported in adolescent **regardless of the dose number**.

Clinical summary of fatal cases reported to have occurred after 3rd dose or booster dose

After request the MAH submitted available information for the 7 fatal cases in adolescent that were reported in the overview as having occurred after 3rd or booster dose. The provided information revealed that the fatal cases occurred after dose 1 or dose 2, or after an unknown dose. The fatal cases are none the less summarised here for information.

Case 1: 15 year old female, received dose 2 of Spikevax, 1 dosage form.

Previous medical history: Relevant multimorbidity including amongst others bronchopulmonary dysplasia, renal dysplasia, sleep apnoea syndrome, asthma, hypothyroidism, atrioventricular septal defect, Trisomy 21, drug hypersensitivity. The patient experienced Cardiac arrest. The patient died on the next day. The reported cause of death was Cardiac arrest. It is unknown if an autopsy was performed. The paediatric intensive care unit (PICU) attending the patient believed the events started about 3-4 days after her second Moderna Vaccine.

Case 2: 13 year old male, received 1 dosage form of Spikevax, the dose number is not known, also unknown route. No medical history information was reported. The boy died on an unknown date. According to the MAH, he died one day after receiving the vaccine, while in the submitted case report it is stated that death occurred 3 days after vaccination. The cause of death was not reported. It is unknown if an autopsy was performed. The information is rather limited. Further information has been requested.

Case 3: 15-year-old male. The patient's relevant underlying condition is cerebral arteriovenous malformation. The patient received the 1st dose of Spikevax. Approximately 9 hours later, the patient had a headache and vomiting and was taken to the hospital. The patients Japan Scale Coma was 300 on arrival, corresponding to a GCS score of 3 (the minimum score is a 3 which indicates deep coma or a brain-dead state). CT showed cerebral haemorrhage and cerebral ventricular rupture from cerebral arteriovenous malformation. Four days after hospital admission, the patient was confirmed dead. The outcome of cerebral haemorrhage and cerebral ventricular rupture was reported as fatal.

Case 4: 17 year old male. The patient received a dose of Spikevax via unknown route (1 dosage form). Concurrent medical conditions included Cardiomyopathy (Had risk in situations of stress.). On an unknown date, the patient experienced myocarditis (Bilateral Myocarditis) and died. The cause of death was not reported and the death date was unknown. It is unknown if an autopsy was performed. At the time of death, myocarditis (Bilateral myocarditis) outcome was unknown.

Case 5: 17 year old male, received the second dose of mRNA-1273 (Moderna) (unknown route) 1 dosage form. The patient was found dead in his bedroom and the case was reported by a non- health professional. Death occurred on 2021. The cause of death was not reported. It is unknown if an autopsy was performed. No relevant concomitant medications were reported. Treatment information was unknown.

According to the company, the 17-year-old male subject has an unknown medical history. He experienced the serious unlisted adverse event of death a few days after receiving his second dose of mRNA-1273. The patient was found dead in his bedroom. No further information is currently available on the reason of his death or events that may have resulted in death.

Case 6: A 13 year old male received a dose of Spikevax IM, 1 dosage form. 7 days later, the patient experienced Pyrexia (Fever) and the other day , on the next day, the patient experienced seizure and on the following day, headache. The reported cause of death was Fever, Seizure and Headache. It is unknown if an autopsy was performed. For mRNA-1273 (Moderna) (Intramuscular), the reporter did not provide any causality assessments. No information on previous medical history is available.

There is no information about the number of the vaccine dose the patient received and no information on the date of the death and if the patient died in hospital. No information on previous medical history or treatment and also related to the symptoms (i.e. the grade of the fever, if the seizures happened at a certain grade of the temperature) is available.

Case 7: A 14 year old female received the 1st dose of Spikevax IM, 1 dosage form. Approximately 2 weeks later the patient experienced Dizziness, Headache and Pyrexia. On the following day, the patient experienced Cardiac arrest, Brain injury, Brain herniation, multiple organ dysfunction syndrome. On an unknown date, the patient experienced nausea. The patient died the day after. The cause of death was not reported. The interim cause of death certificate stated no gross morphologic cause of death. Neuropathology, histology, and virology toxicology results are pending. The girl fainted at school 2 months prior to presentation but has nil significant past medical history.

The onset of symptoms: the girl complained that she felt unwell and dizzy. CPR was performed and Patient was transported via ambulance to hospital where Patient was declared deceased. Treatment notes: 16 days post vaccination patient complained of headache and nausea; the following morning she

was found unconscious. RoSC achieved after two shocks; LMA inserted and transported to Hospital; loss of output en route however RoSC achieved after adrenaline and CPR; at hospital. Lab Data: lactate 20 and pH <6.8; in resuscitation, patient had recurrent episodes of loss of cardiac output (non-shockable rhythm) followed by CPR and return of spontaneous circulation. CT brain was performed and showed changes in keeping with global ischemia. In ICU the girl sustained rapid development of multiorgan failure as well as hypoxic brain injury with tonsillar herniation; patient passed away on the morning after the onset of symptoms.

Assessor´s comment:

The clinical information for all cases are rather limited and results and further information is pending. Some of the deceased participants had underlying conditions that could be attributable for the outcome, but not all of them. The safety of Spikevax administered to adolescent is under monitoring by the PRAC.

Event Reporting Rates by dose

Upon request the MAH submitted reporting rates for any event, for SAEs, non-SAEs, and AESIs by dose, age, and sex. Results are presented in Table 13. The reporting rates for all of the events for adolescent and young adults are not higher post dose 3 compared to post dose 2.

Assessor´s comment:

The reporting rates do not raise concerns with regard to the administration of a booster dose and are considered qualified to support the extrapolation approach from young adults to adolescents. Reporting rates are critically dependent on the denominator which needs to be clarified (OC).

Table 13 Reporting rate of cases per million SPIKEVAX doses administered - Moderna Global Safety Database (Cumulative to 31 Dec 2021), source: Table 4, responses to ITEM 3

	Males			Females		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
Estimated doses administered						
Age Group (years)						
12-17	2,925,641	2,393,440	1,000,285	3,233,603	2,645,381	1,105,578
18-24	9,238,867	7,558,232	3,158,795	10,211,379	8,353,835	3,491,299
25-39	22,583,897	18,475,678	7,721,498	24,961,150	20,420,486	8,534,287
Rate of All Events						
Age Group (years)						
12-17	800.85	264.06	6.00	1,031.98	275.20	39.80
18-24	1,099.27	1,009.10	135.81	2,743.70	2,307.44	357.75
25-39	1,490.35	1,588.95	283.36	5,343.30	4,493.77	857.25
Rate of Non-Serious Events						
Age Group (years)						
12-17	762.57	203.47	6.00	950.95	227.19	38.89
18-24	855.73	678.07	63.00	2,379.89	1,943.90	142.64
25-39	1,203.25	1,223.28	121.61	4,733.72	3,784.73	339.57
Rate of Serious Events						
Age Group (years)						
12-17	38.28	60.58	0.00	81.02	48.01	0.90
18-24	243.54	331.03	72.81	363.81	363.55	215.11
25-39	287.11	365.67	161.76	609.59	709.04	517.68

Analysis of Adverse Events of Special Interest

Analysis of Myocarditis and Pericarditis

An observed versus expected analysis of myocarditis by dose was performed and described in the clinical overview. This analysis covered all age groups from below 12 years of age to more than 75 years of age. The analysis confirms what is currently known about the epidemiology of mRNA COVID-19 vaccine associated myocarditis. The analysis shows that myocarditis rates appear to be lower following Dose 3 compared with dose 2. This is more evident for the age groups up to 49 years of age than for the older age groups. For adolescents of note post dose 3 data are not available. The analysis indicates that the rates are higher in males compared with females, which is also in line with what is currently known about mRNA COVID-19 vaccine associated myocarditis and pericarditis. The highest rate, i.e. 8.41 (6.23, 11.36) is observed in males 18-24 years of age post dose 2. Results are shown in Table 14.

Table 14: Observed Versus Expected Analyses of Myocarditis, Reported Cases in the Moderna Global Safety Database Occurring Within 7 Days of a Known Dose, Cumulative Through 31 Dec 2021, source: table 16, clinical overview

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

Abbreviations: CI = confidence interval; NA = not available.
Note: Reference rates from Boehmer 2021. Because age by sex stratified estimates of the reference rate were not available in the source material, estimates are obtained by multiplying the age specific rate estimate by the ratio of the sex-specific stratum-specific rate to the overall rate.
Data Source: Safety Summary Report #11

Adolescents (12 to 17 Years Old) Analysis of Myocarditis and Pericarditis – Cumulative to 31 Dec 2021

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

Cumulatively, there were 101 events of myocarditis reported in adolescents (including 1 event of myocarditis infectious), with the greatest proportion of the events (45.5%) occurring after the second dose (46 events as shown in Table 16). Results for myocarditis and pericarditis together and for myocarditis alone by dose and TTO are summarised in Table 15 and Table 16 and 17. The majority of myocarditis cases occur within the first 4 days, i.e. 11/18 cases (61%) post dose 1 and 40/46 cases (87%) post dose 2.

Table 15: Number and Percentage of Myocarditis and Pericarditis Cases in Adolescents (12 to 17 Years Old) by Age and Gender (Any Dose) - Cumulative to 31 Dec 2021, source: Table 19, clinical summary

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

Table 16 Number and Percentage of Events Reporting Myocarditis in Adolescents (12 to 17 Years Old) by Dose and Time to Onset (TTO) –Cumulative to 31 Dec 2021, source: Table 20, clinical overview

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

Source: Safety Summary Report #11

The reporting rates for myocarditis within 7 days after dose 1, 2, and 3 again confirm the above-mentioned findings. Reporting rates were highest post dose 2, and higher in males compared with

females. The highest rate was reported for males 18-24 years of age post dose 2 (40.26 [9,065,023]). There have been no fatal reports in adolescents due to myocarditis or pericarditis. No cases of myocarditis in adolescents 12 to 17 years of age after a third/booster dose of Spikevax have been reported. Reporting rates by dose age group and sex are shown in Table 17.

Table 17: Reporting Rates of Myocarditis Within 7 Days After Dose 1, 2, and 3 per Million Doses Administered of SPIKEVAX Stratified by Age and Sex – Moderna Global Safety Database (Cumulative to 31 Dec 2021), source: Table 22, clinical overview

Age Group (years)	Males			Females		
	Dose 1 (n)*	Dose 2 (n)*	Dose 3 (n)*	Dose 1 (n)*	Dose 2 (n)*	Dose 3 (n)*
12-17	2.56 (3,508,936)	13.93 (2,870,590)	0.00 (1,466,482)	0.52 (3,878,298)	0.95 (3,172,758)	0.00 (1,620,848)
18-24	7.85 (11,080,852)	40.26 (9,065,023)	1.51 (4,630,995)	1.22 (12,247,257)	3.49 (10,019,236)	0.00 (5,118,468)
25-39	3.77 (27,086,526)	12.55 (22,158,945)	1.41 (11,320,210)	1.17 (29,937,739)	1.76 (24,491,466)	1.12 (12,511,811)

(n)* = estimated number of doses administered.
Source: Safety Summary Report #11

Other AESI

As of 31 Dec 2021, there were no reports of most AESIs in third-dose recipients 18 to 24 years of age. Small numbers of cases of convulsions, myocarditis, pericarditis, arrhythmia, Bell's Palsy, narcolepsy/hypersomnia, erythema multiforme, pancreatitis, and thyrotoxicosis were reported. None of these AESIs occurred at a reporting rate that exceeded the expected based on population-based studies estimating background incidence. For the AESIs of Myocarditis (with or without pericarditis), Pericarditis (with or without myocarditis), and pericarditis without myocarditis of note the observed rate after any dose was higher than the expected rate. The rate ratio was above 1 for Myocarditis (with or without pericarditis) and pericarditis without myocarditis, and above 2 for Pericarditis (with or without myocarditis). There was no AESI for which the observed to expected rate ratio was higher for dose 3 than for the overall Global Safety Database. Results are shown in Table 18.

Table 18: Observed Versus Expected Analyses of AESI, Vaccine Recipients Ages 18 to 24 Years, Data Through 31 Dec 2021, source: Table 23, clinical overview.

Outcome	Any Dose					Dose 3				
	Observed		Expected		As Observed: RR (95% CI)	Observed		Expected		As observed: RR (95% CI)
	Cases	Rate	Cases	Rate		Cases	Rate	Cases	Rate	
Generalized Convulsions	429	14.81	596	20.56	0.72 (0.64, 0.82)	12	2.62	94	20.56	0.13 (0.07, 0.23)
Myocarditis (with or without pericarditis)	797	27.51	563	19.45	1.41 (1.27, 1.58)	11	2.40	89	19.45	0.12 (0.07, 0.23)
Pericarditis (with or without myocarditis)	251	8.66	107	3.70	2.34 (1.87, 2.94)	5	1.09	17	3.70	0.29 (0.11, 0.8)
Pericarditis without myocarditis	176	6.08	107	3.70	1.64 (1.29, 2.09)	5	1.09	17	3.70	0.29 (0.11, 0.8)
Arrhythmia	173	5.97	2,798	96.57	0.06 (0.05, 0.07)	5	1.09	443	96.57	0.01 (0, 0.03)
Bell's Palsy	93	3.21	582	20.10	0.16 (0.13, 0.2)	2	0.44	92	20.10	0.02 (0.01, 0.09)
Narcolepsy/Hypersomnia	31	1.07	2,578	89.00	0.01 (0.01, 0.02)	2	0.44	408	89.00	0 (0, 0.02)
Erythema Multiforme	30	1.04	147	5.09	0.2 (0.14, 0.3)	1	0.22	23	5.09	0.04 (0.01, 0.32)
Pancreatitis	7	0.24	33	1.14	0.21 (0.09, 0.48)	1	0.22	5	1.14	0.19 (0.02, 1.64)
Thyrotoxicosis	7	0.24	414	14.29	0.02 (0.01, 0.04)	1	0.22	66	14.29	0.02 (0, 0.11)

Abbreviations: AESI = adverse event of special interest; CI = confidence interval.

Source: Safety Summary Report #11

Incidence rate ratios from age and sex standardised comparison of post vaccination and historical incidence of AESIs were submitted in the clinical overview and are presented in Table 19.

Table 19: Comparison of the Incidence of Adverse Events of Special Interest After Vaccination to Historical Incidence Rates, HealthVerity Database Through 31 August 2021

	Incidence Rate Ratio (95% CI^) Age < 18 Years		Incidence Rate Ratio (95% CI) Age 18-29 Years	
	Vaccinated vs. Pre-Covid era	Vaccinated vs. Covid era	Vaccinated vs. Pre-Covid era	Vaccinated vs. Covid era
Aseptic arthritis	0 (NE, 13.14)	0 (NE, 19.18)	0.52 (0.4, 0.67)	0.72 (0.54, 0.93)
Acute disseminated encephalomyelitis	NE (NE, NE)	NE (NE, NE)	0 (NE, 5.16)	NE (NE, NE)
Acute kidney injury	1.24 (0.65, 2.09)	1.48 (0.77, 2.5)	0.67 (0.64, 0.7)	0.77 (0.73, 0.8)
Acute liver injury	0 (NE, 32.01)	0 (-, 37.38)	0.75 (0.44, 1.2)	0.85 (0.5, 1.36)
Acute myocardial infarction	4.39 (0.16, 23.1)	6.34 (0.23, 33.52)	0.84 (0.66, 1.06)	0.92 (0.72, 1.16)
Acute respiratory distress	0.32 (0.04, 1.01)	0.56 (0.07, 1.8)	0.27 (0.21, 0.35)	0.3 (0.23, 0.39)
Anosmia	37.91 (20.52, 63.72)	3.23 (1.76, 5.36)	10.32 (9.34, 11.4)	0.94 (0.88, 1.01)
Arrhythmia	0.48 (0.18, 1.05)	0.56 (0.21, 1.22)	1.03 (0.98, 1.09)	1.11 (1.05, 1.17)
Aseptic meningitis	0 (NE, 9.85)	0 (NE, 18.44)	0.6 (0.4, 0.89)	1.13 (0.73, 1.68)
Anaphylaxis	3.68 (1.01, 8.81)	5.35 (1.47, 12.83)	1.71 (1.49, 1.97)	2.15 (1.86, 2.47)
Bell's palsy	3 (0.65, 8.16)	3.13 (0.68, 8.51)	0.75 (0.61, 0.91)	0.9 (0.73, 1.09)
Chilblain-like lesions	0.24 (0.01, 34.05)	0.17 (0, 23.17)	2.76 (1.96, 3.84)	2.39 (1.7, 3.32)
Cerebral sinus venous thrombosis	NE (NE, NE)	NE (NE, NE)	0.46 (0.16, 1.09)	0.59 (0.2, 1.41)
Coagulation disorders	1.38 (0.57, 2.72)	1.72 (0.71, 3.41)	0.7 (0.65, 0.76)	0.78 (0.73, 0.84)
Deep vein thrombosis	0.22 (0.08, 4.61)	0.27 (0.1, 5.6)	0.68 (0.58, 0.78)	0.81 (0.7, 0.93)
Disseminated intravascular coagulation	0 (NE, 15.7)	0 (NE, 18.09)	0.27 (0.13, 0.5)	0.36 (0.17, 0.68)
Encephalitis/encephalomyelitis	0 (NE, 15.86)	0 (NE, 20.08)	0.51 (0.22, 1.02)	0.6 (0.26, 1.21)
Erythema multiforme	6.87 (3.15, 12.62)	11.12 (5.09, 20.47)	1.2 (0.86, 1.63)	1.41 (1.01, 1.94)
Glomerulonephritis	0 (NE, 1300.68)	0 (NE, 562.06)	0 (NE, 13.23)	0 (NE, 18.78)
Guillain-Barre syndrome	0 (NE, 58.24)	0 (NE, 74.64)	0.63 (0.24, 1.38)	1.03 (0.38, 2.32)
Heart failure	0.06 (0, 8.92)	0.08 (0, 11.49)	0.58 (0.43, 0.76)	0.73 (0.54, 0.96)
Immune thrombocytopenia	2.32 (0.07, 11.02)	3.1 (0.09, 14.73)	0.82 (0.61, 1.07)	1.06 (0.79, 1.39)
Ischemic heart disease	3.01 (0.11, 15.69)	3.85 (0.15, 20.07)	0.89 (0.76, 1.04)	0.95 (0.81, 1.1)
Kawasaki disease	1.35 (0.03, 6.34)	1.67 (0.04, 7.84)	1.19 (0.65, 2.03)	1.42 (0.77, 2.46)
Meningoencephalitis	1.54 (0.19, 5.45)	1.83 (0.23, 6.45)	0.53 (0.44, 0.63)	0.58 (0.48, 0.7)
Microangiopathy	0 (NE, 45.85)	0 (NE, 63.57)	0.84 (0.36, 1.73)	1.08 (0.46, 2.27)
Multisystem inflammatory syndrome	0 (NE, 252)	0 (NE, 22.85)	1.87 (0.33, 6.58)	2.77 (0.46, 11.01)
Narcolepsy	0 (NE, 8.76)	0 (NE, 10.93)	1.43 (1.22, 1.68)	1.74 (1.48, 2.05)
Pericarditis	0.13 (0, 13.24)	0.19 (0, 19.8)	1.36 (1.09, 1.67)	1.78 (1.43, 2.2)
Pulmonary embolism	0.53 (0.14, 18.66)	0.59 (0.16, 20.71)	0.8 (0.68, 0.94)	0.9 (0.76, 1.05)
Seizure	0.85 (0.51, 1.33)	1.06 (0.63, 1.65)	0.89 (0.85, 0.94)	1.04 (0.99, 1.1)

	Incidence Rate Ratio (95% CI^) Age < 18 Years		Incidence Rate Ratio (95% CI) Age 18-29 Years	
	Vaccinated vs. Pre-Covid era	Vaccinated vs. Covid era	Vaccinated vs. Pre-Covid era	Vaccinated vs. Covid era
Single organ cutaneous vasculitis	1.03 (1.03, 0.03)	1.57 (0.05, 7.26)	1.11 (0.83, 1.46)	1.33 (0.99, 1.77)
Stroke, hemorrhagic	2.13 (0.05, 11.38)	2.46 (0.06, 13.14)	0.63 (0.45, 0.86)	0.66 (0.47, 0.9)
Stroke, non-hemorrhagic	0.09 (0, 11.9)	0.1 (0, 13.75)	0.7 (0.53, 0.92)	0.78 (0.58, 1.02)
Thrombosis with thrombocytopenia	1.37 (0.56, 2.7)	1.71 (0.7, 3.38)	0.71 (0.66, 0.76)	0.79 (0.73, 0.85)
Transverse myelitis	0 (NE, 104.16)	0 (NE, 200.68)	0.12 (0, 0.83)	0.15 (0, 1.06)

Abbreviations: CI = confidence interval, NE = not estimable

Source: P903 Interim Report #4.

A full description of the study methodology and applicable underlying event rates has been provided in Interim Report 4 of the US Post-Authorisation Safety Study (mRNA-1273-P903) submitted on 31 January 2022. IR 4 of mRNA-1273-P903 has been assessed and discussed within PRAC procedure EMEA/H/C/005791/MEA/003.5. Due to patient privacy, the HealthVerity data is limited to reporting year of birth. Therefore, there is a potential to misclassify individuals who are 18 years of age at the time of vaccination in the paediatric cohort. This is in line with the fact that 63% of the paediatric cohort was 17 years old, potentially reflecting the reporting limitation in HealthVerity.

Spikevax is not authorised for use in <18-year-olds. Therefore, for a proportion of paediatric individuals Spikevax exposure could have been miscoded to authorised products. Alternatively, clinicians may have recommended off-label use due to an elevated risk of severe COVID-19 due to underlying health conditions. This would impact risk estimates if the underlying conditions are associated with the outcomes of interest. Moreover, this paediatric population is unlikely representative of the general US paediatric population. AESIs will continuously be followed by PRAC. The increased incidence rate ratios of AEs between vaccinated and unvaccinated <18-year-olds in this study are based on very few events, limiting the interpretation. A more robust observed/expected (O/E) analysis which considers relevant risk windows of the AESI is performed for any AESI with an IRR of ≥2 (if based on more than 5 events). This was done for Acute Kidney Injury where the O/E was not elevated for all <18-year-olds. It should however be noted, that it was elevated for <12-year-olds (based on 6 events). This potential signal will be evaluated via Self-controlled risk interval (SCRI) analysis with the next interim report. PRAC does not see any immediate safety concern based on the data in <18-year-olds from this US PASS.

Assessor´s comment:

The Incidence RRs provided for many of the AESIS could raise concerns with regard to the extrapolation from adolescent to young adults as the IRRs appear to be elevated for the adolescent population, but not for the adult population. However, IRR estimation is considered as only an initial crude signal detection step and more robust O/E analysis should be performed for AESIS with an elevated IRR. Moreover, IRRs from age and sex standardised comparison of post vaccination and historical incidence of AESIs cannot be interpreted without information on the underlying methodology of this analysis and the event numbers of each AESI. The MAH was therefore asked to describe the methodology of the analysis and discuss the findings, particularly for the events with IRRs over 2. The answer clarified, that the AESIs are under monitoring of PRAC. PRAC does not see any immediate safety concern based on the data in <18-year-olds from this US PASS. The CHMP and the PRAC Rapporteurs were in communication concerning the elevated AESI IRRs in the paediatric population in study mRNA-1273-P903.

4.3. Discussion of safety

With its submission the MAH requests to extend the use of a 50 µg booster dose of Spikevax to adolescents (12 to < 18 years) at a dosing interval of at least 3 months after completion of the primary series to prevent COVID-19. The submission is based on the extrapolation of safety data from young adults (18 to 25 years of age). Comparing data collected for the primary vaccination schedule, local reactogenicity seems to be slightly higher in adolescent (data from study P203) than in young adults (data from study P302) as already evaluated in the course of procedure EMEA/H/C/005791/II/0021. No clinical meaningful difference could be observed for solicited systemic ARs but it appears that the incidence of systemic solicited ARs tends to be comparable or slightly higher in young adults (18-25 years of age) compared with adolescents. Due to the comparable reactogenicity and safety profile observed for adolescents and young adults 18-25 years of age after mRNA-1273 primary vaccination and taking into consideration results from the ongoing safety monitoring in study P203 with Spikevax, extrapolation of reactogenicity profile after the booster dose from young adults to adolescents could in principle be considered.

To further support the approval of a booster dose in adolescents the MAH submitted a summary of spontaneous post-authorisation AE reported to Moderna with a cut-off date 31 Dec 2021 (taken from SSR #11). Considering that Spikevax is not licensed in the US for individuals below 18 years of age for primary vaccination, and in the EU not yet for booster vaccination, the 3rd dose exposure of approximately 2,600,000 doses in individuals below 18 years of age seems high.

Considering that Spikevax is not licensed in the US for individuals below 18 years of age for primary vaccination, and in the EU not yet for booster vaccination the estimated 3rd dose exposure of approximately 3 million doses appeared unexpectedly high and on the other hand the number of reported cases with AE in this age group very small (45). The MAH was therefore asked to discuss the numbers. In fact, the previously reported 3rd dose exposure of approximately 3 million doses is far too high, and has been re estimated to be 120,000 3rd doses administered to individuals below 18 years of age. It should be noted, that this exposure estimation is not restricted to adolescents but includes also individuals below 12 years of age. The case number for AEs after dose 3 was confirmed by the MAH, but is now related to approximately 120.000 administered 3rd doses. The reported AEs post dose 3 for which information was provided in the clinical overview were due to medication error under the PT of "Product administered to patient of inappropriate age" and "Inappropriate schedule of product administration". The MAH was asked to submit information for the 3 remaining cases and events in children below 18 years of age post dose 3. Two cases represent expected reactogenicity events that are labelled for Spikevax. One of the 2 cases occurred after heterologous booster administration (Comirnaty primary vaccination without ARs, booster with Spikevax 3 month after primary vaccination). The third case describes a myasthenia gravis crisis in a 16-17 year old subject with known myasthenia gravis acquired after COVID-19. A causal relationship cannot be excluded. Upon request the MAH submitted reporting rates for any event, for SAEs, non-SAEs, and AESIs by dose, age, and sex. The reporting rates for all of the events for adolescent and young adults, including all events, SAEs, non-serious AEs, and AESIs are not higher post dose 3 compared to post dose 2. The reporting rates do not raise concerns with regard to the administration of a booster dose in adolescents and could support the extrapolation approach from young adults to this population. The observed versus expected analysis of myocarditis as well as the reporting rates per million doses of Spikevax administered in adolescents confirm, what is currently known about mRNA COVID-19 associated myocarditis, i.e. reporting rates are highest post dose 2, and higher in males compared with females. The highest rate of myocarditis was reported for males 18-24 years of age post dose 2. No cases of myocarditis in adolescents 12 to 17 years of age after a third/booster dose of Spikevax was reported to date. In young adults 18-24 years of age, no AESIs except for myocarditis and pericarditis after any dose occurred at a reporting rate that exceeded the expected population-based studies estimating background incidence. There was no AESI for which the observed to expected rate ratio was higher for dose 3 than for

the overall Global Safety Database. The performed observed versus expected analysis as well as the reporting rates of myocarditis within 7 Days after Dose 1, 2, and 3 per million doses are in line with what is currently known for mRNA COVID-19 associated myocarditis. In adolescent, so far no cases of myocarditis post dose 3 have been recorded in the Moderna safety data bank.

Therefore, the MAH was asked to provide an updated analyses of the myocarditis cases with an extended time frame of at least 30 days into account as the time frame of 7 days post dose was considered short. Regarding to this item the MAH has provided an extended time period of a 21-day risk window, with a more highly sensitive estimate of the reporting rate, including data for cases beyond the 30-day. The analysis has been updated based on the methods previously requested by PRAC, including cases per 100 000 per person-year- cumulative to 15 April 2022. The higher reference rate has been used to support observed vs. expected analyses in Table 4 and the majority of adverse event reports (not only limited to myocarditis) in the adolescent population occur in individuals ages 16-17 years of age. If the lower estimate were to be selected, the observed vs. expected rate ratio would be comparable between adolescents and young adults (O/E in ages 12 – 17: 3.11, 95% CI 2.19 – 4.41). The rate O/E in the males of age group 12-17 was 24.32/17.33 in contrary with the rate in females with O/E 1.99/ 8.67.

Within the previous EMA procedures for the extension of the primary vaccination indication to adolescent and later to children below 12 years of age, causality of the events of cardiac rhythm disorders, chest pain, and dyspnoea could not finally be estimated. These events appear as top 10 SAEs in the post approval safety surveillance and in a list summarising SAE preferred terms for adolescents after any dose. It is acknowledged, that the safety assessment for Spikevax after any dose, i.e. including primary vaccination is not scope of this procedure. However, the post approval data for these SAEs cannot be ignored.

In summary, the extrapolation approach from young adults to adolescents to estimate the safety of a booster dose given to adolescents at least 3 months after full primary vaccination with Spikevax seems justified due to the comparable reactogenicity in these two age groups after primary vaccination with Spikevax. Clinical information stemming from a limited number of cases for administration of a booster dose in adolescents together with the post approval safety data after booster administration in young adults do currently not raise safety concerns with regard to a homologous booster dose for adolescents. The MAH however did not provide the requested comprehensive and comparative analysis (adolescents vs. young adults) and discussion of safety based on post-marketing data. This was requested to support the extrapolation approach. Before approval of the booster dose for adolescents can be granted, the MAH is requested to submit this analysis and discussion.

5. Changes to the Product Information

As a result of this variation, sections 4.2 and 4.4 of the SmPC are being updated to include a 50 µg booster dose for adolescents 12 to 18 years of age. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

6. 1st request for supplementary information

6.1. Other concerns

Immunogenicity and Efficacy

1. The MAH is asked to provide additional information on the status of study P203 Part C regarding timelines and availability of interim or final study reports (OC1).
2. The MAH is requested to comment on the proposed boosting interval for adolescents, considering the slower rate decline of the immune response and the duration of protection in this population (OC2).

Population IS/ID Modelling

3. The MAH is asked to provide the original data set and should indicate the excluded values per study and reason for exclusion. The MAH should further discuss the use of appropriate methods in order to justify the exclusion of observed values
4. The MAH is asked to justify the assumption that a linear function would be appropriate to characterise the drug effect.
5. The MAH is asked to provide further information on the selection of kMAB, that seems to be a sensitive parameter for both, primary and booster response.
6. Again, no further data to support the setting of this scaling factor to 0.45 could be found in the modelling report and should be provided. Of note, this parameter is reflected with 0.44 in the table listing the final parameter estimates.
7. The MAH is asked to discuss the role of volume V in the modelling framework, including this would represent a physiological systems variable or just needed to describe the data. In this regard, a re-discussion of covariate selection is to be provided by the MAH taking other potentially clinically relevant covariates such as weight into account. V as the single parameter for testing covariate effects should be further justified. As long as no maturation is included in the model, and AGE and weight effects are not clearly reflected, the inclusion of data from very young subjects for model building is not supported.
8. The MAH is asked to provide VPC plots stratified by age groups, study, and dose.
9. In order to improve the comparability between age groups and to meet the claimed extrapolation, the MAH is asked to simulate the following scenarios:

    a) - Adolescents receiving 50 µg booster dose 3 months and 9 months after second dose
    b) - Adolescents receiving 25 µg booster dose 3, 6 and 9 months after second dose
    c) - Adult age groups (18-25 and 18-65) receiving 50 µg booster dose 3, 6 and 9 months after second dose.

    GMT (+ 95% CI) should be provided post second dose, pre-booster and post-booster and GMFR (+95% CI) should be calculated and compared.

Safety

10. Considering that Spikevax is not licensed in the US for individuals below 18 years of age for primary vaccination, and in the EU not yet for booster vaccination the following observations are made:

    - The estimated 3rd dose exposure of more 3 million doses appears unexpectedly high and should be confirmed and discussed.
    - On the other hand the number of reported cases with AE in this age group is very small (45) and in contradiction to the estimated exposure. This number needs to be confirmed and discussed.

- The MAH is requested to describe in detail the methodology and data sources (countries/jurisdiction for use) that lead to the estimated exposure in the different age categories as well as estimates according to age and numbers of doses received. Based on this evaluation a comprehensive and comparative analysis (adolescents vs. young adults) and discussion of safety is expected.

11. Reporting rates for myocarditis are given for a time frame of 7 days post dose. This is considered short, and analyses of myocarditis cases should take an extended time frame of at least 30 days into account. The MAH is requested to present updated analyses.
12. IRRs from age and sex standardised comparison of post vaccination and historical incidence of AESIs (Table 24 in the clinical overview) cannot be interpreted without information on the underlying methodology of this analysis and the event numbers of each AESI. The MAH is asked to describe the methodology of the analysis and discuss the findings, particularly for the AESI with IRRs over 2.

7. Assessment of the responses to the 1st request for supplementary information

7.1. Other concerns

Clinical aspects

Question 1

The MAH is asked to provide additional information on the status of study P203 Part C regarding timelines and availability of interim or final study reports.

MAH's response

The MAH clarified that mRNA-1273 is being studied in adolescents 12 to < 18 years of age in the US in Study mRNA 1273-P203, a Phase 2/3, randomised, observer-blind, placebo controlled study that evaluates the safety, reactogenicity, and effectiveness of the mRNA-1273 vaccine in healthy adolescents. The goal of the study was to support an indication for use of mRNA-1273 (100 µg IM, given as 2 doses, 28 days apart) in the 12 to < 18 years of age group. The blinded placebo controlled portion of this study was submitted and approved under procedure EMEA/H/C/005791/II/0021. As per protocol upon FDA granting an EUA in the adolescent age group (for a SARS-CoV-2 mRNA vaccine other than mRNA-1273), subjects were unblinded and crossed over.

Recently, protocol Amendment #3 was implemented to provide a 50 µg booster dose of mRNA-1273 to all participants. This change was prompted by the authorisation of a 50 ug booster dose for adults 18 years and older, supported by data from study P201B. The use of mRNA-1273 as a booster dose regimen in adolescents 12 - <18 years of age is currently investigated in clinical study P203 Part C. The booster portion of the clinical trial P203 Part C is on-going (first subject dosed late December 2021) (Protocol Amendment #3).

The generation of an interim analysis on at least the first 1000 subjects boosted with at least 2 months follow-up post booster, and corresponding regulatory submission package is currently planned for Q3 2022.

Assessment of the MAH's response and Conclusion:

The issue is partly resolved. The MAH provided information on the status as requested. Interim data for this study are expected in Q3. The MAH is requested to submit the interim and the final clinical study report from study P203 Part C as soon as it becomes available. The interim CSR is expected Q3 2022.

Conclusion

Issue solved following a commitment by the MAH to include the data becoming available on the reactogenicity/safety in adolescents and young adults along with the sound data analysis in the upcoming interim reports from study mRNA-1273-P203 Part C.

Question 2

The MAH was requested to comment on the proposed boosting interval for adolescents, considering the slower rate decline of the immune response and the duration of protection in this population.

MAH's Response:

The MAH explained that the booster data on shortened intervals is being extrapolated from the NIH/DMID 21-0012 study, which included young adults (18-25 years of age), Study P201B, and post-authorisation safety data, in order to provide regulatory agency flexibility to best meet their local dosing interval recommendations.

It is also important to note, that current post-authorisation safety data, does not distinguish the different dosing intervals that have been recommended for booster implementation in different countries, for example, France (3 months), Germany (3 months), UK (3 months), Canada - Ontario (3 months), Switzerland (4 months), and U.S. (5 months). By providing flexibility in the dosing interval, the decision when and for whom to implement a third dose of Spikevax can be made based on local recommending bodies needs and the evolution of the pandemic.

Assessment of the MAH's Response:

In summary the MAH's response is not satisfactory. The MAH justifies the booster interval of 3 months in adolescents with the extrapolation approach from young adults, without discussing the slower rate decline of immune response and the duration of protection in this population as requested. This should be done subsequently. The MAH is asked to submit and discuss:

•all available immunogenicity data comparing the decline of antibodies in adolescents and young adults 18-25 years of age beyond of the data from study P203

•all available data on the duration of protection in the 2 age cohorts

•to justify the identical booster interval for the 2 groups.

Conclusion

Issue not solved

The MAH is asked to submit and discuss:

•all available immunogenicity data comparing the decline of antibodies in adolescents and young adults 18-25 years of age beyond of the data from study P203

•all available data on the duration of protection in the 2 age cohorts

•to justify the identical booster interval for the 2 groups.

Population IS/ID Modelling

Question 3
The MAH as asked to provide the original data set and should indicate the excluded values per study and reason for exclusion. The MAH should further discuss the use of appropriate methods in order to justify the exclusion of observed values.

Summary of the MAH's response

No additional data on GMTs was censored specifically for the model since all immunogenicity test values <LLOQ are imputed with LLOQ, as the % of <LLOQ is the same as the % of imputed LLOQ. Such that:

• In the per-protocol immunogenicity subset, because all subjects included have SARSCoV- 2 negative status (RT-PCR and Elecsys serology both negative) at baseline, >95% subjects have <LLOQ at baseline (i.e. imputed with LLOQ at baseline).

• At Day 57, the seroresponse rate is very high (>95%) for >=4* LLOQ if baseline <LLOQ, or >= 4 fold-rise is baseline >=LLOQ. Thus, for Day 57, <5% subjects have <LLOQ (i.e. imputed with LLOQ)

This data can be found in the previously submitted Immunogenicity Tables for Study P203 (Adolescent indication extension), Study P204 (Paediatric 6 to <12yr indication extension), Study P301 (Adult primary series indication), and Study P201 Part A & B (Ph2 and booster portion):

Table 14.2.3.1.1.2 Summary of Pseudovirus Neutralising Antibody ID50 and ID80 Titers by Age Group Per-Protocol Immunogenicity Subset Table 14.2.1.2.3.1.2 Analysis of Pseudovirus Neutralising Antibody ID50 and ID80 Titers by Age Group – Seroresponse Rate Per-Protocol Immunogenicity Subset

For example, data can be found in P204, 6-11y age group immunogenicity data in Part 2 (screenshot below):

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mRNA-1273-P204 Part 2 Arm 8 (Data Cutoff Date: 10NOV2021)

Table 14.2.3.1.1.2
Summary of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Age Group
Per-Protocol Immunogenicity Subset

Age Group: >=6 and <12 Years, Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118)

	P204 mRNA-1273	P301 mRNA-1273
Timepoint Data Category Statistic	50 µg (N=320)	100 µg (N=295)
Baseline (Day 1)		
n [1]	317	295
GMT	9.250	9.285
95% CI [2]	(NE, NE)	(9.216, 9.355)
Median	9.250	9.250
Min, Max	9.25, 9.25	9.25, 28.50
Number of Participants <LLOQ, n (%) [3]	317 (100)	294 (99.7)
Number of Participants >=LLOQ, n (%) [3]	0	1 (0.3)

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mRNA-1273-P204 Part 2 Arm 8 (Data Cutoff Date: 10NOV2021)

Table 14.2.1.2.3.1.2
Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Age Group – Seroresponse Rate
Per-Protocol Immunogenicity Subset

Age Group: >=6 and <12 Years, Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118)

	P204 mRNA-1273	P301 mRNA-1273
Timepoint Statistic	50 µg (N=320)	100 µg (N=295)
Day 57		
N1	316	295
Seroresponse, n (%) [1]	313 (99.1)	292 (99.0)
95% CI [2]	(97.3, 99.8)	(97.1, 99.8)
Difference (P204 vs. P301) (%)	0.1	
95% CI [3]	(-1.9, 2.1)	

Assessment of the MAH's response

The MAH elaborated on the data set and below LLOQ samples.

Conclusion
Issue will not be further pursued

Question 4
The MAH is asked to justify the assumption that a linear function would be appropriate to characterise the drug effect.

Summary of the MAH's response
The MAH referred to the response provided in OC7 for the "V" scaling factor question. To summarise, dose effect is on MBmax, the maximum number of memory B-cells that can be formed. The MAH agreed the dose effect is linear. It is a simpler assumption to make given the range of doses studied (note that the Phase 1 50 ug data could not be used as it used a different assay).

The MAH did not evaluate other functions, as linear function was well established in our other vaccine programs that used a similar IS/ID model. However, the MAH will evaluate other functions going forward.

The MAH does not anticipate this to impact the predictive ability of the model, given that most predictions are being performed in dose ranges already included in the model, hence no extrapolation was performed, only interpolating. Secondly, the predictive ability of the model was well captured by the validation routines such as VPC's and the table of % differences.

Assessment of the MAH's response
As no regulatory decision will be made based on the modelling, this concern will not be further pursued. Nevertheless, the justification for assuming a linear function would be appropriate to characterise the drug effect is still considered poor. The MAH admits that no further functions were tested and this will be addressed in updated version of the model. However, this is regarded inconsistent with the Modelling and Simulation report (p.13) where it was stated that indeed, different drug effect relationships were tested (linear, Emax) and it was concluded that the dose-response relationship was best described by a linear model.

Conclusion
Issue will not be further pursued in the context of this variation.

Question 5
The MAH is asked to provide further information on the selection of kMAB, that seems to be a sensitive parameter for both, primary and booster response.

Summary of the MAH's response
The value of kMAB (secretion rate of antibody by plasma cells) was fixed and based on literature (Chen et al). This section in the model text has been corrected. We thank the reviewer to bringing this to notice. The secretion rate of antibodies is assumed to be same for plasma cells (short-lived and long-lived). The scaling factors reflect the proportion of the activated B cells pool converting into SLPCs and secreting the antibodies. Detailed assumption list is provided below regarding the model and parameters.

Assessment of the MAH's response
In response, the MAH detailed that kMAB, reflecting the secretion rate of antibody by plasma cells, was fixed based on literature data and reported some correction in the model text, but it is not clear which parts and wording has changed. Given that no regulatory decision is based on modelling and simulation, the issue is not further pursued.

Conclusion
Issue will not be further pursued in the context of this variation.

Question 6
Again, no further data to support the setting of this scaling factor to 0.45 could be found in the modelling report and should be provided. Of note, this parameter is reflected with 0.44 in the table listing the final parameter estimates.

Summary of the MAH's response
The scaling factors 0.45 and 0.55 represent the percentage of activated B cells differentiating into short-lived plasma cells and memory B cells. These parameter values were based on literature (Chen et al) and were fixed based on sensitivity analysis. The mentioned 0.44 value in Table 4-3 has been corrected to 0.45 as used in the model. Detailed assumption lists are provided below regarding the model and parameters.

Assessment of the MAH's response
In response, the MAH detailed that also the scaling factors have been fixed based on the same publication that was wrongly reflected in the table listing the final parameter estimates. Fixing was based on a sensitivity analysis that in turn has not been provided or taken into account in the discussion to respond

to item 6. Given that no regulatory decision is based on modelling and simulation, the issue is not further pursued.

Conclusion
Issue will not be further pursued in the context of this variation.

Question 7
The MAH is asked to discuss the role of volume V in the modelling framework, including this would represent a physiological system variable or just needed to describe the data. In this regard, a re-discussion of covariate selection is to be provided by the MAH taking other potentially clinically relevant covariates such as weight into account. V as the single parameter for testing covariate effects should be further justified. As long as no maturation is included in the model, and AGE and weight effects are not clearly reflected, the inclusion of data from very young subjects for model building is not supported.

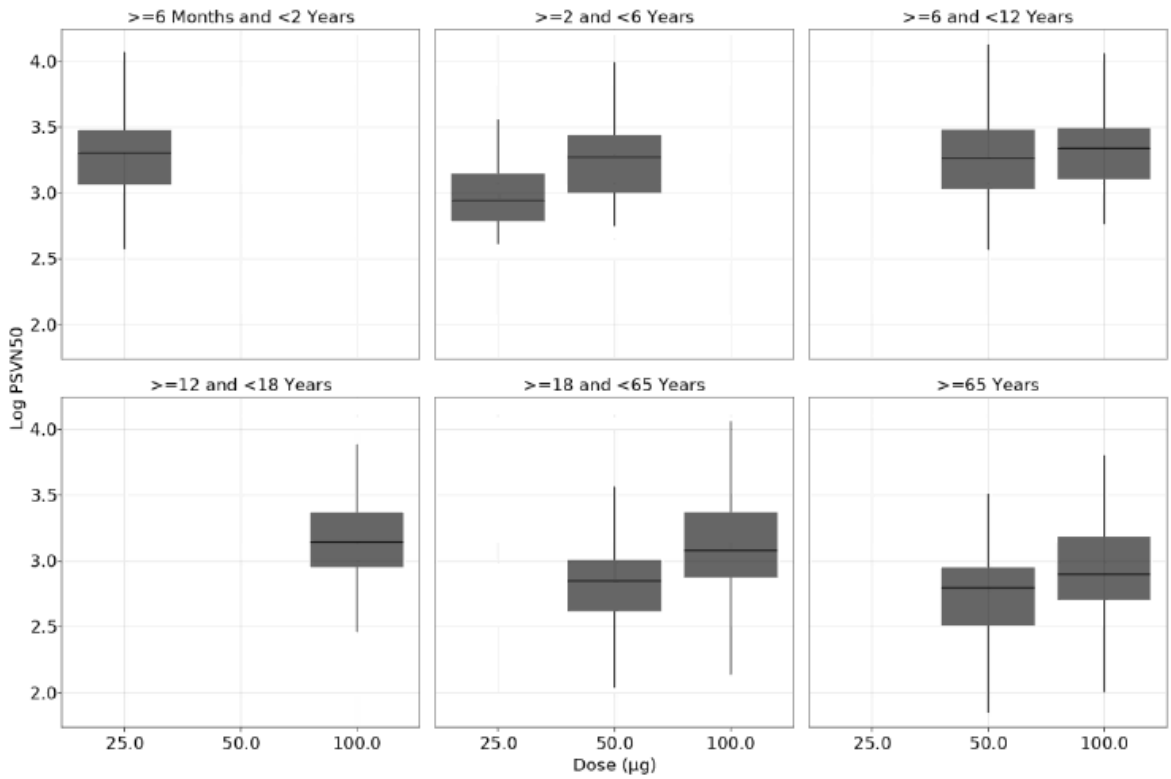
Summary of the MAH's response

As with any other model, there are certain assumptions that had to be made. We acknowledge that the assumption should have been clearer. The mechanistic model represented here has strong underpinnings of the dynamics of B-cells and the system parameters derived from literature. Our first goal was to represent the biology. This resulted in us capturing the trends of the observed data as raw antibody numbers secreted from the LLPC's and SLPC's. The surrogate for these raw antibodies generated from the model are the measured antibody titers.

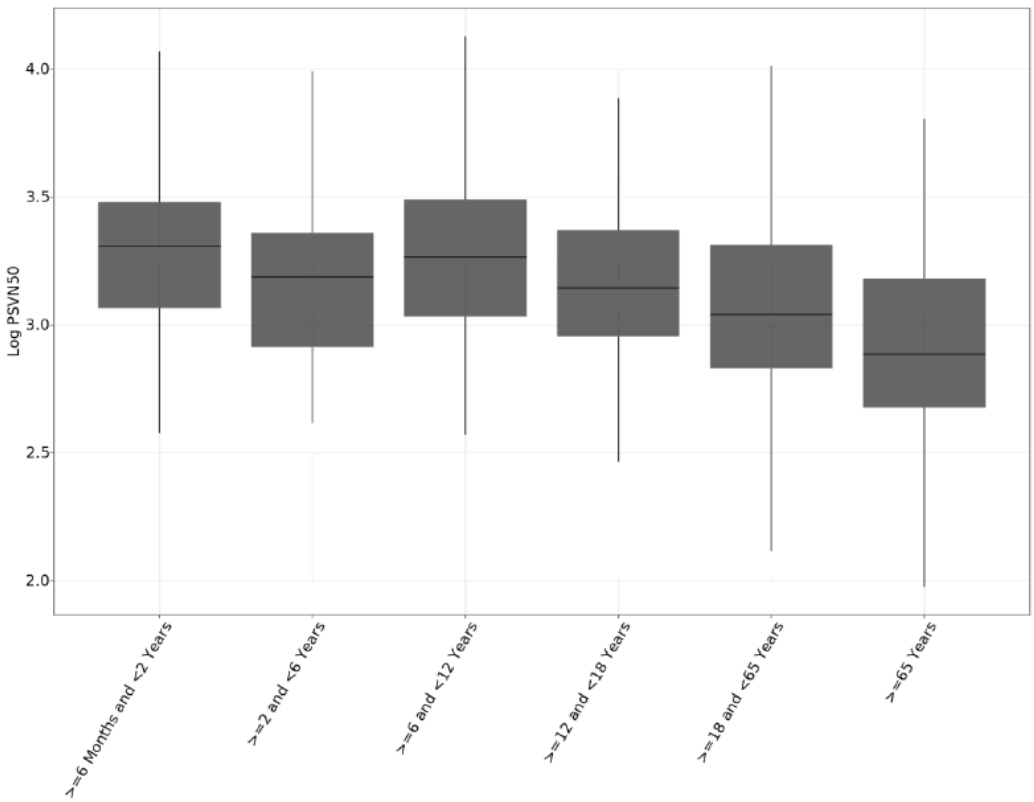
The volume scaling factor "V" was to link that connected the number of antibodies in the body to the measured antibody titer, similar to how amount in the body is related concentration measured in a PK model. In a PK model, Volume is defined as the proportionality constant that relates the amount in the body to the concentration measured.

While we strive to provide a physiological meaning to it, in most instances, it is treated as a proportionality factor. Even in our case, the "V" is one such proportionality factor that scales the antibody numbers to the antibody titers. The expectation is that this parameter will be a function of dose and age as the measured titers will be a function of amount of vaccine in the body and age at which vaccine was received. One could argue that age and weight are correlated, so why not use weight. It turns out that clinically most vaccines are dose based on age and hence we stuck with this parameter.

The plot below shows that at day 57 (after second primary series dose), within an age group there is clear dose-response relationship as long as there is more than one dose, except maybe for 6-12 years.



Further combined with the observed day 57 titer vs age plot below, there seems to be a downward trend with increasing age. Taking these two into account, both age and dose have an effect and having them together will tease out the effects of each of these parameters.



For all practical purposes, especially for clinical dosing of vaccines, age-based dosing has been the standard and hence we did not evaluate or consider other predictors of interest for immunogenicity modelling.

Assessment of the MAH's response

The MAH's effort to further explain the meaning of V in the modelling framework is acknowledged, however, the Assessor's conclusion and issues remain from the methodological point of view (covariates, maturation). The MAH is also referred to the EMA Q&A document in this regard (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers)

Conclusion

Issue will not be further pursued in the context of this variation.

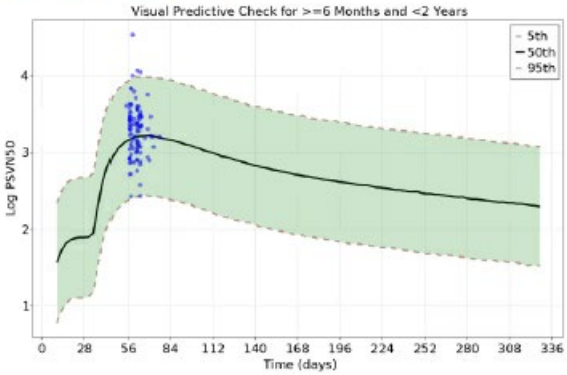
Question 8

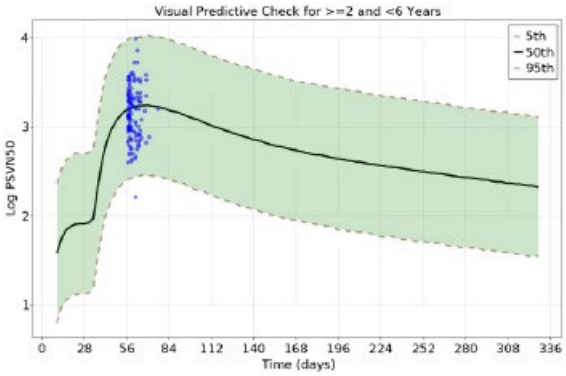
The MAH is asked to provide VPC plots stratified by age groups, study, and dose

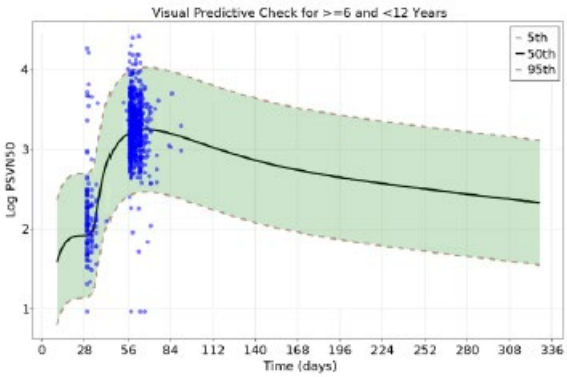
Summary of the MAH's response

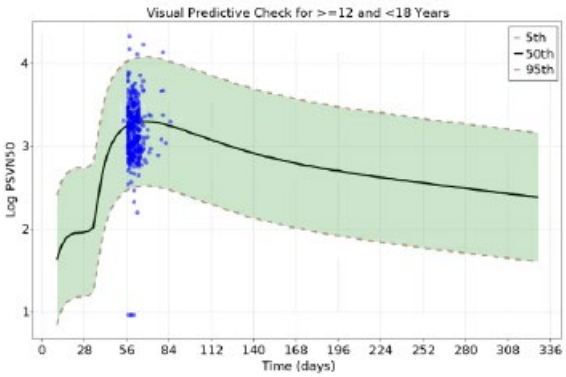
As requested by the reviewer the VPC plots given below are across different age groups, dose cohorts and by study. The prediction intervals capture 90% of the observed data.

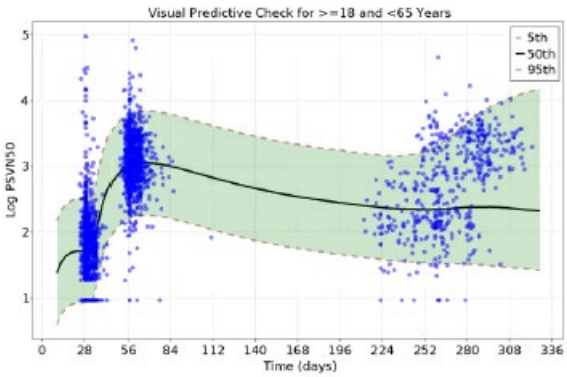
VPCs by age groups

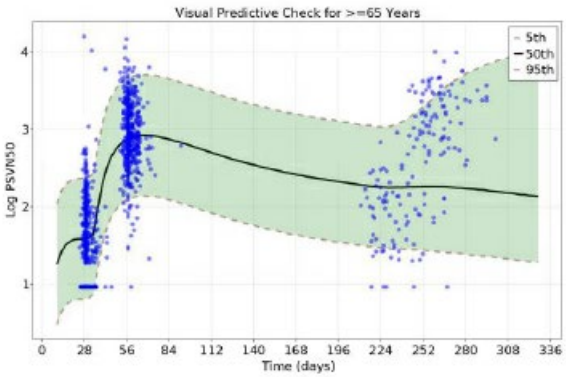




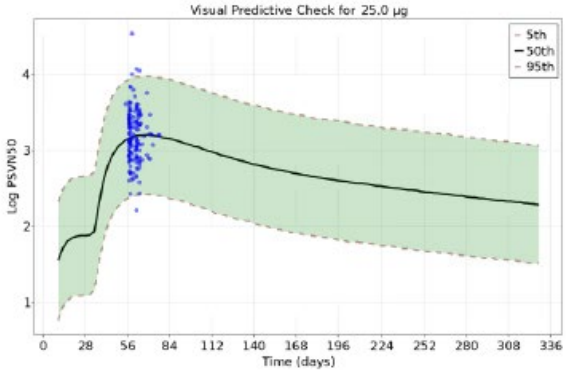


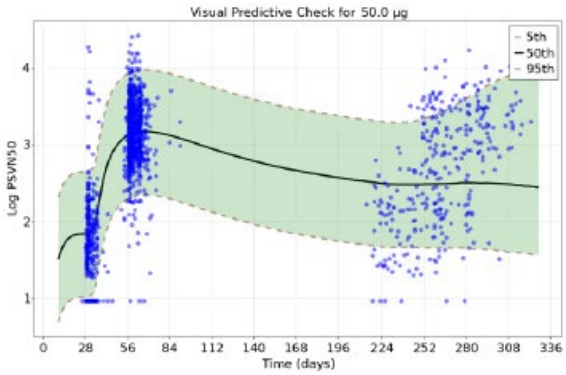


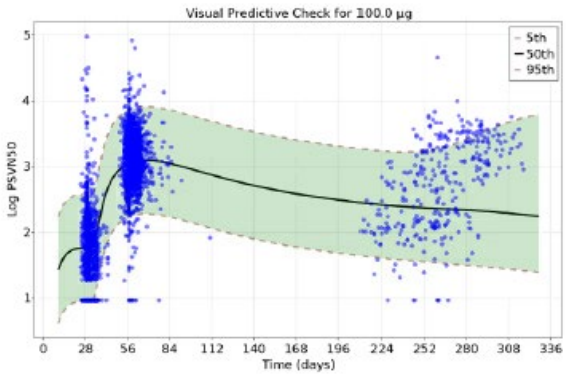




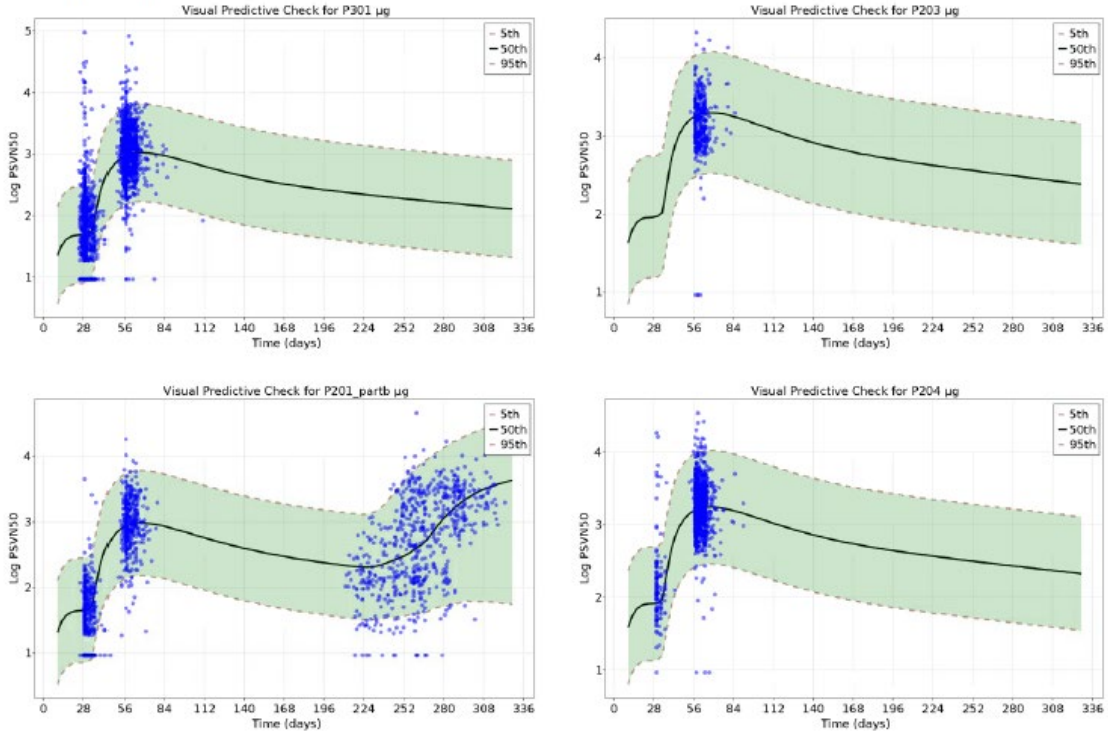
VPCs by dose


Visual Predictive Check for 25.0 µg
5th
50th
95th
Log PSVN50
Time (days)


Visual Predictive Check for 50.0 µg
5th
50th
95th
Log PSVN50
Time (days)


Visual Predictive Check for 100.0 µg
5th
50th
95th
Log PSVN50
Time (days)

VPCs by study



Assessment of the MAH's response
The requested plots have been provided.

Conclusion
Issue solved.

Question 9
In order to improve the comparability between age groups and to meet the claimed EOI, the MAH is asked to simulate the following scenarios (OC9):

- Adolescents receiving 50 µg booster dose 3 months and 9 months after second dose

- Adolescents receiving 25 µg booster dose 3, 6 and 9 months after second dose

- Adult age groups (18-25 and 18-65) receiving 50 µg booster dose 3, 6 and 9 months after second dose.

GMT (+ 95% CI) should be provided post second dose, pre-booster and post-booster and GMFR (+95% CI) should be calculated and compared

Summary of the MAH's response
As requested by the reviewer, the two tables below represent the simulations of the alternative dosing scenarios. The first table is the GMT (95% CI) and the second table is the GMFR (95% CI).

Table 1: Simulated GMT (95% CI) across various booster dose and timing scenarios

Age Group	Time	GMT (95% CI)	N	Booster Dose	Booster Dose Time after Second dose
>=18 and <65 Years	28day-post-1st-dose-(d29)	70.81 (65.608, 76.013)	1062	25 ug	3 months
>=18 and <65 Years	28day-post-2nd-dose-(d57)	918.83 (851.327, 986.332)	1062	25 ug	3 months
>=18 and <65 Years	pre-3month-booster-(d117)	536.796 (497.36, 576.232)	1062	25 ug	3 months
>=18 and <65 Years	28day-post-3month-booster-(d146)	2149.371 (1991.467, 2307.276)	1062	25 ug	3 months
>=65 Years	28day-post-1st-dose-(d29)	46.901 (43.174, 50.629)	461	25 ug	3 months
>=65 Years	28day-post-2nd-dose-(d57)	609.744 (561.451, 658.037)	461	25 ug	3 months
>=65 Years	pre-3month-booster-(d117)	356.275 (328.062, 384.488)	461	25 ug	3 months
>=65 Years	28day-post-3month-booster-(d146)	1427.23 (1314.26, 1540.201)	461	25 ug	3 months
>=12 and <18 Years	28day-post-1st-dose-(d29)	88.313 (85.235, 91.391)	379	25 ug	3 months
>=12 and <18 Years	28day-post-2nd-dose-(d57)	1145.939 (1105.997, 1185.88)	379	25 ug	3 months
>=12 and <18 Years	pre-3month-booster-(d117)	669.477 (646.142, 692.812)	379	25 ug	3 months
>=12 and <18 Years	28day-post-3month-booster-(d146)	2680.636 (2587.203, 2774.07)	379	25 ug	3 months
>=18 and <25 Years	28day-post-1st-dose-(d29)	78.806 (64.335, 93.276)	58	25 ug	3 months
>=18 and <25 Years	28day-post-2nd-dose-(d57)	1022.575 (834.806, 1210.343)	58	25 ug	3 months
>=18 and <25 Years	pre-3month-booster-(d117)	597.406 (487.708, 707.103)	58	25 ug	3 months
>=18 and <25 Years	28day-post-3month-booster-(d146)	2392.058 (1952.82, 2831.295)	58	25 ug	3 months
>=18 and <65 Years	28day-post-1st-dose-(d29)	70.81 (65.608, 76.013)	1062	25 ug	6 months
>=18 and <65 Years	28day-post-2nd-dose-(d57)	918.83 (851.327, 986.332)	1062	25 ug	6 months
>=18 and <65 Years	pre-6month-booster-(d207)	224.214 (207.742, 240.686)	1062	25 ug	6 months
>=18 and <65 Years	28day-post-6month-booster-(d236)	1960.867 (1816.811, 2104.922)	1062	25 ug	6 months
>=65 Years	28day-post-1st-dose-(d29)	46.901 (43.174, 50.629)	461	25 ug	6 months
>=65 Years	28day-post-2nd-dose-(d57)	609.744 (561.451, 658.037)	461	25 ug	6 months
>=65 Years	pre-6month-booster-(d207)	148.816 (137.031, 160.6)	461	25 ug	6 months
>=65 Years	28day-post-6month-booster-(d236)	1302.108 (1199.045, 1405.172)	461	25 ug	6 months
>=12 and <18 Years	28day-post-1st-dose-(d29)	88.313 (85.235, 91.391)	379	25 ug	6 months

Age Group	Time	GMT (95% CI)	N	Booster Dose	Booster Dose Time after Second dose
>=18 and <65 Years	28day-post-3month-booster-(d146)	2774.319 (2570.502, 2978.135)	1062	50 ug	3 months
>=65 Years	28day-post-1st-dose-(d29)	46.901 (43.174, 50.629)	461	50 ug	3 months
>=65 Years	28day-post-2nd-dose-(d57)	732.1 (674.121, 790.079)	461	50 ug	3 months
>=65 Years	pre-3month-booster-(d117)	442.606 (407.556, 477.655)	461	50 ug	3 months
>=65 Years	28day-post-3month-booster-(d146)	1842.192 (1696.375, 1988.01)	461	50 ug	3 months
>=12 and <18 Years	28day-post-1st-dose-(d29)	88.313 (85.235, 91.391)	379	50 ug	3 months
>=12 and <18 Years	28day-post-2nd-dose-(d57)	1375.801 (1327.848, 1423.755)	379	50 ug	3 months
>=12 and <18 Years	pre-3month-booster-(d117)	831.711 (802.722, 860.701)	379	50 ug	3 months
>=12 and <18 Years	28day-post-3month-booster-(d146)	3460.053 (3339.453, 3580.654)	379	50 ug	3 months
>=18 and <25 Years	28day-post-1st-dose-(d29)	78.806 (64.335, 93.276)	58	50 ug	3 months
>=18 and <25 Years	28day-post-2nd-dose-(d57)	1227.692 (1002.259, 1453.125)	58	50 ug	3 months
>=18 and <25 Years	pre-3month-booster-(d117)	742.175 (605.894, 878.456)	58	50 ug	3 months
>=18 and <25 Years	28day-post-3month-booster-(d146)	3087.568 (2520.619, 3654.518)	58	50 ug	3 months
>=18 and <65 Years	28day-post-1st-dose-(d29)	70.81 (65.608, 76.013)	1062	50 ug	6 months
>=18 and <65 Years	28day-post-2nd-dose-(d57)	1103.137 (1022.094, 1184.179)	1062	50 ug	6 months
>=18 and <65 Years	pre-6month-booster-(d207)	280.146 (259.565, 300.727)	1062	50 ug	6 months
>=18 and <65 Years	28day-post-6month-booster-(d236)	2532.992 (2346.904, 2719.079)	1062	50 ug	6 months
>=65 Years	28day-post-1st-dose-(d29)	46.901 (43.174, 50.629)	461	50 ug	6 months
>=65 Years	28day-post-2nd-dose-(d57)	732.1 (674.121, 790.079)	461	50 ug	6 months
>=65 Years	pre-6month-booster-(d207)	185.935 (171.211, 200.659)	461	50 ug	6 months
>=65 Years	28day-post-6month-booster-(d236)	1682.044 (1548.909, 1815.179)	461	50 ug	6 months
>=12 and <18 Years	28day-post-1st-dose-(d29)	88.313 (85.235, 91.391)	379	50 ug	6 months
>=12 and <18 Years	28day-post-2nd-dose-(d57)	1375.801 (1327.848, 1423.755)	379	50 ug	6 months
>=12 and <18 Years	pre-6month-booster-(d207)	349.39 (337.212, 361.568)	379	50 ug	6 months
>=12 and <18 Years	28day-post-6month-booster-(d236)	3159.077 (3048.967, 3269.187)	379	50 ug	6 months
>=18 and <25 Years	28day-post-1st-dose-(d29)	78.806 (64.335, 93.276)	58	50 ug	6 months

Age Group	Time	GMT (95% CI)	N	Booster Dose	Booster Dose Time after Second dose
>=12 and <18 Years	28day-post-2nd-dose-(d57)	1145.939 (1105.997, 1185.88)	379	25 ug	6 months
>=12 and <18 Years	pre-6month-booster-(d207)	279.633 (269.887, 289.38)	379	25 ug	6 months
>=12 and <18 Years	28day-post-6month-booster-(d236)	2445.538 (2360.299, 2530.778)	379	25 ug	6 months
>=18 and <25 Years	28day-post-1st-dose-(d29)	78.806 (64.335, 93.276)	58	25 ug	6 months
>=18 and <25 Years	28day-post-2nd-dose-(d57)	1022.575 (834.806, 1210.343)	58	25 ug	6 months
>=18 and <25 Years	pre-6month-booster-(d207)	249.53 (203.71, 295.349)	58	25 ug	6 months
>=18 and <25 Years	28day-post-6month-booster-(d236)	2182.269 (1781.553, 2582.984)	58	25 ug	6 months
>=18 and <65 Years	28day-post-1st-dose-(d29)	70.81 (65.608, 76.013)	1062	25 ug	9 months
>=18 and <65 Years	28day-post-2nd-dose-(d57)	918.83 (851.327, 986.332)	1062	25 ug	9 months
>=18 and <65 Years	pre-9month-booster-(d297)	136.722 (126.678, 146.766)	1062	25 ug	9 months
>=18 and <65 Years	28day-post-9month-booster-(d326)	1892.632 (1753.589, 2031.675)	1062	25 ug	9 months
>=65 Years	28day-post-1st-dose-(d29)	46.901 (43.174, 50.629)	461	25 ug	9 months
>=65 Years	28day-post-2nd-dose-(d57)	609.744 (561.451, 658.037)	461	25 ug	9 months
>=65 Years	pre-9month-booster-(d297)	90.746 (83.56, 97.932)	461	25 ug	9 months
>=65 Years	28day-post-9month-booster-(d326)	1256.829 (1157.351, 1356.307)	461	25 ug	9 months
>=12 and <18 Years	28day-post-1st-dose-(d29)	88.313 (85.235, 91.391)	379	25 ug	9 months
>=12 and <18 Years	28day-post-2nd-dose-(d57)	1145.939 (1105.997, 1185.88)	379	25 ug	9 months
>=12 and <18 Years	pre-9month-booster-(d297)	170.516 (164.573, 176.459)	379	25 ug	9 months
>=12 and <18 Years	28day-post-9month-booster-(d326)	2360.437 (2278.164, 2442.711)	379	25 ug	9 months
>=18 and <25 Years	28day-post-1st-dose-(d29)	78.806 (64.335, 93.276)	58	25 ug	9 months
>=18 and <25 Years	28day-post-2nd-dose-(d57)	1022.575 (834.806, 1210.343)	58	25 ug	9 months
>=18 and <25 Years	pre-9month-booster-(d297)	152.159 (124.219, 180.099)	58	25 ug	9 months
>=18 and <25 Years	28day-post-9month-booster-(d326)	2106.329 (1719.558, 2493.1)	58	25 ug	9 months
>=18 and <65 Years	28day-post-1st-dose-(d29)	70.81 (65.608, 76.013)	1062	50 ug	3 months
>=18 and <65 Years	28day-post-2nd-dose-(d57)	1103.137 (1022.094, 1184.179)	1062	50 ug	3 months
>=18 and <65 Years	pre-3month-booster-(d117)	666.878 (617.885, 715.87)	1062	50 ug	3 months

Age Group	Time	GMT (95% CI)	N	Booster Dose	Booster Dose Time after Second dose
>=18 and <65 Years	28day-post-3month-booster-(d146)	2774.319 (2570.502, 2978.135)	1062	50 ug	3 months
>=65 Years	28day-post-1st-dose-(d29)	46.901 (43.174, 50.629)	461	50 ug	3 months
>=65 Years	28day-post-2nd-dose-(d57)	732.1 (674.121, 790.079)	461	50 ug	3 months
>=65 Years	pre-3month-booster-(d117)	442.606 (407.556, 477.655)	461	50 ug	3 months
>=65 Years	28day-post-3month-booster-(d146)	1842.192 (1696.375, 1988.01)	461	50 ug	3 months
>=12 and <18 Years	28day-post-1st-dose-(d29)	88.313 (85.235, 91.391)	379	50 ug	3 months
>=12 and <18 Years	28day-post-2nd-dose-(d57)	1375.801 (1327.848, 1423.755)	379	50 ug	3 months
>=12 and <18 Years	pre-3month-booster-(d117)	831.711 (802.722, 860.701)	379	50 ug	3 months
>=12 and <18 Years	28day-post-3month-booster-(d146)	3460.053 (3339.453, 3580.654)	379	50 ug	3 months
>=18 and <25 Years	28day-post-1st-dose-(d29)	78.806 (64.335, 93.276)	58	50 ug	3 months
>=18 and <25 Years	28day-post-2nd-dose-(d57)	1227.692 (1002.259, 1453.125)	58	50 ug	3 months
>=18 and <25 Years	pre-3month-booster-(d117)	742.175 (605.894, 878.456)	58	50 ug	3 months
>=18 and <25 Years	28day-post-3month-booster-(d146)	3087.568 (2520.619, 3654.518)	58	50 ug	3 months
>=18 and <65 Years	28day-post-1st-dose-(d29)	70.81 (65.608, 76.013)	1062	50 ug	6 months
>=18 and <65 Years	28day-post-2nd-dose-(d57)	1103.137 (1022.094, 1184.179)	1062	50 ug	6 months
>=18 and <65 Years	pre-6month-booster-(d207)	280.146 (259.565, 300.727)	1062	50 ug	6 months
>=18 and <65 Years	28day-post-6month-booster-(d236)	2532.992 (2346.904, 2719.079)	1062	50 ug	6 months
>=65 Years	28day-post-1st-dose-(d29)	46.901 (43.174, 50.629)	461	50 ug	6 months
>=65 Years	28day-post-2nd-dose-(d57)	732.1 (674.121, 790.079)	461	50 ug	6 months
>=65 Years	pre-6month-booster-(d207)	185.935 (171.211, 200.659)	461	50 ug	6 months
>=65 Years	28day-post-6month-booster-(d236)	1682.044 (1548.909, 1815.179)	461	50 ug	6 months
>=12 and <18 Years	28day-post-1st-dose-(d29)	88.313 (85.235, 91.391)	379	50 ug	6 months
>=12 and <18 Years	28day-post-2nd-dose-(d57)	1375.801 (1327.848, 1423.755)	379	50 ug	6 months
>=12 and <18 Years	pre-6month-booster-(d207)	349.39 (337.212, 361.568)	379	50 ug	6 months
>=12 and <18 Years	28day-post-6month-booster-(d236)	3159.077 (3048.967, 3269.187)	379	50 ug	6 months
>=18 and <25 Years	28day-post-1st-dose-(d29)	78.806 (64.335, 93.276)	58	50 ug	6 months

Age Group	Time	GMT (95% CI)	N	Booster Dose	Booster Dose Time after Second dose
>=18 and <25 Years	28day-post-2nd-dose-(d57)	1227.692 (1002.259, 1453.125)	58	50 ug	6 months
>=18 and <25 Years	pre-6month-booster-(d207)	311.777 (254.528, 369.027)	58	50 ug	6 months
>=18 and <25 Years	28day-post-6month-booster-(d236)	2818.993 (2301.36, 3336.625)	58	50 ug	6 months
>=18 and <65 Years	28day-post-1st-dose-(d29)	70.81 (65.608, 76.013)	1062	50 ug	9 months
>=18 and <65 Years	28day-post-2nd-dose-(d57)	1103.137 (1022.094, 1184.179)	1062	50 ug	9 months
>=18 and <65 Years	pre-9month-booster-(d297)	170.962 (158.402, 183.522)	1062	50 ug	9 months
>=18 and <65 Years	28day-post-9month-booster-(d326)	2457.838 (2277.272, 2638.404)	1062	50 ug	9 months
>=65 Years	28day-post-1st-dose-(d29)	46.901 (43.174, 50.629)	461	50 ug	9 months
>=65 Years	28day-post-2nd-dose-(d57)	732.1 (674.121, 790.079)	461	50 ug	9 months
>=65 Years	pre-9month-booster-(d297)	113.469 (104.484, 122.455)	461	50 ug	9 months
>=65 Years	28day-post-9month-booster-(d326)	1632.154 (1502.968, 1761.339)	461	50 ug	9 months
>=12 and <18 Years	28day-post-1st-dose-(d29)	88.313 (85.235, 91.391)	379	50 ug	9 months
>=12 and <18 Years	28day-post-2nd-dose-(d57)	1375.801 (1327.848, 1423.755)	379	50 ug	9 months
>=12 and <18 Years	pre-9month-booster-(d297)	213.219 (205.787, 220.651)	379	50 ug	9 months
>=12 and <18 Years	28day-post-9month-booster-(d326)	3065.347 (2958.504, 3172.19)	379	50 ug	9 months
>=18 and <25 Years	28day-post-1st-dose-(d29)	78.806 (64.335, 93.276)	58	50 ug	9 months
>=18 and <25 Years	28day-post-2nd-dose-(d57)	1227.692 (1002.259, 1453.125)	58	50 ug	9 months
>=18 and <25 Years	pre-9month-booster-(d297)	190.266 (155.328, 225.203)	58	50 ug	9 months
>=18 and <25 Years	28day-post-9month-booster-(d326)	2735.353 (2233.079, 3237.628)	58	50 ug	9 months

Table 2: Simulated GMFR (95% CI) across various booster dose and timing scenarios

Age Group	GMFR (95 % CI)	N	Booster Dose	Booster Dose Time after Second dose
>=18 and <65 Years	4.009 (3.793, 4.227)	1062	25 ug	3 months
>=65 Years	4.009 (3.707, 4.335)	461	25 ug	3 months
>=12 and <18 Years	4.009 (3.802, 4.217)	379	25 ug	3 months
>=18 and <25 Years	4.009 (3.214, 4.989)	58	25 ug	3 months
>=18 and <65 Years	8.75 (8.299, 9.226)	1062	25 ug	6 months
>=65 Years	8.75 (8.091, 9.462)	461	25 ug	6 months
>=12 and <18 Years	8.75 (8.299, 9.226)	379	25 ug	6 months
>=18 and <25 Years	8.75 (7.015, 10.889)	58	25 ug	6 months
>=18 and <65 Years	13.836 (13.122, 14.588)	1062	25 ug	9 months
>=65 Years	13.836 (12.823, 14.962)	461	25 ug	9 months
>=12 and <18 Years	13.836 (13.122, 14.588)	379	25 ug	9 months
>=18 and <25 Years	13.836 (11.117, 17.258)	58	25 ug	9 months
>=18 and <65 Years	4.159 (3.945, 4.385)	1062	50 ug	3 months
>=65 Years	4.159 (3.846, 4.498)	461	50 ug	3 months
>=12 and <18 Years	4.159 (3.945, 4.385)	379	50 ug	3 months
>=18 and <25 Years	4.159 (3.342, 5.188)	58	50 ug	3 months
>=18 and <65 Years	9.036 (8.57, 9.528)	1062	50 ug	6 months
>=65 Years	9.036 (8.375, 9.772)	461	50 ug	6 months
>=12 and <18 Years	9.036 (8.57, 9.528)	379	50 ug	6 months
>=18 and <25 Years	9.036 (7.261, 11.272)	58	50 ug	6 months
>=18 and <65 Years	14.388 (13.646, 15.171)	1062	50 ug	9 months
>=65 Years	14.388 (13.305, 15.56)	461	50 ug	9 months
>=12 and <18 Years	14.388 (13.646, 15.171)	379	50 ug	9 months
>=18 and <25 Years	14.388 (11.535, 17.906)	58	50 ug	9 months

IS/ID Model Assumptions

- **Initial conditions**
  - The assumption is that there is no immunological memory towards the vaccine or the virus. The model doesn't have any naïve B cells and introduction of the dose starts with increase in activated B cells. B cells are activated in presence of antigen; thus, the initial conditions are all set to 0 (activated B +SLPC cells, memory B cells, LLPCs, Antibody titers).
- **Activation Function**: $\delta = a \cdot \left(e^{\frac{-(t-b)^2}{2c^2}} + e^{\frac{-(t-(b+revac\_time))^2}{2c^2}} \right) - (1)$
  - a is a scalar that scales the shape of the activated B cell recruitment rate parameter, δ. An increase in a is expected to increase the magnitude of the Activated B cell population and therefore the response overall, a does not regulate the timings of the recruitment only the absolute number of activated B cells.
  - b is the Gaussian equation mean and affects the activated B cell recruitment time.
  - c is the variance in the Gaussian equation that describes the activated B cell recruitment rate parameter δ and acts on the overall magnitude of response. t is time, measured in days, and $revac\_time$ is revaccination time measured in days.
- **Activated B cells**
  - B cell activation rate, δ, is nonlinear. δ is initiated at time of primary and re-vaccination and is assumed to be the same at all vaccination points.
  - effect of mRNA dose is implemented on the rate at which B cells are activated (δ).
  - Affinity maturation is not included in the model to capture any germinal center dynamics. A fraction of activated B cells transitions to memory B cells and LLPCs at a rate.
- **Memory B cells**
  - The number of memory B cells that could be generated after vaccination was dependent on the vaccine dose and was limited to a maximum by controlling the proliferation rate of memory B cells.
  - Germinal center dynamics are not included exclusively in the model.
  - Differentiation of memory B cells towards long lived plasma cells in presence of previously exposed antigen (vaccine) is quicker compared to activated B cells on revaccination. Memory B cells can form plasma cells independent of germinal center. Activated B cells on the other hand need to go through the germinal center to form a round of memory B cells and LLPCs.
  - It is assumed that memory B cells will replicate only in the presence of antigen. Thus, the duration of replication is set to 5 days, representing the antigen lifetime. Furthermore, the mRNA half-life is known to be 2-3 days based on the current delivery platforms. So, 5 days was considered to be a reasonable duration.

- Death rate constant of memory B cell is based on literature.

- **Short lived Plasma Cells (SLPC)**
  - These are not modelled as a separate compartment. They are included in the activated B cell compartment. Transition rate to SLPCs is not included in the model and instead SLPC and activated B cell formation occur at the same time dependent on dose.
  - A fraction of the activated B cells converts into SLPCs to release antibody at a rate (used from literature for plasma cells).
  - As these are not modelled as a separate compartment, their life span is assumed to be same as activated B cells which are usually present if the antigen is present in the system.
- Long lived Plasma Cells (LLPC)
  - LLPCs have longer life than SLPC.
  - Antibody secretion rate is assumed to be same as that of LLPC.
  - The transition rate to LLPCs is allowed to at each re-vaccination.
- Antibody titer
  - Antibodies are generated by SLPCs (a fraction of the activated B cell subset) and LLPCs at a constant rate (literature based). The model doesn't assume different rates for each cell type currently.
  - The elimination rate constant of antibody titer is literature based.
  - Competition between secreted antibodies and any B cell subset is not included in this model.
- Antigen/Dose
  - Antigen in the system is introduced by the dose.
  - Interaction between the antigen and antibody during revaccination is not included in the model.

Assessment of the MAH's response

In response, the MAH provided the requested simulations, showing that indeed, no distinct selection of dose and timing of the booster dose could be made while comparing adolescents with adult subpopulations. Given that no regulatory decision is based on modelling and simulation, this is acceptable.

Conclusion

Issue solved and not further pursued in the context of this variation procedure.

Safety

Question 10

Considering that Spikevax is not licensed in the US for individuals below 18 years of age for primary vaccination, and in the EU not yet for booster vaccination the following observations are made:

- -The estimated 3rd dose exposure of more 3 million doses appears unexpectedly high and should be confirmed and discussed.
- -On the other hand, the number of reported cases with AE in this age group is very small (45) and in contradiction to the estimated exposure. This number needs to be confirmed and discussed.

The MAH is requested to describe in detail the methodology and data sources (countries/jurisdiction for use) that lead to the estimated exposure in the different age categories as well as estimates according to age and numbers of doses received. Based on this evaluation a comprehensive and comparative analysis (adolescents vs. young adults) and discussion of safety is expected.

Summary of the MAH's response

Moderna supply chain estimates are used to define the number of doses SPIKEVAX distributed by country; however, administration data are tracked by health officials within countries receiving the vaccine. Therefore, Moderna estimates administration of SPIKEVAX based on information retrieved through the US Centers for Disease Control and Prevention (https://covid.cdc.gov/covid-data-tracker/#vaccinations), the European Centres for Disease Control (https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccinetracker.html#distribution-tab), Health

Canada (https://health-infobase.canada.ca/covid-19/vaccination-coverage/), the Swiss Federal Office of Public Health (https://www.covid19.admin.ch/en/epidemiologic/vacc-doses), and Our World in Data (https://ourworldindata.org/covid-vaccinations).

Cumulatively, as of the end of 15 February 2022, a total of 965,468,760 doses of SPIKEVAX had been delivered to 82 countries, and an estimated total of 568,668,391 doses of SPIKEVAX had been administered. North America, Europe, and Asia accounted for >90% of SPIKEVAX doses distributed and >85% of SPIKEVAX doses administered (Table 1). A proportion of doses distributed have been subsequently donated via either bilateral agreements or collaborative efforts such as COVAX. Based on data shared by the CDC for the US, the MAH has estimated that approximately 15% of all Moderna doses distributed may be part of such agreements. As tracking data on the administration of doses donated after initial distribution is not available at this time, the MAH has conservatively assumed that only 25% of these doses have been administered globally.

Table 1. SPIKEVAX Doses Distributed and Administered through the End of the Review Period

	Doses Distributed		Doses Administered	
	N	%	N	%
Total	**965,468,760**	**100**	**568,668,391**	**100**
North America	422,417,300	43.8	219,084,959	38.5
United States	379,406,660	39.3	206,773,482	36.4
Europe	250,352,800	25.9	171,267,038	30.1
European Economic Area	218,541,300	22.6	146,673,243	25.8
Asia	212,327,120	22.0	101,925,546	17.9
Middle East	18,459,180	1.9	9,229,590	1.6
Latin America	20,532,480	2.1	10,266,240	1.8
Oceana	16,163,800	1.7	8,081,900	1.4
Africa	25,216,080	2.6	12,608,040	2.2
Governmental donations [1]	--	--	36,205,079	6.4

1: The safety summary report (Data Lock Point: 31 December 2021) had a systematic error that overestimated the governmental donation doses by approximately 93 million doses. The error was clerical in nature: all estimated bilateral donations (124,091,211 doses) were included as administered rather than the stated assumption of 25% of estimated bilateral donation (31,022,803 doses). Importantly, review of revised observed to expected analyses for the affected data did not materially change interpretation of safety assessment for any topic evaluated. Current estimates of new doses administered during this interval are based on the corrected December 2021 data.

Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 252,321,116 individuals received a first dose, 206,346,040 received a second dose, and 110,001,235 received a third dose. Age, gender, and age by gender stratified assessments of observed to expected rates are routinely performed as has been required by regulatory authorities. Our knowledge of demographics for administration data is limited to the information tracked and published by health officials within countries receiving the vaccine. Not all health authorities provide the same age strata when sharing this information, and none provide demographic data that are specific by brand and dose number. Since a large proportion of SPIKEVAX doses to date have been administered in the US, a correspondingly large proportion of reported events have been identified in the US. For adults, we therefore applied the US age distribution to the total administered doses of vaccine administered and corresponding person-time accrued. Because the Pfizer-BioNTech vaccine has been authorised for use in adolescents (12-17 years) in the US, it is expected that the large majority of COVID-19 vaccine doses seen in this age group are not Moderna's SPIKEVAX. To account for this, we limited the total assumed accrued exposure in individuals < 18 years to 3% of the total. The estimate of 3% was selected based on the assumption that adolescent use in the United States, where approximately half of global administrations have occurred and authorisation is limited to age ≥ 18 years, is substantially lower than

use in the European Economic Area, where adolescent use is authorised and approximately 6% of COVID-19 vaccinations across all brands have been administered to individuals < 18. Based on the distribution of adverse event reports of all types in safety database, is it estimated that 95% of doses in individuals <18 years of age have been administered to adolescents. Because no source has yet made available describing demographic characteristics of Moderna booster vaccine recipients from a major health authority, the MAH has for purposes of estimation applied the same age and sex distribution described for global vaccine recipients to each dose. Based on this assumption, it was estimated that approximately 0.6% of globally administered doses could have been given as a third dose (either booster or primary series in immunocompromised persons) in persons <18 years of age. Compared to the 0.6% doses estimated to apply to the subgroup of children and adolescents receiving a third dose, the distribution of spontaneous reports to this age by dose number subgroup is lower, at 0.02% of the total cases with known age and dose. Generally, reporting rates are substantially lower after the third dose than after the primary series, with only <7% of events identified through the most recent safety summary report identified as following dose 3. As such, it is expected that the number of dose 3 events would be lower than reported adverse events for other doses and disproportionate to administration. Even taking this most extreme scenario of dose 3 use in adolescents as only 0.02% of the total global administered doses, an estimate of approximately 120,000 doses compared to the original estimate of approximately 3 million, no emerging information concerning the safety profile of the vaccine emerges as only known reactogenicity symptoms are reported >1 case and only one serious event (PT of influenza) was identified.

Cumulatively, Moderna had received 17,511 cases for individuals of all ages after a third dose or booster dose of SPIKEVAX as of 31 December 2021. From those cases, there were 45 reports concerning individuals <18 years of age, as reported before. See table below.

Table 2 Distribution of Cases After a Third Dose or Booster Dose of SPIKEVAX by Age Group and Gender Cumulative as of 31 December 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
<2	12	0.07	4	0.02	1	0.01	17	0.10
02-11	0	0.00	6	0.03	0	0.00	6	0.03
12-15	6	0.03	1	0.01	0	0.00	7	0.04
16-17	9	0.05	5	0.03	1	0.01	15	0.09
18-29	969	5.53	355	2.03	37	0.21	1361	7.77
30-39	1686	9.63	536	3.06	50	0.29	2272	12.97
40-49	2050	11.71	709	4.05	78	0.45	2837	16.20
50-64	3484	19.90	1460	8.34	137	0.78	5081	29.02
65-74	1462	8.35	847	4.84	86	0.49	2395	13.68
75+	883	5.04	611	3.49	47	0.27	1541	8.80
Missing	1112	6.35	362	2.07	505	2.88	1979	11.30
Grand total	**11673**	**66.66**	**4896**	**27.96**	**942**	**5.38**	**17511**	**100.00**

Assessment of the MAH's response

The MAH response with regards to 3rd dose exposure reveals that the exposure number is rather based on assumptions than on reported information. Of note, this is due to the reporting system and the sources used by the company to estimate dose distribution and administration. Supply chain estimates are used to define the number of SPIKEVAX doses distributed by country, administration data are tracked by health officials within countries receiving the vaccine. Knowledge of demographics for administration data is limited to the information tracked and published by health officials within countries receiving the vaccine. Not all health authorities provide the same age strata when sharing this information, and none provide demographic data that are specific by brand and dose number. In fact, the previously reported 3rd dose exposure of 3 million doses is far too high, and has been corrected to 120,000 3rd doses administered to individuals below 18 years of age. It should be noted, that this exposure estimation is not restricted to adolescents but includes also individuals below 12 years of age). The difficulties due to the reporting methods are acknowledged, but it is not understood, why the MAH reports such different numbers. The described methodology and the two largely different numbers reveal the uncertainties related to the 3rd dose estimation and in consequence to the calculation of related incidence rates of AEs.

The case number of 45 cases in individuals below 18 years of age however was confirmed by the MAH, but is now as said related to approximately 120.000 3rd dose administrations. 42 AEs were due to medication error under the PT of "Product administered to patient of inappropriate age" and "Inappropriate schedule of product administration". The MAH was already within the procedure asked to submit information with regard to the nature and severity of the remaining 3 cases and events in children below 18 years of age including a causality assessment. The clinical information for the remaining 3 cases has been submitted by the MAH as requested and is described and discussed in the AR. Two of the cases represent expected reactogenicity events that are labelled for Spikevax. One of these 2 cases occurred after heterologous booster administration (Comirnaty primary vaccination without ARs, booster with Spikevax 3 month after primary vaccination). The third case describes a myasthenia gravis crisis in a 16-17 year old subject with known myasthenia gravis acquired after COVID-19. The time frames of COVID-19 and the vaccination with 3 doses of Spikevax is not provided. A causal relationship cannot be excluded. Within the responses the MAH describes one SAE of influenza, which cannot be traced. The last part of the question has not been addressed. The MAH did not provide a comprehensive and comparative analysis (adolescents vs. young adults) and discussion of safety.

Moreover, having the uncertainties with regard to the methodology of spontaneous reporting for the assessment of age and dose related safety evaluations in mind the submitted data from spontaneous reporting to the MAH is not considered adequate to support the extrapolation approach. To support the extrapolation approach on a larger safety database the MAH is asked to submit:

Information on the proportion of adolescents 12-<18 years of age and young adults 18-25 years of age enrolled in ongoing PASSs.

A comprehensive comparison of the reactogenicity and safety profile of adolescents versus young adults based on the data available in the PASSs in the 2 populations

A comprehensive comparison of the reactogenicity and safety profile post dose 2 versus post dose 3 in young adults based on available safety data from PASSs.

Conclusion

The issue is not solved.

To support the extrapolation approach on a larger safety database the MAH is asked to submit:

- Information on the proportion of adolescents 12-<18 years of age and young adults 18-25 years of age enrolled in ongoing PASSs.
- A comprehensive comparison of the reactogenicity and safety profile of adolescents versus young adults based on the data available in the PASSs in the 2 populations
- A comprehensive comparison of the reactogenicity and safety profile post dose 2 versus post dose 3 in young adults based on available safety data from PASSs.

Question 11

Reporting rates for myocarditis are given for a time frame of 7 days post dose. This is considered short and analyses of myocarditis cases should take an extended time frame of at least 30 days into account. The MAH is requested to present updated analyses.

Summary of the MAH's response

The MAH has used the 7 days post dose analysis based on all the evaluations conducted by health authorities, research organisations, as well as information from the MAH's safety database that have identified the 0-7 days as the greatest risk interval to experienced vaccine related myocarditis or pericarditis events. Analysis conducted by the Centers for Disease Control and Prevention (CDC) utilising the Vaccine Safety Datalink (VSD) as of 15 January 2022, showed an increased risk for myocarditis and pericarditis observed after both dose 1 and dose 2 of Spikevax in the 0–7-day risk interval, with a greater risk following dose 2 (ACIP 2022):

- Dose 2 adjusted rate ratio=18.75 vs. Dose 1 adjusted rate ratio=3.46
- Highest excess cases per million doses administered observed after dose 2
- 31.2 excess cases in 0–7-day risk interval per million doses administered in both males and females
- 61.8 excess cases in 0–7-day risk interval per million doses administered to males

Table 3 Confirmed Myocarditis and Pericarditis in the 0-7-Day Risk Interval Among Person Ages 18-39 Years Compared With Outcome Events in Vaccinated Comparators on the Same Calendar Days for Spikevax (Thru 15 Jan 2022)

Moderna COVID-19 vaccine	Events in risk interval, 0–7d* (per million doses)	Events in comparison interval, 22–42d*	Adjusted rate ratio† (95% CI)	2-sided P-value	Excess cases in risk interval (per million doses)
Both doses	38 (21.1)	7	9.18 (4.12 – 22.89)	<0.001	18.8
Dose 1	9 (9.7)	7	3.46 (1.12 – 11.07)	0.031	6.9
Dose 2	29 (33.0)	4	18.75 (6.73 – 64.94)	<0.001	31.2
Dose 2 males	26 (65.7)	4	16.96 (6.02 – 59.17)	<0.001	61.8
Dose 2 females	3 (6.2)	0	NE‡ (0.93 – ∞)	0.056	6.2

A population-based cohort studies in 4 Nordic countries (Denmark, Finland, Norway, and Sweden) using linked data from nationwide health registers on SARS-CoV-2 vaccination, myocarditis and pericarditis diagnoses, and other covariates, including 23.1 million residents aged 12 years or older also showed that rates of myocarditis and pericarditis were higher within 28 days after being vaccinated with SARS-CoV-2

mRNA vaccines compared with being unvaccinated, and that the risks of myocarditis and pericarditis were highest within the first 7 days of being vaccinated for all combinations of mRNA vaccines, and were more pronounced after the second dose (Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, Hansen JV, Nohynek H, Gunnes N, Sundström A, Wohlfahrt J, Nieminen TA, Grünewald M, Gulseth HL, Hviid A, Ljung R. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort. Study of 23 Million Residents. JAMA Cardiol. 2022 Apr 20. doi: 0.1001/jamacardio.2022.0583. Epub ahead of print. PMID: 35442390).

The MAH updated the analysis based on the methods previously requested by PRAC for Moderna's routine safety summary reports. In this analysis, person-time is estimated on the assumption of a 21-day risk window following each estimated dose administered, however all cases are included regardless of time to onset, producing a more highly sensitive estimate of the reporting rate, including data for cases beyond the 30-day window requested. Myocarditis (with or without pericarditis) was reported in 3,514 cases cumulatively (reporting rate 9.65 per 100,000 person-years) and in 497 as of 15 April 2022 (reporting rate 13.42 per 100,000 person-years).

Overall, this reporting rate was similar to population-based data estimates derived from individuals without a diagnosis of COVID-19, between March 2020 and January 2021, from the US Premier Healthcare Database (Boehmer 2021). As has been described previously, there is a marked increase in the reporting rate of myocarditis that is observed in young men. It should be noted that the reference source includes slightly different age categories than are available from some public health authorities when describing the demographic characteristics of vaccine recipients. In this source, age groups for younger individuals are described as <16 (4 cases per 100,000 person-years) and 16-24 (13 cases per 100,000 person-years). The higher reference rate is used to support observed vs. expected analyses in Table 4 because a large majority of adverse event reports (all terms, not limited to myocarditis) in the adolescent population occur in individuals ages 16-17 years of age. If instead the lower rate were to be selected, the observed vs. expected rate ratio would be comparable between adolescents and young adults (O/E in ages 12 – 17: 3.11, 95% CI 2.19 – 4.41). The reporting rate was comparable to population-based estimates from the US (Kang 2021: 10 per 100,000 person-years, 3,640 cases expected, rate ratio 0.97, 95% CI 0.92 – 1.01) when considering a 21-day risk window following vaccination. It should be noted that background estimates of the incidence of myocarditis vary widely, with some sources citing a range of 1-10 cases per 100,000 person-years (Gubernot 2021) and others citing a range of 10-20 per 100,000 person-years (Kang 2021).

Table 4 Observed/Expected Analyses Stratified by Age, Myocarditis, Expected Rate* from the United States, Cases per 100,000 Person-Years – Cumulative to 15 April 2022

	Person- years	Observed		Expected		As observed: RR (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
		Cases	Rate*	Cases	Rate*			
All	36,398,374	3,514	9.65	3276	9.00	1.07 (1.02, 1.12)	2.15 (2.06, 2.24)	4.29 (4.13, 4.46)
By age								
<12 years	54,598	0	0.00	2	4.00	NA	NA	NA
12-17 years	1,037,354	129	12.44	135	13.00	0.96 (0.75, 1.22)	1.91 (1.55, 2.36)	3.83 (3.17, 4.62)
18-24 years	3,057,463	964	31.53	397	13.00	2.43 (2.16, 2.73)	4.85 (4.35, 5.4)	9.7 (8.75, 10.76)
25-39 years	7,461,667	1,147	15.37	746	10.00	1.54 (1.4, 1.69)	3.07 (2.83, 3.34)	6.15 (5.69, 6.64)
40-49 years	5,277,764	370	7.01	528	10.00	0.7 (0.61, 0.8)	1.4 (1.25, 1.57)	2.8 (2.54, 3.1)
50-64 years	9,499,976	333	3.51	760	8.00	0.44 (0.39, 0.5)	0.88 (0.79, 0.97)	1.75 (1.6, 1.92)
65-74 years	5,932,935	143	2.41	475	8.00	0.3 (0.25, 0.36)	0.6 (0.52, 0.7)	1.21 (1.07, 1.36)
75+ years	4,076,618	55	1.35	285	7.00	0.19 (0.14, 0.26)	0.39 (0.31, 0.48)	0.77 (0.65, 0.92)
By gender								
Male	17,021,239	2,624	15.42	2043	12.00	1.28 (1.21, 1.36)	2.57 (2.44, 2.7)	5.14 (4.9, 5.39)
Female	19,377,136	831	4.29	1163	6.00	0.71 (0.65, 0.78)	1.43 (1.33, 1.54)	2.86 (2.67, 3.06)
By age and gender								
Male								
<12 years	25,532	0	0.00	1	5.33	NA	NA	NA
12-17 years	485,105	118	24.32	84	17.33	1.4 (1.06, 1.86)	2.81 (2.19, 3.6)	5.61 (4.45, 7.08)
18-24 years	1,429,784	841	58.82	248	17.33	3.39 (2.95, 3.91)	6.79 (5.94, 7.76)	13.57 (11.93, 15.44)
25-39 years	3,489,354	896	25.68	465	13.33	1.93 (1.72, 2.15)	3.85 (3.48, 4.27)	7.7 (6.99, 8.48)
40-49 years	2,468,080	229	9.28	329	13.33	0.7 (0.59, 0.82)	1.39 (1.21, 1.6)	2.78 (2.45, 3.16)
50-64 years	4,442,543	188	4.23	474	10.67	0.4 (0.34, 0.47)	0.79 (0.69, 0.91)	1.59 (1.41, 1.78)
65-74 years	2,774,462	72	2.60	296	10.67	0.24 (0.19, 0.31)	0.49 (0.4, 0.59)	0.97 (0.83, 1.14)
75+ years	1,906,379	25	1.31	178	9.33	0.14 (0.09, 0.21)	0.28 (0.21, 0.38)	0.56 (0.44, 0.72)
Female								
<12 years	29,066	0	0.00	1	2.67	NA	NA	NA
12-17 years	552,248	11	1.99	48	8.67	0.23 (0.12, 0.44)	0.46 (0.28, 0.76)	0.92 (0.61, 1.38)
18-24 years	1,627,679	122	7.50	141	8.67	0.86 (0.68, 1.1)	1.73 (1.41, 2.13)	3.46 (2.87, 4.17)
25-39 years	3,972,313	243	6.12	265	6.67	0.92 (0.77, 1.09)	1.84 (1.58, 2.13)	3.67 (3.2, 4.2)
40-49 years	2,809,685	139	4.95	187	6.67	0.74 (0.6, 0.92)	1.48 (1.23, 1.79)	2.97 (2.52, 3.5)
50-64 years	5,057,432	140	2.77	270	5.33	0.52 (0.42, 0.64)	1.04 (0.88, 1.23)	2.08 (1.8, 2.4)
65-74 years	3,158,473	71	2.25	168	5.33	0.42 (0.32, 0.56)	0.84 (0.67, 1.05)	1.69 (1.39, 2.04)
75+ years	2,170,239	30	1.38	101	4.67	0.3 (0.2, 0.45)	0.59 (0.43, 0.82)	1.18 (0.91, 1.54)

*Rates presented per 100,000 person-years with calculation of person-time based on a 21-day risk window. All reported cases were included regardless of time to onset. Boehmer 2021. Because age by sex stratified estimates of the reference rate were not available in the source material, estimates are obtained by multiplying the age specific rate estimate by the ratio of the sex-specific stratum-specific rate to the overall rate.

Assessment of the MAH's response

Myocarditis and pericarditis have been observed in younger men more often following the second vaccination of the primary series. Uncertainties are related to the number of cases with myocarditis with or without pericarditis following the 3rd booster in adolescents because the exposure number is based rather on assumptions. However, the MAH this time has provided an extended time period of a 21-day risk window, with a more highly sensitive estimate of the reporting rate, including data for cases beyond the 30-day. The analysis has been updated based on the methods previously requested by PRAC, including cases per 100 000 per person-year- cumulative to 15 April 2022. The higher reference rate has been used to support observed vs. expected analyses in Table 4 and the majority of adverse event reports (not only limited to myocarditis) in the adolescent population occur in individuals ages 16-17 years of age. If the lower estimate were to be selected, the observed vs. expected rate ratio would be comparable between adolescents and young adults (O/E in ages 12 – 17: 3.11, 95% CI 2.19 – 4.41). The rate O/E in the males of age group 12-17 was 24.32/17.33 in contrary with the rate in females with O/E 1.99/ 8.67.

Conclusion

Issue solved.

Question 12

IRRs from age and sex standardised comparison of post vaccination and historical incidence of AESIs (Table 24 in the clinical overview) cannot be interpreted without information on the underlying methodology of this analysis and the event numbers of each AESI. The MAH is asked to describe the methodology of the analysis and discuss the findings, particularly for the AESI with IRRs over 2.

Summary of the MAH's response

A full discussion of the study methodology and applicable underlying event rates is provided in Interim Report 4 of the US Post-Authorisation Safety Study (mRNA-1273-P903) submitted on 31 January 2022. To summarise methods of this study, this retrospective observational cohort study uses secondary, de-identified individual-level medical and pharmacy claims data provided by HealthVerity. This data source includes open and closed claims for patients insured under commercial, Medicare or Medicaid plans, and/or served by providers participating in several large US medical and pharmacy insurance claims submission systems. The currently presented analyses include individuals meeting the following study entry criteria. Cohorts were defined separately for adults (≥18 years of age) and children/adolescents (<18 years of age) during each time period, overall and by subpopulation of interest (influenza vaccinated individuals in the pre-COVID era and immunocompromised individuals within each time period). To estimate incidence rate ratios for AESI, the following cohorts were formed:

Pre-COVID and COVID era Historical Cohorts:

• Included in a health plan covered by HealthVerity database with capture of closed administrative healthcare claims

• Covered by a health plan during the pre-COVID or COVID eras

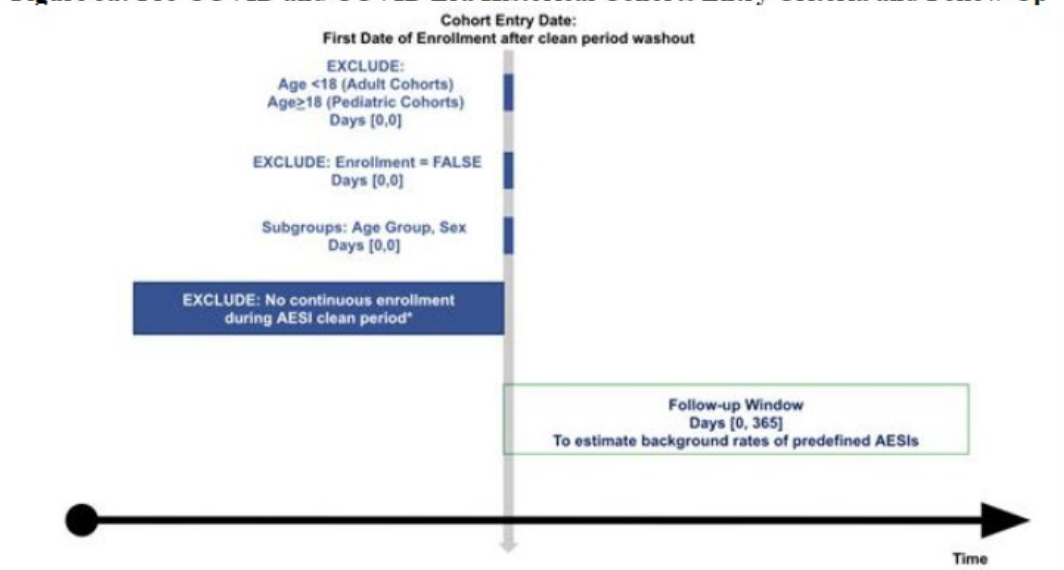
• For analysis of each outcome, data includes a clean period (variable by AESI) of continuous baseline enrolment or activity before the period of interest during which the patient is covered by continuous health plan eligibility

• Aged 18 years old or above at cohort entry date for the adult-specific cohorts, and under 18 years of age at cohort entry date for the paediatric-specific cohorts

• Non missing and non-conflicting values of gender at cohort entry date

Qualifying individuals within the historical cohorts were then followed from the end of the clean period (for most outcomes, 365 days used to establish baseline characteristics and identify prevalent AESI diagnoses) through the end of the time period (i.e., 30 Nov 2019 for the pre-COVID era and 10 December 2020 for the COVID era), the end of continuous health plan enrolment, or the first occurrence of the AESI considered in a given analysis. Similarly, the same study entry criteria were utilised to identify immunocompromised adult and adolescent populations within the pre-COVID and COVID era, where we required evidence of immunocompromised status on the cohort entry date. A summary of cohort selection is shown in Figure 5a.

Figure 5a: Pre-COVID and COVID Era Historical Cohorts Entry Criteria and Follow-Up



Post-EUA Spikevax-Vaccinated Cohorts

• Included the HealthVerity database with capture of open or closed administrative healthcare claims

• At least one dose of Spikevax vaccine

• For analysis of each outcome, data includes a clean period (variable by AESI) of continuous baseline enrolment or open claim activity before vaccination

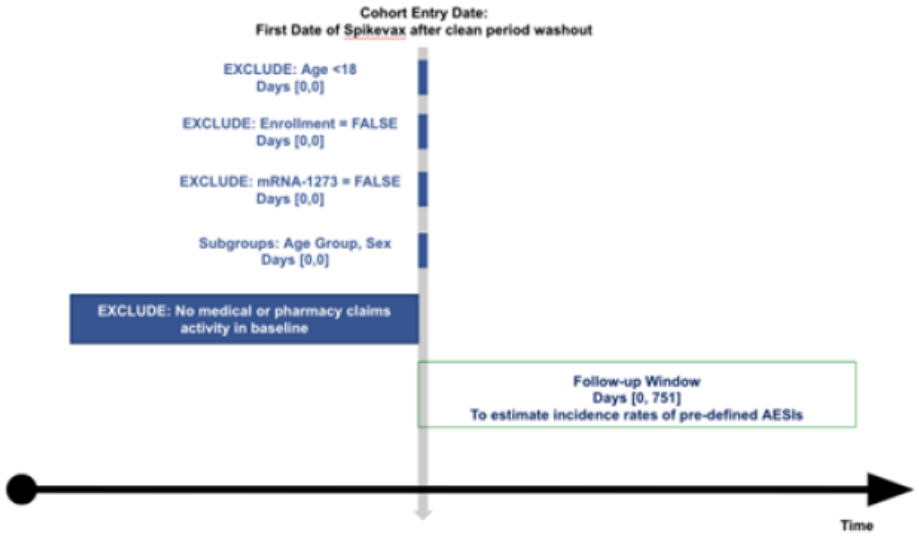
• Aged 18 years old or above at cohort entry date for the adult-specific cohorts, and under 18 years of age at cohort entry date for the paediatric-specific cohorts

• Non missing or conflicting values of gender at cohort entry date

Qualifying patients in the post-EUA cohorts were then followed from the date of the first vaccine dose administration through the end of data availability (24 November 2021), the end of HealthVerity data capture (defined as the end of continuous health plan enrolment for closed claims or >60 days after the last healthcare encounter for those with open claims), receipt of a non-Spikevax COVID-19 vaccine, or the first occurrence of the AESI considered in a given analysis. A summary of cohort selection is shown in Figure 6. The subpopulation of Spikevax-vaccinated immunocompromised individuals used the same selection criteria and follow-up and were identified as having evidence of immunocompromised status on the day of their Spikevax vaccination.

For analyses of a second dose of Spikevax, patients with evidence of a second dose at least 7 days after the first dose were identified within each AESI-specific cohort. Additionally, patients were required to not have the AESI of interest between the first and second dose. Individuals' index date was set on the second dose of Spikevax for these analyses.

Figure 6: Post -vaccination Vaccinated Cohort Entry Criteria and Follow-Up



For these cohorts, incidence rates were calculated as the number of patients with an event divided by the sum of person-time at risk, where person-time was the total days from the index date through the date of the first instance of the applicable AESI or the end of observation (i.e., earliest of end of health plan enrolment, end of study period, or end of data). Incidence rates are presented per 100,000 person-years and are shown with an associated 95% confidence interval (CI) overall and for each age, sex, and age-by-sex specific stratum. Standardisation to the age and sex distribution of the 2019 US population was also performed for males and females. In the preliminary screening objective for which results were presented, the incidence rate ratio (IRR) with 95% CI was calculated to estimate the relative change in IRs in the post-EUA Spikevax vaccination cohort compared to the Pre-COVID and COVID era cohorts. IRRs were calculated overall and stratified by age, sex, and age by sex.

Additional analyses are ongoing, noting that an Interim Report will be delivered for this study 30 April 2022, which includes new analyses of these outcomes in the paediatric sub-population including self-controlled risk interval assessments that more fully characterise these outcomes in the paediatric population where numbers support meaningful analyses.

Summary of the MAH's response

The MAH provided a summary of the study methodology as requested. A full description of the study methodology and applicable underlying event rates has been provided in Interim Report 4 of the US Post-Authorisation Safety Study (mRNA-1273-P903) submitted on 31 January 2022. The IR 4 of mRNA-1273-P903 has been assessed and discussed within PRAC procedure EMEA/H/C/005791/MEA/003.5.

The results of the ESI assessment in this study were summarised by the MAH as follows:
as follows:

Paediatric Population

In addition to myocarditis and pericarditis, results of the study suggested elevated crude and standardised IRR in one or more strata among paediatric vaccinated patients for acute kidney injury, anaphylaxis, anosmia, arrhythmia, Bell's palsy, deep vein thrombosis, and erythema multiforme. With respect to acute kidney injury, the standardised incidence rate ratio was elevated for the post-vaccination age <12 stratum of the paediatric cohort when compared to the COVID-era. Among all paediatric patients, the observed vs expected analysis, utilising a 28-day risk window following the first dose of mRNA-127, did not demonstrate an elevated O/E ratio. However, based on an observed count of

6 cases, O/E ratios were elevated for <12 age stratum when compared to the pre-COVID and COVID eras. The results of this observed vs expected analysis among paediatric patients meets the pre- specified criteria for a SCRI analysis. A protocol annex will be submitted to the US Food and Drug Administration, and results will be included in Interim Report #5.

O/E analyses of arrhythmia, Bell's palsy, deep vein thrombosis, and erythema multiforme did not demonstrate a greater than expected number of events compared to expectation and thus did not move forward to a self-controlled analysis. These and other AESI will continue to be monitored in subsequent reports. All other outcomes did not show a meaningfully increased rate following receipt of mRNA-1273.

Limitations

In this study, administrative claims are used to identify diagnoses relevant to vaccine safety monitoring, however, estimated incidence in these settings may vary substantially based on the algorithm used. Algorithms that are overly sensitive may identify "rule out" or other tentative diagnoses, and this can inflate the apparent rate. Algorithms must therefore balance the competing objectives of sensitivity and specificity based on the objectives of a given study.

Administrative claims collect data based on healthcare encounters, creating a longitudinal view of the patient on the basis of codes used primarily for billing. As such, conditions that do not affect reimbursement or come to medical attention can be missing. This type of data source also necessarily conflates absence of evidence with evidence of absence, which can be a source of bias. In our analysis, slightly lower rates of several comorbidities were observed following vaccination compared to the historical time frame regardless of an older age distribution. This may have multiple explanations. It is possible that individuals with substantial comorbidity were more likely to be vaccinated quickly in the campaign, which may have more often included mass vaccination centres not captured in integrated healthcare delivery systems or healthcare claims environments including HealthVerity. Alternatively, care seeking behaviour during the baseline timeframe for this population could be reduced by the pandemic, producing less opportunity to capture baseline health status via medical encounters for individuals vaccinated early on in the post-vaccination time period in the former situation, a concern may arise for generalisability. In the latter, control of confounding by adjustment may become questionable. Finally, this might be due to the healthy vaccinee effect. This would be addressed in SCRI analyses used to evaluate signals, however, given that this design efficiently manages time- invariant confounding.

Specific to the paediatric population, it is noteworthy that due to patient privacy, the HealthVerity data is limited to reporting year of birth to indicate an individual's age. Thus, there is the potential for misclassification of individuals age 18 years at the time of vaccination in the paediatric cohort. Further, the vaccine is not authorised for use in the paediatric population in the United States. As such, it is possible that some proportion of these cases could be miscoded exposures to products authorised in this age group. Conversely, if exposure coding is in fact accurate, it is possible that this could reflect use where the treating clinician saw an elevated risk of severe COVID-19 due to underlying health conditions.

Interpretation

Interim estimates of incidence for AESI relevant to vaccine safety monitoring show substantial variation in estimated incidence rates by outcome, age, and gender. This was expected based on known epidemiology and published sources and underscores the importance of subgroup analyses as planned in our ongoing assessments. SCRI analyses demonstrate an increased rate of myocarditis and pericarditis most pronounced in young men after dose 2 which is consistent with findings from surveillance and other published Real-World Evidence studies. SCRI analyses to refine results for anaphylaxis, acute kidney

injury (among paediatric patients), anosmia/ageusia and Chilblain-like lesions will also be conducted and included in interim report #5.

Generalisability

Because these rates are assessed in US patients, the rates observed may be less generalisable to other countries or subpopulations where there are meaningful differences in the underlying risk of the AESI considered. Patient and population-based characteristics should be considered prior to use of these background rates. Further, as described in Section 11.5, it is possible that vaccinated individuals captured in HealthVerity data may differ from other US vaccine recipients, particularly those who accessed mass vaccination sites or employer-sponsored vaccination sites. Likewise, vaccinated individuals captured in US claims may differ from vaccine recipients in other countries, especially where vaccination practice, indicated populations, and characteristics of the vaccine roll out have varied. A mechanism that would produce the expectation that these differences should change the relationship between vaccination and outcomes of interest is not presently clear, reducing the expected impact to interpretation. Lastly, it is notable that currently the mRNA-1273 is not authorised for emergency use among individuals <18 years in the United States. Thus, capture of vaccinated paediatric patients may represent a patient population with a different risk profile than the general paediatric population, and may include paediatric patients at higher risk for severe COVID-19, including those who are immunocompromised.

PRAC discussion

The MAH discussion has been acknowledged by PRAC with the following additional remarks:

Most points have been addressed in previous procedures related to this PAM. In addition, the limitations and the generalisability of the data regarding the paediatric population were discussed:

- Due to patient privacy, the HealthVerity data is limited to reporting year of birth. Therefore, there is a potential to misclassify individuals who are 18 years of age at the time of vaccination in the paediatric cohort. This is in line with the fact that 63% of the paediatric cohort was 17 years old, potentially reflecting the reporting limitation in HealthVerity.
- Spikevax is not authorised for use in <18-year-olds. Therefore, for a proportion of paediatric individuals Spikevax exposure could have been miscoded to authorised products. Alternatively, clinicians may have recommended off-label use due to an elevated risk of severe COVID-19 due to underlying health conditions. This would impact risk estimates if the underlying conditions are associated with the outcomes of interest. Moreover, this paediatric population is unlikely representative of the general US paediatric population.

Conclusion

AESIs will continuously be followed by PRAC. The increased incidence rate ratios of AEs between vaccinated and unvaccinated <18-year-olds in this study are based on very few events, limiting the interpretation. A more robust observed/expected (O/E) analysis which considers relevant risk windows of the AESI is performed for any AESI with an IRR of ≥2 (if based on more than 5 events). This was done for Acute Kidney Injury where the O/E was not elevated for all <18-year-olds. It should however be noted, that it was elevated for <12-year-olds (based on 6 events). This potential signal will be evaluated via Self-controlled risk interval (SCRI) analysis with the next interim report. PRAC does not see any immediate safety concern based on the data in <18-year-olds from this US PASS.

CHMP Rapp and PRAC were in communication concerning the elevated AESI IRRs in the paediatric population in study mRNA-1273-P903.

Conclusion

The issue is solved.

OVERALL CONCLUSION AFTER ASSESSMENT OF RESPONSES

Not all issues are solved. The MAH is asked to submit responses to the below listed outstanding RSIs before the adolescent booster can be approved.

8. 2nd request for supplementary information

8.1. Other concerns

Safety

1. To support the extrapolation approach on a larger safety database the MAH is asked to submit:

    a) information on the proportion of adolescents 12-<18 years of age and young adults 18-25 years of age enrolled in ongoing PASSs.
    b) a comprehensive comparison of the reactogenicity and safety profile of adolescents versus young adults based on the data available in the PASSs in the 2 populations
    c) a comprehensive comparison of the reactogenicity and safety profile post dose 2 versus post dose 3 in young adults based on available safety data from PASSs.

Immunogenicity

2. Regarding the dosing interval of 3 months for the 3rd booster dose after initial vaccination in the adolescent age group (≤12 – 18 years) the MAH is asked to submit and discuss:

    a) all available immunogenicity data comparing the decline of antibodies in adolescents and young adults 18-25 years of age beyond of the data from study P203
    b) all available data on the duration of protection in the 2 age cohorts
    c) as far as available: clinical post authorisation immunogenicity data (including published literature) beyond study NIH/DMID 21-0012 that could further support the booster interval for adolescents

Commitment

3. 3) The MAH is requested to submit the interim and the final clinical study report on results from study P203 Part C as soon as it becomes available. The interim CSR is expected Q3.

9. Assessment of the responses to the 2nd request for supplementary information

9.1. Other concerns

Safety

1) To support the extrapolation approach on a larger safety database the MAH is asked to submit:

a) Information on the proportion of adolescents 12-<18 years of age and young adults 18-25 years of age enrolled in ongoing PASSs.

Summary of the MAH's response

The MAH has two ongoing PASS that include children and adolescents using Spikevax in routine clinical practice, namely mRNA-1273-P903 in the US, and mRNA-1273-P904 in Denmark, Norway, Italy, Spain, and the United Kingdom.

In study mRNA-1273-P903 in the US where Spikevax has been approved in adults only, the study population described in Interim Report #5 (30 April 2022) includes data captured through November 2022 and includes 18,161,726 adults and 101,083 children/adolescents <18 years of age (off-label) exposed to Spikevax. Data on dose 3 were not available in the interim report but will be described in Interim Report #6 (scheduled on 31 July 2022). Considering updated Health Verity data through 02 February 2022, the study has identified 2,760,791 vaccinated individuals ages 18-29 years and 233,618 third dose recipients in this age range. Of the 79,670 presumably off-label vaccine recipients ages 12-17 identified, 2,152 received a third dose. As of the latest data cut received from Health Verity, there have not been any cases of myocarditis following a third dose identified in adolescents in the study, noting that full analyses of AESI following a third dose of Spikevax are anticipated in the 31 July 2022 interim report. To date, no outcome that has completed the signal evaluation phase analyses has shown a statistically increased risk specific to adolescents, noting that sample size is small and use off-label.

In Study mRNA-1273-P904, Interim Report 2 included descriptive analyses and preliminary analyses from Italy (data through July 2021) and the United Kingdom (data through December 2021); Spikevax is authorised in both countries for use in adolescents 12 to 17 years old. In Italy, there were 21,599 individuals ages 12-17 with at least one dose of Spikevax (6.2% of all Spikevax recipients in the study cohort), however the last date of data availability was prior to availability of booster doses. In the United Kingdom, there were 1,699 children and adolescents included in the study cohort (0.8% of total). No adolescents receiving a third dose were observed, however only 1% of all vaccinees in the study population for any age received a third dose. This study considers all AESI and has not to date identified differences in the safety profile between adolescents and young adults. Interim Report # 3 will be submitted on 30 September 2022.

An updated report from the US PASS study describing safety data from young adults boosted with mRNA-1273 is included in this submission.

Assessment of the MAH's response

The MAH has provided an update on the use of Spikevax in adolescents and young adults. Further, reference is made to upcoming interim reports from studies P903 and P904 that will provide additional info. The MAH mentioned an updated report which is missing in the present submission. However, overall the response is considered appropriate for the time being. The upcoming reports shall be submitted immediately upon availability.

Conclusion

Issue solved.

b) A comprehensive comparison of the reactogenicity and safety profile of adolescents versus young adults based on the data available in the PASSs in the 2 populations

Summary of the MAH's response

Reactogenicity post-booster (50 µg booster) dose has been observed to be less than post-dose 2 (100 µg dose) in the MAH's clinical trials in adults (Study 201B and Study 301). This has been confirmed in the V-Safe system health check-in survey monitoring conducted by the US CDC, in all adults (Hause, et al., 2022), as well as in the post-authorisation safety data collected in the MAH global safety database. The MAH would like to further clarify that no additional PASS data is available beyond what has been previously provided during review, and further that reactogenicity is not captured in post-authorisation studies. Please refer to Section 2.5.6 Overview of Safety (m2.5 Clinical Overview) for a detailed analysis of (i) reactogenicity and safety profile of a 100 ug primary series in adolescents & young adults from clinical studies and post-authorisation (Section 2.5.6.1.1); (ii) summary of reactogenicity and safety profile of a 50 µg booster dose (see also, Booster series submission PM-2021-05131-1-2).

There are two ongoing PASS that include children and adolescents using Spikevax in routine clinical practice. Both studies include vaccine recipients of all ages and are designed to characterise risk of adverse events of special interest to support enhanced understanding of the safety profile of Spikevax. Because both studies are conducted using routinely collected administrative healthcare data, they are poorly suited to characterisation of reactogenicity. The majority of reactogenicity events are expected to be managed at home, and they are considered expected and are often transient in duration. These events are not well captured in administrative databases, given that the inclusion of diagnosis codes used in case ascertainment is driven by reimbursement of healthcare encounters. As such, reactogenicity outcomes have not been included in the study protocols previously discussed and approved by the EMA and US FDA. As stated in response to item #1, preliminary analyses are limited due to exclusively off-label use in the United States and longer data lags in the European study.

Assessment of the MAH's response

The MAH clarifies that no data in addition to the already submitted are available on the reactogenicity and safety in the mentioned population groups. At the present point in time the available data do not provide any evidence of enhanced reactogenicity/adverse events after the booster dose. Therefore, the answer given by the MAH can be accepted for the time being; however, the MAH is requested to include any data becoming available on the reactogenicity/safety in adolescents and young adults as well their analysis in the upcoming interim reports (see 1a).

Conclusion

Issue solved with the commitment from the MAH to present additional analyses of the outcomes of ongoing safety-related studies in the next full Interim Report.

c) A comprehensive comparison of the reactogenicity and safety profile post dose 2 versus post dose 3 in young adults based on available safety data from PASSs.

Summary of the MAH's response

Data concerning the dose specific safety profile for SPIKEVAX are currently available based on the US Post Authorisation Safety Study (PASS), study mRNA-1273-P903. Due to the data lags of participating sites for the European PASS (mRNA-1273-P904), no information concerning the safety of dose 3 has yet been identified in that setting. Both studies consider myocarditis, pericarditis, and other AESI relevant to vaccine safety monitoring, however there is no assessment of reactogenicity. This is due to the fact that these outcomes are not typically well captured in the administrative data sources used by the projects.

Interim Report 5 of study mRNA-1273-P903 was submitted on 27th April 2022, and contained data through 24th November 2021. Given this data lag, dose 3 analyses had not yet been conducted. In support of the query in Item 3, the MAH has expedited selected analyses planned for Interim Report 6 to assess the differences in the safety profile of dose 2 and dose 3. Specifically, analyses were conducted comparing historical incidence rates and post-vaccination incidence rates for non-pregnancy related adverse events of special interest (AESI) after dose 2 and dose 3 in young adults (18-25 years). A full study report including the final version of these and other analyses for study mRNA-1273-P903 will be submitted in Interim Report 6 on 31 July 2022.

Within young adults 18 to 29 years of age, there were 1,828,649 individuals who received a second and 244,334 individuals who received a third dose of SPIKEVAX, respectively. Considering the overall incidence rate ratios of AESI after SPIKEVAX versus incidence in the pre-COVID era, results for dose 2 and dose 3 analyses were comparable for most outcomes. Based on Health Verity data in young adults 18-29 years of age, the crude incidence rate ratio was ≥ 2 for myocarditis and anosmia after dose 2 and dose 3 of SPIKEVAX. Skin reactions may be increased, with Chilblain like lesions and erythema multiforme meeting this threshold after dose 3 but not after dose 2. Given that the dose 3 cohort included only 244,334 individuals in the age group of interest, estimates of incidence for very rare AESI are in some cases imprecise.

Per protocol, observed to expected analyses considering the etiologically relevant time period after vaccination were conducted for myocarditis, pericarditis, and other AESIs with a crude incidence rate ratio ≥ 2 with at least 5 cases observed. The expected background rates presented here were estimated using

Table 2: Observed to expected analyses for adverse events for special interest among adults 18-29 years of age

Outcome	Dose 2 (N = 1,828,649)		Dose 3 (N = 244,334)	
	Cases	O/E ratio (95% CI)	Cases	O/E ratio (95% CI)
Myocarditis	35	16.04 (11.17 - 22.31)	3	9.85 (2.03 – 28.80)
Males	29	21.38 (14.32 - 30.70)	3	17.11 (3.53 – 50.0)
Females	6	7.27 (2.67 - 15.82)	0	0.00 (0.0 – 28.58)
Pericarditis	16	2.34 (1.34 – 3.80)	3	4.21 (0.87 – 12.29)
Males	20	7.12 (4.35 - 11.00)	1	2.75 (0.07 – 15.35)
Females	4	1.79 (0.49 - 4.57)	2	5.71 (0.69 – 20.62)
Chilblain Like Lesions	6	3.83 (2.45 – 5.69)	3	4.29 (0.88 – 12.53)
Anosmia	179	8.11 (6.96 – 9.39)	31	9.57 (6.50 – 13.58)
Erythema Multiforme	Not applicable (did not meet the threshold for observed to expected analyses)		6	3.95 (1.45 – 8.60)

the pre-COVID era cohort. For these analyses, myocarditis and pericarditis were assessed using a 7-day risk window. Chilblain-like lesions, anosmia, and erythema multiforme considered a 28-day risk window. Across these outcomes, the safety profile of dose 3 and dose 2 appears to be similar, with results for dose 2 and dose 3 more similar for chilblain-like lesions in the 28-day risk interval (Table 2 below) than in all person-time after vaccination. A possible exception is erythema multiforme, which is currently undergoing further evaluation in advance of Interim Report 6. There appears to be a small reduction in the risk of myocarditis observed, however estimates are very imprecise. Additional analyses of these outcomes will be presented in the next full Interim Report.

Assessment of the MAH's response

The MAH has conducted analyses to identify risk ratios in younger adults (18-29 years of age) of selected adverse events after vaccination in comparison to the pre-COVID era. The initial results indicated potential higher risk after the third dose for Myocarditis, Pericarditis, Chilblain like Lesions and Erythema Multiforme. Therefore, these AE (plus Anosmia) were further investigated by an observed vs expected analysis. Except for Erythema Multiforme, which will be further monitored, no increased risk rate after the third dose could be detected. The MAH commits to include additional analyses of adverse events in the next full interim report.

Conclusion

Issue solved with the commitment from the MAH to present additional analyses of the outcomes of ongoing safety-related studies in the next full Interim Report.

Immunogenicity

2) Regarding the dosing interval of 3 months for the 3rd booster dose after initial vaccination in the adolescent age group (≤12 – 18 years) the MAH is asked to submit and discuss:

a) all available immunogenicity data comparing the decline of antibodies in adolescents and young adults 18-25 years of age beyond of the data from study P203

b) all available data on the duration of protection in the 2 age cohorts

c) as far as available: clinical post authorisation immunogenicity data (including published literature) beyond study NIH/DMID 21-0012 that could further support the booster interval for adolescents

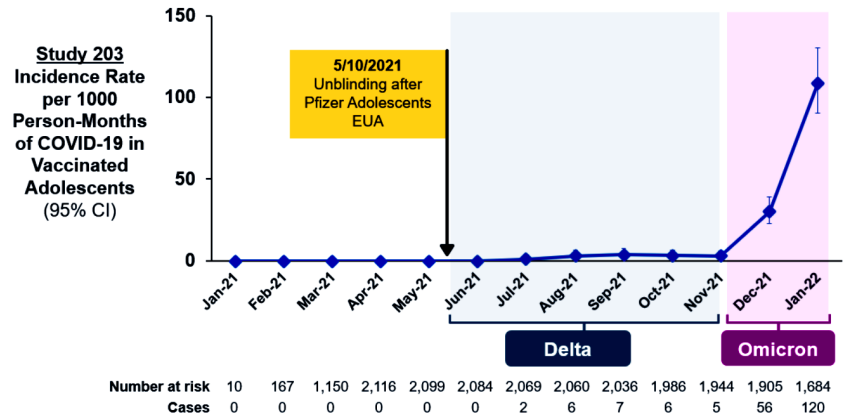
Summary of the MAH's response

Reference is made to the MAH's response to EMA Clinical Questions Q2 (28 Apr22 to EMEA/H/C/005791/II/57 Response to RSI) stating that the shortened booster interval of 3 months was requested to provide regulatory agencies the flexibility to best comply with local dosing interval recommendations, the current surge in cases linked to the emergence of VOC, the potential for emergence of other VOCs. The currently approved interval for Spikevax booster administration to adults (≥ 18 year) by EMA is 3m (intervals from 3-6m are approved/recommended globally). Based on demonstrated immunobridging of the primary series of mRNA-1273 between adolescents and young adults (in study P203), extrapolation from adult booster recipients to adolescents is applied here. Accordingly, if the agency deems appropriate an interval of 6m based on the clinical trial data collected in P301, P201 Part B, P203 Part C can be considered for adolescent boosters in EU. Recent data from

adolescent study P203 regarding the monthly incidence rates (graphed per person months) allows examination of the influence of emerging variants on duration of protection (Figure below).

Incidence of COVID-19 Cases Increased During Delta & Omicron

Study 203: Adolescents (12-17 Years), Per Protocol Set, Study 301 Case Definition, Starting 14 Days After Dose 2

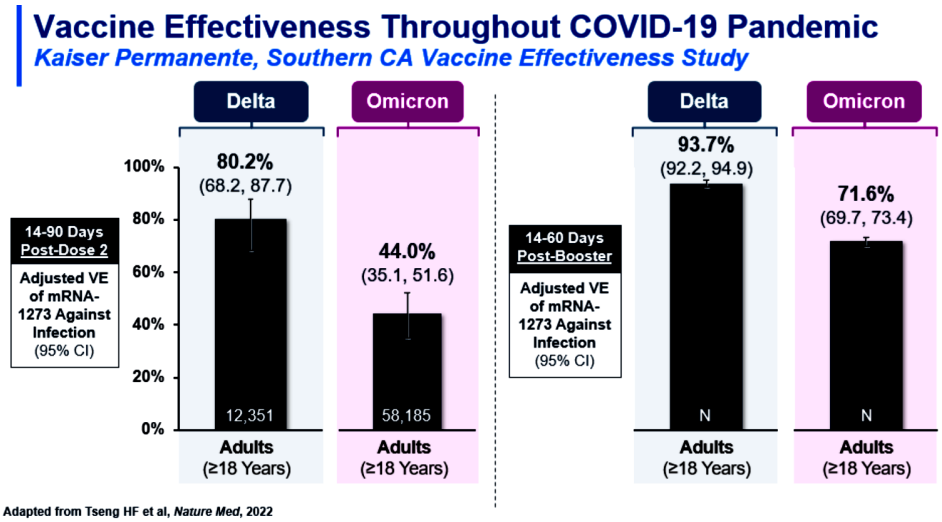


This figure provides long-term assessment of monthly incidence rates among all mRNA-1273 adolescent recipients remaining on study as of the 31 Jan 2022 data cut. Although no placebo control group is available (as the study had been unblinded and placebo participants had sought vaccination), results shows low monthly incidence rates of COVID-19 among participants until November 2021. Even during the US Delta surge (July to September 2021), incidence rates among vaccinated study participants (adolescents) generally remained stable. Not unexpectedly, an increase in COVID 19 incidence was observed in the months of December 2021 and January 2022 (9 to 12 months after dose 2), when the Omicron variant prevailed. These findings are consistent with real-world increases in COVID-19 incidence during the US Omicron surge (December to January). This surge occurred 9 to 12 months after receipt of Dose 2 of mRNA-1273 in those who were initially randomised to mRNA-1273. The rise in incidence among study participants coincided with the prevalence of the Omicron variant with its more divergent sequence and potentially with concurrent waning immunity after Dose 2.

Although long-term (>6m post-dose 2) adolescent primary series antibody data is not available, Moderna has been tracking the persistence and durability of the immune response against the ancestral strain as well as variants in adult clinical trials where booster doses are being investigated. Administration of the mRNA-1273 booster leads to increase in neutralising antibody titers against the ancestral strain, Beta variant and Delta variant. Immunogenicity data against the Omicron variant (N=20) over time demonstrates detectable nAb ID50 titers at 1 month post-dose 2, which wanes over 6 months to a value which is at the limit of detection.

As described in the m2.5 Clinical overview (section 2.5.5.1.2), a 50 µg boost in Study P201 Part B resulted in a 15.06 GMFR between pre-booster and post-booster titers, against the prototype strain. The 50 µg boost also resulted in marked higher titers compared with the Day 28 post-primary series (post-dose 2) titer in Study P301, in which efficacy was established. This booster also induced ID50 GMTs against the Omicron variant that were 20 fold higher than those assessed 1 month after the second vaccination.

Corresponding with these induced increases in nAb levels, booster inoculation (50 ug mRNA-1273) of adults enrolled in the ongoing vaccine effectiveness study with Kaiser Southern California demonstrated enhanced vaccine effectiveness (VE) against both Delta and Omicron SARS-CoV-2 infection. VE against Omicron infection increased from 44% after dose 2 to 72% after booster (Figure below).



Adapted from Tseng HF et al, *Nature Med*, 2022

The demonstrated similar immunobridging and effectiveness profiles of two doses of 100 ug in adolescents and in adults (study P203) forms the basis to extrapolate the behaviour of the 50 ug mRNA booster dose. Data from adults shows that booster administration enhances nAb levels (including against the Omicron variant) and adult vaccine effectiveness studies show improved effectiveness against Omicron. These same benefits would thus be anticipated to be conferred to adolescents receiving the mRNA-1273 booster (50 ug). As also noted by the Rapporteur, there is currently no scientifically justified reason to assume that booster immune responses in these two age groups should differ significantly while primary vaccination responses are highly comparable.

Assessment of the MAH's response:

The MAH has provided additional data as regards the timing and dosage of the booster dose as requested. The timing of booster from 3 months post second dose is endorsed as it provides sufficient flexibility. Further, also the boost dose of 50 µg is considered sufficiently confirmed by the study data available and is expected to be applicable also to adolescents.

Conclusion

Issue solved.

Commitment

The MAH is requested to submit the interim and the final clinical study report on results from study P203 Part C as soon as it becomes available. The interim CSR is expected Q3.

Summary of the MAH's response

The MAH clarified that the generation of an interim analysis on at least the first 1000 subjects boosted

with at least 2 months follow-up post booster, is currently planned to be available Q3 2022. This will include a summary of the data with supportive TFLs, no formal CSR will be available at that time. A full CSR will be available late Q1 2023 when a median of 6 months of follow-up post booster and a database lock will occur.

Assessment of the MAH's response

The MAH confirms that the current plan for submission of the interim CSR is still Q3 2022. Further, the MAH states that the full CSR will be available late in Q1 2023.

Conclusion

Issue solved.

OVERALL CONCLUSION AFTER ASSESSMENT OF RESPONSES CIRCULATED ON 21 JUNE 2022

Most of the open issues are solved and the open issue (point 1b) is considered resolved following the MAH commitment to include the data becoming available on the reactogenicity/safety in adolescents and young adults along with the sound data analysis in the upcoming interim reports from study mRNA-1273-P203 Part C. All issues are therefore considered resolved.

10. Overall conclusion and impact on the benefit-risk balance

With this submission the MAH requested an extension of the approved booster indication for adults (i.e. one 50 µg booster dose administered at least three months after completion of primary vaccination) to adolescents (12 to < 18 years). Only a homologous booster dose after primary vaccination with Spikevax is proposed by the MAH for this adolescent population. The data submitted in support of this proposed extension of indication is rather heterogeneous and contains information compiled from multiple sources and study scenarios.

Efficacy/Immunogenicity

No specific data for efficacy, immunogenicity or effectiveness of booster vaccination in the targeted age group of adolescents have been provided by the MAH. Rather, evidence from multiple clinical studies – mostly not including the adolescent age group - and "real world data" from effectiveness studies have been compiled to substantiate the proposed indication extension. In essence, these include:

- Efficacy of a primary vaccination series in adults and young adults from clinical study mRNA-1273-P301
- Immunogenicity results in young adults (≥18 to 25 years of age) receiving booster doses in clinical studies mRNA-1273-P201 Part B, DMID Study 21-0012, mRNA-1273-P301, and post-licensure.
- Immuno-bridging for primary vaccination responses in adolescents and young adults based on immunogenicity data from study mRNA-1273-P203 (12 to <18 years of age) and study mRNA-1273-P301 (≥18 to 25 years of age).
- DMID 21-0012 Study results for heterologous booster indication in adults
- Published Post-licensure Booster Vaccine Effectiveness data

The majority of these data have already been submitted and evaluated in the context of previously completed regulatory procedures:

- EMEA/H/C/005791/II/0021: Extension of primary immunisation indication from adults to adolescents

12 - <18 years of age
- EMEA/H/C/005791/II/0042: Indication for heterologous boosting in adults 18 years of age and older

As a whole, these data are considered relevant to justify the claim for the extension of the current booster indication for Spikevax to adolescents, even in the current absence of adolescent-specific data in terms of efficacy/immunogenicity. In particular, the comparison of vaccine-induced nAB titers after primary vaccination in young adults and adolescents confirms the equivalence of the measured immune responses in these two age groups. There is currently no scientifically justified reason to assume that booster immune responses in these two age groups should differ significantly while primary vaccination responses are highly comparable.

Modelling for immunogenicity

Of note, the MAH has developed a population IS/ID model to support the extension of the 50 µg booster dose in the adolescent population. However, such a modelling approach has not been used before in any regulatory evaluation regarding the determination of vaccine efficacy or immunogenicity. It is therefore deemed premature to include such a totally new approach that has no regulatory/procedural precedent in the context of this variation procedure. Nevertheless, the modelling approach as such has been soundly evaluated and certain weaknesses and deficiencies have been discussed and assessed as listed in the RSI section of this report. Importantly, the model has not been included in the regulatory decision-making for the present variation procedure.

Safety

As explained already in terms of efficacy, the safety database submitted is also quite diverse. It includes safety data from the above-mentioned clinical trials in adults and adolescents for primary vaccination and booster vaccination in adults. Further, post-authorisation data and data from pharmacovigilance monitoring are included.

As for the efficacy part above, no study data are currently available as regards the safety profile of a booster dose in adolescents. Data from primary vaccination studies indicate that the local reactogenicity in the age cohort 12 to <18 years of age is slightly increased when compared to the age cohort 18 to 25 years of age. No clinical meaningful difference could be observed for solicited systemic ARs. The incidence of systemic solicited ARs tended to be comparable or slightly higher in the age cohort 18 to 25 years of age compared with the adolescents after primary immunisation. In summary, no clinical meaningful difference in reactogenicity were detected after full primary vaccination with Spikevax in adolescents and young adults 18-25 years of age. There is at current no scientific reason to expect a significantly different/adverse safety/reactogenicity profile after the booster dose in adolescents. However, to support this extrapolation, the MAH was requested within the first round of RSI to provide a comprehensive and comparative analysis (adolescents vs. young adults) and discussion of safety based on post-marketing data. The post-marketing surveillance data include safety data from adults and adolescents. The reviewed safety data do not raise concerns regarding the administration of a 50 µg booster dose of Spikevax to adolescents at least 3 months after full primary vaccination with Spikevax. The performed expected versus observed analysis as well as the reporting rates of myocarditis within 7 days after Dose 1, 2, and 3 are in line with what is currently known about mRNA vaccine-associated myocarditis. In adolescents, so far, no cases of myocarditis post dose 3 have been recorded in the MAH safety database.

Overall conclusion

With the submission of responses circulated on 21st June 2022, most of the identified open issues from the first RSI were adequately resolved. The one remaining issue (point 1b) was resolved by commitment by the MAH to include the data becoming available on the reactogenicity/safety in adolescents and young adults along with the sound data analysis in the upcoming interim reports from study mRNA-1273-P203 Part C.

As a result, the CHMP considers that the benefit-risk balance of Spikevax remains positive after implementation of the indication for a booster dose in adolescents 12 – 18 years of age.

11. Recommendations

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

Variation requested		**Type**	**Annexes affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type II	I and IIIB

Update of sections 4.2 and 4.4 of the Spikevax SmPC to include a 50 µg booster dose for adolescents 12 to 18 years of age, based on the extrapolation of safety and efficacy data from young adults (18 to 24 years of age). The package leaflet is updated accordingly.

☒is recommended for approval.

Amendments to the marketing authorisation

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

12. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

A booster dose of Spikevax should be given intramuscularly to individuals 12 years of age and older at least 3 months after completion of the primary series.

Myocarditis and pericarditis have been observed more often after the second dose compared to the first dose, and more often in younger males. The risk profile appears to be similar for the second and the third dose.

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