EMADOC-1700519818-1857217
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMA/VR/0000245103

Invented name: Spikevax

Common name: COVID-19 mRNA vaccine

Note

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

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Submission deadline	10 January 2025	10 January 2025	☐
☐	Validation	26 January 2025	26 January 2025	☐
☐	Start date	27 January 2025	27 January 2025	☐
☐	CHMP Rapporteur AR	3 March 2025	13 March 2025	☐
☐	CHMP Comments	17 March 2025	17 March 2025	☐
☐	Updated CHMP Rapporteur AR	20 March 2025	20 March 2025	☐
☒	CHMP Outcome	27 March 2025	27 March 2025	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain S.L. submitted to the European Medicines Agency on 08 January 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II

Submission of the final report from study mRNA-1273-P203 listed as a category 3 study in the RMP. This is a phase 2/3, randomised, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents 12 to <18 Years of Age.

The requested variation(s) proposed no amendments to the Product information.

2. Overall conclusion and impact on the benefit/risk balance

Within this type II variation, the MAH is submitting the final Clinical Study Report (CSR) for mRNA-1273-P203 (A Phase 2/3, Randomised, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to <18 Years of Age) listed as a category 3 study in the RMP, for Spikevax while fulfilling the requirement set out in Article 46 of the Regulation (EC) No 1901/2006, as amended.

The interim results and details of study mRNA-1273-P203 have already been reported and assessed in procedure EMEA/H/C/005791/II/0021 and EMEA/H/C/005791/MEA/040 and MEA/040.1. With this submission, the MAH also meets the recommendation outlined in the Procedure EMEA/H/C/005791/ II/0021 (Variation - Extension of indication to include use in adolescents from 12 to 17 years of age for Spikevax): "*Since no dose finding trial in this population has been conducted it is not possible to conclude whether lower dose could have resulted in a lower reactogenicity with comparable immune response and efficacy. The MAH should further explore lower dose levels in adolescents 12-17 years of age given the high reactogenicity of Spikevax and the usually mild course of infection caused by SARS-CoV-2 in this age group"*.

The results now presented in the final study report include data up to last patient last visit for Parts 1A and 1B, 1C-1, 1C-2, Part 2 and Part 3.

The data presented showed that a booster dose with 50µg increases GMCs reliably by 14-18- fold increase for antibodies directed against the vaccine strain as well as against the ancestral strain. GMCs were higher with higher baseline concentrations, as it would be expected.

Over the following 150 days antibody concentrations decline to about 50% but still remain at a high level. Over the next 150 days there is no significant further decline seen. Whether this is also attributable to natural boosters or GMCs just reach a plateau is unknown.

After the two-dose priming with 50µg GMCs increase with each dose, as expected. Further conclusions seemed unwarranted as the sample size of 46 is very small.

For the bivalent vaccine the prespecified success criteria for the primary immunogenicity objective were met, thus enabling the inference of vaccine effectiveness of a single 50 µg dose of mRNA-

1273.222 in previously unvaccinated adolescents in Study 203 Part 3 from that observed in Study P301.

With the strain-adapted bivalent vaccine persistence of antibodies is also shown reliably over 180 days post vaccination. After the D29 datapoint antibodies decline but remain 5-fold (Omicron) or 3-fold (Ancestral) higher than at baseline.

No safety issues are reported regardless of the number of doses or antigen strain. The safety profile of the vaccine is unchanged.

An updated version of the RMP will be submitted at the next regulatory opportunity. This update will include changes to the Pharmacovigilance plan, specifically the removal of the completed study mRNA-1273-P203 from the table of additional pharmacovigilance activities.

The requested variation proposed no amendments to the Product Information.

The benefit-risk balance of Spikevax, remains positive.

3. Recommendations

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

Variation(s) requested		**Type**
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II

Submission of the final report from study mRNA-1273-P203 listed as a category 3 study in the RMP. This is a phase 2/3, randomised, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents 12 to <18 years of age.

☒is recommended for approval.

Amendments to the marketing authorisation

The variation leads to no amendments to the terms of the Community Marketing Authorisation.

4. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion "Spikevax-EMA-VR-0000245103"

Annex: Rapporteur’s assessment comments on the type II variation

1. Introduction

Final Clinical Study Report (CSR) for mRNA-1273-P203 (A Phase 2/3, Randomised, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to <18 Years of Age) listed as a category 3 study in the RMP, for Spikevax and fulfillment of Article 46 of the Paediatric Regulation is submitted here.

The interim results and details of study P203 have already been reported and assessed in procedure EMEA/H/C/005791/II/0021.

The results now presented in the final study report include data up to LPLV for Parts 1A, 1C-1, 1C-2, Part 2 and Part 3. Database lock of 23 Jul 2024.

Table 1: Data reported in this AR (source: Clinical Overview)

Study Part	Scope	Dose
Part 1A: Randomized, placebo-controlled Part 1B: Open-label, crossover Part 1C-1, Part 1C-2, Part 2: Open-label	LPLV safety data and: Part 1A and 1B: Overview of unsolicited AEs only (up to LPLV) Part 1C-1: Secondary immunogenicity endpoint (nAb against other variants); exploratory long-term (12 months after BD) immunogenicity; symptomatic and asymptomatic COVID-19 and SARS-CoV-2 infection up to the LPLV Part 1C-2: Primary immunogenicity endpoint Part 2: Primary immunogenicity endpoint (nAb only)	Part 1A and 1B: 100 µg mRNA-1273 primary series (2 doses) Part 1C-1: 50 µg mRNA-1273 single BD (Homologous) Part 1C-2: 50 µg mRNA-1273 single BD (Heterologous) Part 2: 50 µg mRNA-1273 primary series (2 doses) and BD
Part 3: Open-label	LPLV safety data Primary and secondary immunogenicity endpoints; exploratory long-term (6 months) immunogenicity (nAb only), COVID-19 incidence	50 µg mRNA-1273.222 (single dose and 2 doses)

Abbreviations: AE = adverse event; BD = booster dose; COVID-19 = coronavirus disease 2019; LPLV = last participant last visit; nAb = neutralising antibody; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Part 1A (Blinded Phase): Part 1A was a randomised (2:1, vaccine:placebo), observer-blind, placebo-controlled study evaluating the safety, reactogenicity, and effectiveness of mRNA-1273 100 µg as a 2-dose primary series in healthy adolescents 12 to <18 years of age.
- Part 1B (Open-label Phase): Upon granting of emergency use authorization (EUA) in the U.S. of a nonstudy COVID-19 vaccine in adolescents aged ≥12 years in May 2021, the study transitioned to an open-label phase, designed to offer participants who received placebo in Part 1A and who met EUA eligibility criteria the option to receive mRNA-1273.
- Part 1C-1 (Open-label, homologous booster dose (BD) Phase): Part 1 C-1 was an open-label homologous booster phase designed to offer participants in Part 1A and Part 1B who had received the mRNA-1273 primary series an optional 50 µg mRNA-1273 BD at least 5 months after Dose 2 of the primary series.
- Part 1C-2 (Open-label, heterologous booster phase): Part 1C-2 was an open-label heterologous booster phase designed to offer participants who completed their primary COVID-19 vaccination

series with a non-Moderna vaccine (outside of the study) a 50 µg mRNA-1273 BD at least 3 months from the last dose. Enrollment for this part was discontinued on 16 Aug 2022 due to availability of the more updated variant-containing vaccine (Spikevax bivalent Original/Omicron BA.4-5, mRNA-1273.222) and the need to evaluate it in the adolescent population.

- Part 2 (Open-label): This part was an open-label, single-arm design evaluating the safety, reactogenicity, and immunogenicity of mRNA-1273 50 µg as a 2-dose primary series in healthy adolescents 12 to <18 years of age. Participants were also offered a single mRNA-1273 50 µg BD. Enrollment for this part was discontinued on 16 Aug 2022 due to availability of the more updated variant-containing vaccine (mRNA-1273.222) and the need to evaluate it in the adolescent population.

2. Clinical Efficacy aspects

2.1. Methods – analysis of data submitted

A description of the study design, dose schedule, and number of participants exposed to the study vaccine and key study objectives for each part in Study P203 are presented below.

Table 2: Design and endpoints of the different part of study P203 (source: Table1, Clinical Overview)

Study Part	Study Design Study Population	Active Treatment/ Sponsor Vaccine, Dose, Schedule, and Number of Participants Exposed	Key Immunogenicity and/or Efficacy Objective(s)	Safety Objectives
Part 1A	Observer-Blind, Randomised, Placebo-Controlled Phase Adolescents 12 to <18 years of age were randomised in a 2:1 ratio to receive either mRNA-1273 (100 µg) or placebo as a 2-dose primary series given 28 days apart	2 doses of mRNA-1273 100 µg: Dose 1 N=2486 Dose 2 N=2480 or Placebo: Dose 1 N=1240 Dose 2 N=1222	**Primary immunogenicity:** To infer efficacy of mRNA-1273 (100 µg, 2 doses 28 days apart), serum Ab responses obtained 28 days after Dose 2 of mRNA-1273 (Day 57) **Secondary:** To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of SARS-CoV-2 S-2P specific bAb and nAb through 1 year after Dose 2 To evaluate the effect of mRNA-1273 on the incidence of SARS-CoV-2 infection compared with the incidence among placebo recipients To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo	To evaluate the safety and reactogenicity of 100 µg mRNA-1273 vaccine administered in 2 doses 28 days apart
Part 1B	Open-Label, Crossover Phase Adolescents 12 to <18 years of age who received placebo in Part 1A were offered to receive a 2-dose primary series of mRNA-1273	2 doses of mRNA-1273 100 µg Dose 1 N=96 Dose 2 N=93	No primary objectives Secondary objectives were the same as Part 1A.	To evaluate the safety and reactogenicity of 100 µg mRNA-1273 vaccine administered in 2 doses 28 days apart
Part 1C-1	Open-Label, Single Arm, Homologous Booster Phase Adolescents 12 to <18 years of age who received the 2-dose primary series in Part 1A or Part 1B	Single booster dose of mRNA-1273 50 µg mRNA-1273 50 µg N=1357 Placebo-mRNA-1273 N=51	**Primary:** To infer effectiveness of the 50 µg of mRNA-1273 booster by establishing noninferiority of Ab response after the BD compared to the primary series of mRNA-1273 **Secondary:** To evaluate immune response elicited by the 50 µg prototype booster of mRNA-1273 against variant(s) of interest	**Primary:** To evaluate the safety of the 50 µg BD of mRNA-1273
Part 1C-2	Open-Label, Single Arm, Heterologous Booster Phase Adolescents 12 to <18 years of age who completed their primary COVID-19 vaccination series with a non-Moderna vaccine under EUA (ie, Pfizer BioNTech) Enrolment for this part was discontinued in August 2022 due to availability of the more updated variant-containing vaccine (mRNA-1273.222) and the need to evaluate it in the adolescent population.	Single booster dose of mRNA-1273 50 µg mRNA-1273 50 µg N=155	**Primary:** To evaluate immune response elicited by 50 µg booster of mRNA-1273 in participants who received non-Moderna COVID-19 primary series vaccination	**Primary:** To evaluate the safety of the 50 µg BD of mRNA-1273 in participants who received non-Moderna COVID-19 primary series vaccination
Part 2	Open-Label, single arm, evaluation of mRNA-1273 50 µg 2-dose primary series and a single mRNA-1273 50 µg BD in adolescents 12 to <18 years of age who had not previously received COVID-19 vaccination Enrolment for this part was discontinued in August 2022 due to availability of the more updated variant-containing vaccine (mRNA-1273.222) and the need to evaluate it in the adolescent population.	2-dose primary series and a single booster mRNA-1273 50 µg Dose 1 N=52 Dose 2 N=50 BD N=19	**Primary:** To evaluate immune response elicited by the 50 µg mRNA-1273 vaccine administered in 2 doses 28 days apart	**Primary:** To evaluate the safety and reactogenicity of the 50 µg mRNA-1273 vaccine administered in 2 doses, 28 days apart
Part 3	Open-Label, single arm evaluation of mRNA-1273.222 50 µg 2 doses 6 months apart in adolescents 12 to <18 years of age who had not previously received COVID-19 vaccination The protocol was amended to discontinue administration of Dose 2 in the US based on interim analysis results showing single-dose effectiveness through immunobridging and following authorisation of single-dose regimen in the US.	2 doses of 50 µg mRNA-1273.222 administered 6 months apart Dose 1 N=388 Dose 2 N=335	**Primary:** To infer effectiveness of the 50 µg mRNA-1273.222 vaccine based on immune response against SARS-CoV-2 VOC (Omicron BA.4/BA.5) and Ancestral strain obtained 28 days post-Dose 1 in the baseline SARS-CoV-2-positive population **Secondary:** To evaluate immune response (seroresponse rate) elicited by the 50 µg mRNA-1273.222 vaccine administered as 1 dose based on immune responses against Omicron BA.4/BA.5 and Ancestral strain obtained 28 days post-Dose 1 To evaluate immune response elicited by the 50 µg mRNA-1273.222 vaccine administered as 1 dose against other variant(s) of interest obtained 28 days post-Dose 1	**Primary:** To evaluate the safety and reactogenicity of the 50 µg mRNA-1273.222 vaccine administered as 1 dose

2.1.1. Study Population

Study P203 enrolled adolescent male or female participants who were 12 to <18 years of age. The demographic and baseline characteristics in the Safety Set across all parts are summarized below.

- **Part 1A**: Out of the 3733 randomised participants, a total of 3726 participants received the first dose of study vaccine in Part 1A: 1240 participants in the placebo group and 2486 participants in the mRNA-1273 group. Overall (N=3726), 51.4% of participants were male; the median age at screening was 14.0 years (range: 12 to 17 years); 74.3% of participants were ≥12 to <16 years of age and 25.7% were ≥16 to <18 years. The majority of participants were White (83.8%) and not Hispanic or Latino (87.5%).
- **Part 1B**: A high number of placebo recipients withdrew from the study starting in May 2021. In Part 1B, 96/1243 (7.7%) participants who received placebo in Part 1A received at least 1 dose of mRNA-1273. Although the placebo-mRNA-1273 group included only 96 participants, demographics and baseline characteristics in the Long-term Analysis Safety Set were generally similar between the placebo-mRNA-1273 and mRNA-1273 groups, except a higher proportion of Hispanic or Latino participants in the placebo-mRNA-1273 group (25.3%) was observed compared with the mRNA-1273 group (11.3%).
- **Part 1C-1**: A total of 1408 participants received the booster dose: 51 participants in the placebo-mRNA-1273 booster group (placebo group participants in Part 1A who previously received mRNA-1273 in Part 1B) and 1357 participants in the mRNA-1273-booster group (who previously received mRNA-1273 in Part 1A). Overall, the median age of participants in the Part 1C-1 Safety Set was 14.0 years (range 12 to 17 years) with 1128 (80.1%) participants in the ≥12 to <16 years age group and 280 (19.9%) participants in the ≥16 to <18 years age group. Proportions of males and females were similar. Most participants were White (84.9%) and non-Hispanic or non-Latino in ethnicity (85.7%).
- **Part 1C-2**: Overall, 155 participants were included in the Part 1C-2 Safety Set. The median age of participants was 14.0 years (range 12 to 17 years) with 127 (81.9%) participants in the ≥12 to <16 years age group and 28 (18.1%) participants in the ≥16 to <18 years age group. Most participants were White (74.2%) and non-Hispanic or non-Latino in ethnicity (74.8%).
- **Part 2**: Overall, 52 participants were included in the Part 2 Safety Set. The median age of participants was14.0 years (range 12 to 17 years) with 42 (80.8%) participants in the ≥12 to <16 years age group and 10 (19.2%) participants in the ≥16 to <18 years age group. The majority of participants were White (57.7%), followed by Black (34.6%). Most participants were White (57.7%) and non-Hispanic or non-Latino in ethnicity (69.2%) .
- **Part 3**: Overall, 388 participants were included in the Part 3 the Safety Set. There were 334 (86.1%) participants enrolled in the Dominican Republic and 54 (13.9%) participants enrolled in the US; 94.6% of participants were Hispanic or Latino. The majority of participants enrolled in Study P203 Part 3 were enrolled in the Dominican Republic. This was because of the enrolment challenges in the U.S. for the target group of unvaccinated adolescents (Study P203 Final CSR [Part 3]).

The Per-Protocol Immunogenicity Set (PPIS) was the primary analysis population used in the immunogenicity analyses in Parts 1A, 1C-2, and 2. The PPIS– Prebooster SARS-CoV-2 Negative and PPIS-baseline SARS-CoV-2 positive were the primary analysis populations in Part 1C-1 and Part 3, respectively. The demographic and baseline characteristics in the PPIS were similar to the Safety Set in these parts.

2.1.2. Statistical Methods

Key details of the statistical analyses that were carried out for immunogenicity assessments in Parts 1A, 1B, 1C-1, 1C-2, 2, and 3 are presented in the ensuing subsections.

Immunogenicity Analyses

Immunogenicity was assessed by the measure of neutralising antibodies (nAb) and binding antibodies (bAb) against vaccine antigen at 28 days postvaccination (after Dose 2 for the primary series and after Dose 1 for the BD or single dose assessment): nAb levels against pseudovirus expressing Ancestral strain of SARS-CoV-2 (D614G) S-protein and bAb specific for the S-protein of D614G and other variants of interest as specified in the protocol study objectives (e.g., Alpha [B.1.1.7], Beta [B.1.351], Delta [B.1.617.2], and Gamma [P.1]) were assessed. Persistence of SARS-CoV-2-specific nAb or bAb after 2 doses or 1 dose of mRNA-1273 were summarised over time at specified timepoints as secondary or exploratory endpoints as specified in the protocol study objectives.

For each of the antibodies of interest (e.g., levels of SARS-CoV-2–specific nAb), the geometric mean titres (GMT) with corresponding 95% confidence intervals (CI) at each timepoint and geometric mean fold rations (GMFR) of postbaseline/baseline titres or levels with corresponding 95% CI at each postbaseline timepoint were provided. The 95% CIs were calculated based on the t-distribution of the log-transformed values for GM, and the difference of log-transformed values for GMFR, then back transformed to the original scale for presentation.

The following descriptive statistics were also provided at each timepoint: number of participants (n), median, minimum, and maximum.

The seroresponse rate (SRR), defined as the percentage of participants achieving seroresponse after vaccination, was provided with the 95% CI calculated using the Clopper-Pearson method. The primary definition of seroresponse was defined as a change from below the lower limit of quantification (LLOQ) to equal to or above 4×LLOQ, or a 4-fold rise if baseline (pre-Dose 1 or prebooster) was equal to or above LLOQ; antibody values reported as below the LLOQ were replaced by 0.5×LLOQ.

The analysis population for immunogenicity analyses was the PPIS.

Parts 1A and 1B

The study was considered to meet the primary immunogenicity objective if noninferiority (NI) based on both GMT and SRR at Day 57 was demonstrated at a 2-sided alpha of 0.05 in P203 participants compared with those in Study P301 young adults (≥18 to ≤25 years). Study success criteria were based on the following: NI based on the ratio of GMT (Study P203 vs Study P301 young adults) with an NI margin of 1.5 and a point estimator of GMT >0.8; and NI based on difference of SRR (Study P203 – Study P301 young adults) with an NI margin of 10% and a point estimator of difference in SRR >-5.0%. The analyses of immunogenicity were based on the PPIS and Immunogenicity Subset. The PPIS was the primary analysis population used in the immunogenicity analyses.

Long-term analysis included data collected in the Blinded Phase (Part 1A) and Open-Label Phase (Part 1B) prior to BD if a BD was received. The analysis included participants who were randomised to mRNA-1273 in Part 1A and remained in the study, and participants who were originally randomised to placebo in Part 1A and later crossed over to receive mRNA-1273 in Part 1B after unblinding.

To assess persistence of immunogenicity response after 2 doses of mRNA-1273, nAb and bAb values were summarised over time at specified timepoints in both immunogenicity subset (long-term analysis) and PPIS (long-term analysis).

Part 1C-1

The primary immunogenicity endpoint was to demonstrate the effectiveness of mRNA-1273 BD in adolescents 12 to <18 years of age by demonstrating NI of nAb levels from BD-Day 29 among adolescents in Study P203 compared to nAb levels from Day 57 primary series among Study P301young adults (≥18 to ≤25 years).

The primary immunogenicity analyses used to infer BD vaccine effectiveness was evaluated in the PPIS-Neg set (Per-Protocol Immunogenicity Subset - Prebooster SARS-CoV-2 negative). The NI of the coprimary endpoints (Ab GM levels and SRR against the Ancestral SARS-CoV-2 strain in BD adolescents in Study P203 at BD-Day 29 compared with those in Study P301 young adults [≥18 to ≤25 years] at Day 57 [28 days after Dose 2 in the primary series]) was assessed and considered to meet the primary immunogenicity objective if the NI of the immune response to mRNA-1273 BD was demonstrated in adolescents in this study at a 2-sided alpha of 0.05 with the following success criteria:

- The NI of the immune response to mRNA-1273 as measured by GM was considered demonstrated if the lower bound of the 95% CI of the GMR was >0.667 (based on the NI margin of 1.5), and GMR point estimate was ≥0.8 (minimum threshold).
- The NI in SRR (relative to pre-Dose 1) of adolescents in Study P203 compared to Study P301 young adults (≥18 to ≤25 years of age) was considered demonstrated if the lower bound of the 95% CI of the SRR difference was >-10%, based on the NI margin of 10%. A sensitivity analysis of SRR relative to prebooster was also performed.

A key secondary endpoint was GM value and SRR of postbooster antibody against variant strain (Omicron BA.4/BA.5).

Part 1C-2

The primary immunogenicity endpoint (GM value of postbooster [BD-Day 29] antibody against the Ancestral SARS-CoV-2 strain) was analysed. The GM value was provided with 95% CI summarised using t-distribution of the log-transferred values and then back transformed to the original scale. The PPIS was the primary analysis population in Part 1C-2.

The primary immunogenicity endpoint (GM value of post-Dose 2 [Day 57] antibody against the Ancestral SARS-CoV-2 strain and SRR) was analysed. The GM value at both post-Dose 1 (Day 29) and post-Dose 2 (Day 57) with 95% CI were summarised using t-distribution of the log-transferred values and then back transformed to the original scale. The PPIS was the primary analysis population in Part 2 (negative versus positive).

Part 3

Primary Immunogenicity Endpoints

The primary immunogenicity analysis was based on the PPIS-Pos analysis set. Hypothesis testing was performed for coprimary endpoints that inferred the effectiveness of a single 50 µg dose of mRNA-1273.222 in Study P203 Part 3 compared to the 2-dose primary series in Study P301. Effectiveness of the single 50 µg dose of mRNA-1273.222 was inferred based on the following coprimary endpoints:

- Successful demonstration of superiority required the lower bound of the 2-sided 95% CI of the GMR (nAb GMC in Study P203 participants at Day 29/nAb GMC in Study P301 young adults [≥18 to ≤25 years] at Day 57) to be >1.0.
- Successful demonstration of NI required the lower bound of the 2-sided 95% CI of the GMR (nAb GMC in Study P203 participants at Day 29/nAb GMC in Study P301 young adults [≥18 to ≤25 years] at Day 57) to be >0.667.

Secondary Immunogenicity Endpoints

As secondary endpoints, SRRs against Omicron BA.4/BA.5 and Ancestral SARS-CoV-2 strain in Study P203 Part 3 at Day 29 after a single 50 µg dose of mRNA-1273.222 were compared to SRRs against Omicron BA.4/BA.5 and Ancestral SARS-CoV-2 strain after 2 doses (100 µg each) of mRNA-1273 in baseline SARS-CoV-2 negative young adults ≥18 to ≤25 years from Study P301.

The bAb GM levels and GMFR (compared to pre-Dose 1) against variants of interest with corresponding 95% CI were provided for the Day 29 timepoint. The 95% CIs were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.

Analyses for COVID-19 or SARS-CoV-2 Infection

Table 3 provides the COVID-19 and SARS-CoV-2 case definitions used in Study P203. Vaccine efficacy was assessed until 31 May 2021, the effective end of the blinded period (Part 1A). Cases of COVID-19 and SARS-CoV-2 infection (symptomatic and asymptomatic) continued to be monitored upon unblinding or during the open-label phases, and incidence rates were assessed as secondary or exploratory endpoint (Study P203 Final CSR [Parts 1A and 1B; Study P203 Final CSR [Parts 1A, 1B, 1C-1, 1C-2, and 2]; and Study P203 Final CSR [Part 3].

Incidence cases were presented starting 14 days after the Dose 2 of the primary series using the PP Efficacy set (Part 1A and Part 1B) or 14 days after the Dose 1 of the primary series using the mITT1 Set (Part 1A), 14 days postbooster using the mITT1 Set in the Booster Phase (Part 1C-1), and 14 days after Dose 1 using the Full Analysis Set in Part 3. The incidence rate was calculated as the number of cases divided by the person-time.

Table 3: COVID-19 and SARS-CoV-2 Case Definitions in Study P203 (source: Table 3, clinical overview)

Endpoint	Definition
COVID-19 "P301 case definition"	COVID-19 case was identified as a positive postbaseline RT-PCR test result, together with eligible symptoms as follows: Positive postbaseline PCR result AND At least 2 systemic symptoms: fever (≥38°C/≥100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR At least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.
COVID-19 "CDC case definition"	At least one symptom from a pre-specified list of COVID-19 symptoms derived from the CDC case definition (CDC 2021) Systemic symptoms: fever (temperature >38°C/≥100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhoea, AND At least one positive RT-PCR for SARS-CoV-2.
SARS-CoV-2 Infection (regardless of symptoms)	Combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, OR Positive RT-PCR test.
Asymptomatic SARS-CoV-2 infection	Asymptomatic SARS-CoV-2 infection was identified by absence of symptoms and infections as detected by RT-PCR or serology tests. Absence of COVID-19 symptoms. AND at least one from below: bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, OR Positive RT-PCR test at scheduled or unscheduled/illness visits.

Abbreviations: bAb = binding antibody; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 19; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Source: Study P203 Final CSR (Parts 1A, 1B, 1C-1, 1C-2, and 2), Table 8.

3. Results

3.1. Immunogenicity endpoints

3.1.1. Booster - Part 1C-1

Post booster immune results are shown against the vaccine strain (Table 4) as well as against the ancestral strain (Table 5).

Table 4: Summary of Pseudovirus Neutralising Antibody Values Against B.1.1.529 (VAC122) from Prebooster by Prebooster SARS-CoV-2 Status (Part 1C-1 Per-Protocol Immunogenicity Subset) (source: Table 19, CSR)

	P203 mRNA-1273		
Timepoint Data Category Statistic	**Prebooster SARS-CoV-2 Negative (N=267)**	**Prebooster SARS-CoV-2 Positive (N=51)**	**Overall (N=331)**
BD-Day 1 (prebooster)			
n [a]	248	49	309
GMC (95% CI [b])	34.3 (31.2, 37.7)	396.2 (224.8, 698.2)	49.9 (42.7, 58.2)
Number of participants <LLOQ, n (%) [c]	1 (0.4)	1 (2.0)	2 (0.6)
Number of participants ≥LLOQ, n (%) [c]	247 (99.6)	48 (98.0)	307 (99.4)
BD-Day 29			
n [a]	267	51	331
GMC (95% CI [b])	803.3 (726.2, 888.6)	2441.7 (1949.5, 3058.2)	943.4 (853.5, 1042.8)
N1	248	49	309
GMFR (95% CI [b])	23.1 (20.6, 26.0)	6.1 (3.7, 10.0)	18.8 (16.4, 21.4)
SRR (n/N1)	242/248	21/49	275/309
SRR (%) [d] (95% CI) [e]	97.6 (94.8, 99.1)	42.9 (28.8, 57.8)	89.0 (85.0, 92.3)

Abbreviations: BD = booster dose, CI = confidence interval, GMC = geometric mean concentration, GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; ULOQ = upper limit of quantification.

N1 = Number of participants with nonmissing data at prebooster and the corresponding timepoint.

Antibody: VAC122 Neutralizing Antibody against B.1.1.529 (LLOQ: 8, ULOQ: 24503)

Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available.

a. Number of participants with nonmissing data at the corresponding timepoint.

b. 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMC and GMFR, respectively, then back transformed to the original scale for presentation.

c. Percentages were based on n[a].

d. Number of participants meeting the criterion at the timepoint. Percentages were based on N1.

e. 95% CI was calculated using the Clopper-Pearson method.

Source: Table 14.2.3.1.5.5.2.

Table 5: Summary of Pseudovirus Neutralising Antibody Values (VAC62) From Prebooster by Prebooster SARS-CoV-2 Status (Part 1C-2 Per-Protocol Immunogenicity Subset)) (source: Table 21, CSR)

Timepoint	P203 Heterologous Booster Prebooster SARS-CoV-2 Status		
Data Category Statistic	Negative (N=24)	Positive (N=110)	Overall (N=136)
Baseline (BD-Day 1)			
n [a]	24	108	134
GMC (95% CI [b])	578.6 (319.8, 1047.1)	2834.5 (2352.4, 3415.4)	2056.5 (1659.1, 2549.0)
Number of participants <LLOQ, n (%) [c]	0	0	0
Number of participants ≥LLOQ, n (%) [c]	24 (100)	108 (100)	134 (100)
BD-Day 29			
n [a]	24	108	134
GMC (95% CI [b])	8483.3 (6634.4, 10847.5)	9727.5 (8657.9, 10929.2)	9433.4 (8496.8, 10473.3)
N1	24	106	132
GMFR (95% CI [b])	14.7 (7.8, 27.6)	3.5 (3.0, 4.0)	4.7 (3.9, 5.6)

Abbreviations: BD = booster dose; CI = confidence interval; GMC = geometric mean concentration; GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.
N1 = Number of participants with nonmissing data at Baseline and the corresponding timepoint.
Antibody: VAC62 Neutralizing Antibody (LLOQ: 10, ULOQ: 111433)
Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available.
a. Number of participants with nonmissing data at the corresponding timepoint.
b. 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMC and GMFR, respectively, then back transformed to the original scale for presentation.
c. Percentages were based on n[a].
Source: Table 14.2.3.1.6.1.

In participants who received a 50-µg dose of mRNA-1273 BD after receiving 2-dose 100 µg mRNA-1273 primary series, the overall nAb response against the B.1.1.529 strain at 28 days after BD was 18.8-fold higher than prebooster GMC (BD-Day 29 GMC=943.4 [95% CI: 853.5, 1042.8]). The overall SRR was 89.0% (95% CI: 85.0, 92.3).

Against the Ancestral strain the nAb GMC was 23.5-fold higher than pre-Dose 1 GMC (Day 57 GMC=7351.5 [95% CI: 5621.7, 9613.7]) with an SRR of 91.3% (95% CI: 79.2%, 97.6%).

Generally, nAb responses were observed to be higher in participants whose Baseline SARS-CoV-2 status was positive compared with those who were negative.

3.1.2. One dose using 50µg - Part 3 (bivalent)

In Part 3 of the study the vaccine given was changed to the bivalent version given routinely at that time. The CSR reports a one-dose regimen after a protocol change from two to one dose. The two doses were given 6 months apart in the Dominican Republic only and the results are not shown here as the objectives of the study are focussed on one dose.

The primary objectives strive to show the immune response of 50µg Omicron BA.4/5 vaccine in seropositive subjects vs 100µg "Ancestral" vaccine in seronegative subjects.

Superiority of one 50µg dose against the primary series of the 100µg 2-dose scheme used in study P301 was shown (Table 6) regarding the Omicron BA.4/5 strain.

Table 6: Summary of Pseudovirus nAb GMC (VAC137) against Omicron BA.4/BA.5 Among P203 Part 3 Adolescents (PPIS – POS) and P301 Young Adults (PPIS) (source: Table 10, CSR)

P203 Part 3 mRNA-1273.222 50 µg Adolescents (12 to <18 years)		**P301 mRNA-1273 Young Adults (18 to 25 years)**	
Baseline SARS-CoV-2 Positive (PPIS-POS) N=372		**Baseline SARS-CoV-2 Negative (PPIS) N=296**	
Pre-Dose 1 Baseline (Day 1)		Pre-Dose 1 Baseline (Day 1)	
n[a]	372	n[a]	296
GMC (95% CI[b])	149.8 (136.9, 163.8)	GMC (95% CI[b])	51.5(NE, NE)
Number of participants <LLOQ, n (%)[c]	118 (31.7)	Number of Participants <LLOQ, n (%)[c]	296 (100)
Number of participants ≥LLOQ, n (%)[c]	254 (68.3)	Number of Participants ≥LLOQ, n (%)[c]	0
Day 29		Day 57	
n[a]	372	n[a]	294
GMC (95% CI[b])	2727.8 (2516.8, 2956.6)	GMC (95% CI[b])	56.6 (54.5, 58.8)
N1	372	N1	294
GMFR (95% CI[b])	18.2 (16.5, 20.2)	GMFR (95% CI[b])	1.1 (1.1, 1.1)
SRR (n/N1)	355/372	SRR (n/N1)	0/294
SRR (%) (95% CI[d])	95.4 (92.8, 97.3)	SRR (%) (95% CI[d])	0 (0.0, 1.2)
Day 181			
n[a]	357		-
GMC (95% CI[b])	732.7 (677.4, 792.5)		-
N1	357		-
GMFR (95% CI[b])	5.0 (4.5, 5.5)		-
SRR (n/N1)	162/357		-
SRR (%) (95% CI[d])	45.4 (40.1, 50.7)		-

Abbreviations: CI = confidence interval; GM = geometric mean; GMC = geometric mean concentration; GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; nAb = neutralizing antibody; NE = not evaluable; PPIS = per-protocol immunogenicity set; PPIS-POS = per-protocol immunogenicity set – Baseline SARS-CoV-2 positive; SARS-Co-V-2 = Severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; ULOQ = upper limit of quantification.
N1 = Number of participants with non-missing data at Baseline and the corresponding post Baseline timepoint.

NI of one 50µg dose against the primary series of the 100µg 2-dose scheme used in study P301 was shown (Table 7) regarding the Ancestral strain.

Table 7: Summary of Pseudovirus nAb GMC (VAC62) against Ancestral Strain Among P203 Part 3 Adolescents (PPIS – Pos) and P301 Young Adults (PPIS) (source: Table 11, CSR)

P203 Part 3 mRNA-1273.222 50 µg Adolescents (12 to <18 years)		P301 mRNA-1273 Young Adults (18 to 25 years)	
Baseline SARS-CoV-2 Positive (PPIS-POS) N=372		**Baseline SARS-CoV-2 Negative (PPIS) N=296**	
Pre-Dose 1 Baseline (Day 1)		Pre-Dose 1 Baseline (Day 1)	
n[a]	371	n[a]	296
GMC (95% CI[b])	545.9 (486.5, 612.7)	GMC (95% CI[b])	8.5 (8.0, 9.0)
Number of participants <LLOQ, n (%)[c]	0	Number of Participants <LLOQ, n (%)[c]	143 (48.3)
Number of participants ≥LLOQ, n (%)[c]	371 (100)	Number of Participants ≥LLOQ, n (%)[c]	153 (51.7)
Day 29		Day 57	
n[a]	371	n[a]	295
GMC (95% CI[b])	7603.9 (7022.7, 8233.3)	GMC (95% CI[b])	1692.3 (1537.4, 1862.7)
N1	370	N1	295
GMFR (95% CI[b])	14.0 (12.8, 15.4)	GMFR (95% CI[b])	199.9 (178.5, 223.8)
SRR (n/N1)	351/370	SRR (n/N1)	293/295
SRR (%) (95% CI[d])	94.9 (92.1, 96.9)	SRR (%) (95% CI[d])	99.3 (97.6, 99.9)
Day 181			
n[a]	357		-
GMC (95% CI[b])	1753.2 (1588.4, 1935.1)		-
N1	356		-
GMFR (95% CI[b])	3.2 (3.0, 3.5)		-
SRR (n/N1)	118/356		-
SRR (%) (95% CI[d])	33.1 (28.3, 38.3)		-

Abbreviations: CI = confidence interval; GM = geometric mean; GMC = geometric mean concentration; GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; nAb = neutralizing antibody; NE = not evaluable; PPIS = per-protocol immunogenicity set; PPIS-POS = per-protocol immunogenicity set – Baseline SARS-CoV-2 positive; SARS-Co-V-2 = Severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; ULOQ = upper limit of quantification.

N1 = Number of participants with non-missing data at Baseline and the corresponding post Baseline timepoint.

Antibody values reported as below the LLOQ were replaced by 0.5 x LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available. VAC62 nAb (LLOQ: 10, ULOQ: 111433).

a. Number of participants with non-missing data at the timepoint (Baseline or post 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 GMC and GMFR, respectively, then back transformed to the original scale for presentation.

c. Percentages were based on n[a].

d. 95% CI was calculated using the Clopper-Pearson method.

Source: Table 14.2.3.1.8.2.1

3.1.3. 2-dose priming – Part 2

In participants who received a 2-dose 50-µg of mRNA-1273 primary series, the nAb GMC against the Ancestral strain was 23.5-fold higher than pre-Dose 1 GMC (Day 57 GMC=7351.5 [95% CI: 5621.7, 9613.7]) with an SRR of 91.3% (95% CI: 79.2%, 97.6%).

Generally, nAb responses were observed to be higher in participants whose baseline SARS-CoV-2 status was positive compared with those who were negative.

Table 8: Summary of Pseudovirus Neutralising Antibody Values (VAC62) Against Ancestral Strain by Baseline SARS-CoV-2 Status Per-Protocol Immunogenicity Subset (Part 2). Dose 1 given at baseline, Dose 2 given on D29 (source: Table 22, CSR)

Timepoint	P203 mRNA-1273 50 µg Baseline SARS-CoV-2 Status		
Data Category Statistic	Negative (N=2)	Positive (N=44)	Overall (N=46)
Baseline (Pre-Dose 1)			
n [a]	2	44	46
GMC (95% CI [b])	56.4 (25.6, 124.0)	338.7 (223.8, 512.6)	313.3 (207.8, 472.4)
Number of participants <LLOQ, n (%) [c]	0	0	0
Number of participants ≥LLOQ, n (%) [c]	2 (100)	44 (100)	46 (100)
Day 29			
n [a]	2	43	45
GMC (95% CI [b])	210.4 (151.0, 293.3)	6289.9 (4715.2, 8390.5)	5408.3 (3820.5, 7656.0)
N1	2	43	45
GMFR (95% CI [b])	3.7 (2.4, 5.9)	18.5 (12.9, 26.5)	17.2 (12.0, 24.6)
SRR (n/N1)	0/2	42/43	42/45
SRR (%) [d] (95% CI [e])	0 (0.0, 84.2)	97.7 (87.7, 99.9)	93.3 (81.7, 98.6)
Day 57			
n [a]	2	44	46
GMC (95% CI [b])	2278.4 (0.2, 26999485.4)	7753.6 (5946.3, 10110.3)	7351.5 (5621.7, 9613.7)
N1	2	44	46
GMFR (95% CI [b])	40.4 (0.0, 1052974.2)	22.9 (15.4, 34.1)	23.5 (16.0, 34.5)
SRR (n/N1)	2/2	40/44	42/46
SRR (%) [d] (95% CI [e])	100 (15.8, 100.0)	90.9 (78.3, 97.5)	91.3 (79.2, 97.6)

Abbreviations: CI = confidence interval; GMC = geometric mean concentration; GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; ULOQ = upper limit of quantification.
N1 = Number of participants with nonmissing data at Baseline and the corresponding timepoint.
Antibody: VAC62 Neutralizing Antibody (LLOQ: 10, ULOQ: 111433)
Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available.
a. Number of participants with nonmissing data at the corresponding timepoint.
b. 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMC and GMFR, respectively, then back transformed to the original scale for presentation.
c. Percentages were based on n[a].
d. Number of participants meeting the criterion at the timepoint. Percentages were based on N1.
e. 95% CI was calculated using the Clopper-Pearson method.
Source: Table 14.2.3.1.7.1.

3.1.4. Long term persistence – 1C-1, Part 3

In participants who received a 50-µg dose of mRNA-1273 BD after receiving 2-dose 100 µg mRNA-1273 primary series, the overall nAb response at 28 days after BD was approximately 690-fold higher than pre-Dose 1 and 14-fold higher than BD-Day 1 GMC (BD-Day 29 GMC=7790.2 [95% CI: 7208.7, 8418.5]). The nAb GMCs decreased over time from BD-Day 29 levels, but BD-Day 361 values (GMC=4737.1 [95% CI: 4202.0, 5340.3]) were approximately 426-fold higher than pre-Dose 1 and 9-fold higher than BD-Day 1 values.

Table 9: Summary of Pseudovirus Neutralising Antibody Values (VAC62) from Pre-Dose 1 and Pre-booster SARS-CoV-2 Status Per-Protocol Immunogenicity Subset (Part 1C-1 Homologous Booster)) (source: Table 20, CSR)

Timepoint	P203 mRNA-1273 Prebooster SARS-CoV-2 Status		
Data Category Statistic	Negative (N=267)	Positive (N=51)	Overall (N=331)
Baseline (Pre-Dose 1)			
n [a]	267	51	331
GMC (95% CI [b])	11.2 (10.6, 11.9)	11.1 (9.5, 13.0)	11.3 (10.7, 11.9)
Number of participants <LLOQ, n (%) [c]	56 (21.0)	13 (25.5)	70 (21.1)
Number of participants ≥LLOQ, n (%) [c]	211 (79.0)	38 (74.5)	261 (78.9)
BD-Day 1 (Prebooster)			
n [a]	264	51	327
GMC (95% CI [b])	398.5 (368.7, 430.6)	2885.6 (1878.2, 4433.4)	540.3 (479.0, 609.5)
Number of participants <LLOQ, n (%)[c]	0	0	0
Number of participants ≥LLOQ, n (%)[c]	264 (100)	51 (100)	327 (100)
N1	264	51	327
GMFR (95% CI [b])	35.3 (32.1, 38.8)	260.2 (160.1, 422.9)	47.7 (41.8, 54.6)
BD-Day 29			
n [a]	267	51	331
GMC (95% CI [b])	7130.2 (6577.8, 7729.1)	13456.8 (11061.8, 16370.5)	7790.2 (7208.7, 8418.5)
N1	267	51	331
GMFR (95% CI [b]) from pre-Dose 1	635.6 (576.2, 701.1)	1213.5 (918.3, 1603.5)	689.8 (627.3, 758.5)
N2	264	51	327
GMFR (95% CI [b]) from BD-Day 1	17.9 (16.2, 19.7)	4.7 (3.3, 6.6)	14.4 (12.9, 16.1)
BD-Day 181			
n [a]	239	49	301
GMC (95% CI [b])	4215.4 (3723.1, 4772.9)	5827.9 (4784.2, 7099.3)	4428.9 (3978.3, 4930.5)
N1	239	49	301
GMFR (95% CI [b]) from pre-Dose 1	376.6 (327.3, 433.2)	529.6 (396.2, 708.0)	393.0 (347.2, 444.9)
N2	237	49	298
GMFR (95% CI [b]) from BD-Day 1	10.4 (9.1, 12.0)	1.9 (1.2, 3.0)	7.9 (6.8, 9.2)
BD-Day 361			
n [a]	153	31	193
GMC (95% CI [b])	5062.5 (4412.3, 5808.6)	3827.3 (2956.6, 4954.5)	4737.1 (4202.0, 5340.3)
N1	153	31	193
GMFR (95% CI [b]) from pre-Dose 1	455.7 (390.1, 532.3)	356.7 (257.8, 493.5)	425.6 (371.1, 488.1)
N2	151	31	190
GMFR (95% CI [b]) from BD-Day 1	13.0 (11.0, 15.4)	1.3 (0.7, 2.3)	8.8 (7.2, 10.8)

Abbreviations: BD = booster dose; CI = confidence interval; GMC = geometric mean concentration; GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.
N1 = Number of participants with nonmissing data at pre-Dose 1 Baseline and the corresponding post-Baseline timepoint.
N2 = Number of participants with nonmissing data at pre-BD-Day 1 Baseline and the corresponding post-Baseline timepoint.
Antibody: VAC62 Neutralizing Antibody (LLOQ: 10, ULOQ: 111433).
Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values greater than the ULOQ were replaced by the ULOQ if actual values were not available.
a. Number of participants with nonmissing data at the corresponding timepoint.
b. 95% CI was calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMC and GMFR, respectively, then back transformed to the original scale for presentation.
c. Percentages were based on n[a].
Source: Table 14.2.3.1.5.1.1 and Table 14.2.3.1.5.1.2.

Persistence of nABs over 150 days was also shown for the bivalent vaccine in study Part 3 against the Ancestral strain as well as the bivalent strain.

At Baseline, the nAb GMC against Omicron BA.4/BA.5 for the PPIS-POS was 149.8 (95% CI: 136.9, 163.8). At Day 29 (28 days after Dose 1 of 50 µg mRNA-1273.222), the nAb GMC increased to approximately18-fold higher than Baseline GMC (GMC=2727.8 [95% CI: 2516.8, 2956.6]). At Day 181, the nAb GMC decreased compared with Day 29 level, but was 5-fold higher (GMFR=5.0 [95% CI: 4.5, 5.5]) than Baseline GMC (GMC=732.7 [95% CI: 677.4, 792.5]) . The SRR against Omicron BA.4/BA.5 at Day 181 was 45.4% (95% CI: 40.1, 50.7).

At Baseline, the nAb GMC against Ancestral strain for the PPIS-POS was 545.9 (95% CI: 486.5, 612.7). At Day 29, the nAb GMC increased to approximately 14-fold higher than Baseline GMC (GMC=7603.9 [95% CI: 7022.7, 8233.3]). At Day 181, the nAb GMC decreased compared with Day 29, but was 3.2-fold higher (GMFR=3.2 [95% CI: 3.0, 3.5]) than Baseline GMC (GMC=1753.2 [95% CI: 1588.4, 1935.1]). The SRR against Ancestral strain was 33.1% (95% CI: 28.3, 38.3).

3.2. COVID-19 infection – 1C-1, Part3

1C-1:

Of the 688 participants, 449 (65.3%) participants had SARS-CoV-2 infection with onset 14 days after the BD. The incidence rate per 1,000 person-months (95% CI) was 85.734 (77.986, 94.043). 367 (53.3%) participants had asymptomatic SARS-CoV-2 infection with onset 14 days after the BD. The incidence rate per 1,000 person-months (95% CI) was 69.937 (62.964, 77.471).

Of the 688 participants, 61 (8.9%) participants had COVID-19 with onset 14 days after the BD. The incidence rate per 1,000 person-months (95% CI) was 8.396 (6.422, 10.785). Based on the CDC case definition, of the 688 participants, 82 (11.9%) participants had COVID-19 with onset 14 days after the BD . The incidence rate per 1,000 person-months (95% CI) was 11.593 (9.220, 14.390).

Using the P301 COVID-19 case definition, the rate of COVID-19 among booster participants (0 cases/1,000 person-months) was lower than the rate among nonbooster participants (92.295 cases/1,000 person-months. Lower rates in booster participants were also observed in this time period using the CDC COVID-19 case definition (15.657 cases/1,000 person-months among booster participants vs 124.010 cases/1,000 person-months among nonbooster participants). Beyond Jan 2022, there was a rapid decrease in the size of the nonbooster group due to these participants either receiving a BD or discontinuing the study or developing COVID-19, which further constrained incidence comparisons beyond Jan 2022.

Part 3:

The incidence rate of COVID-19 starting 14 days after Dose 1 of 50 µg mRNA-1273.222 in Study P203 Part 3 was analysed as an exploratory endpoint in the FAS as a single-arm. Of the 388 participants, 3 participants had COVID-19 with onset 14 days after the first injection but before or on the day of the second injection. The incidence rate per 1,000 Person-Years (95% CI) was 17.899 (3.691, 52.307). Results were identical to those based on the COVID-19 P301 case definition.

3.3. Discussion

The data presented here show that a booster dose with 50µg increases GMCs reliably by 14-18- fold increase for antibodies directed against the vaccine strain as well as against the ancestral strain. GMCs were higher with higher baseline concentrations, as it would be expected.

Over the following 150 days antibody concentrations decline to about 50% but still remain at a high level. Over the next 150 days there is no significant further decline seen. Whether this is also attributable to natural boosters or GMCs just reach a plateau is unknown.

After the two-dose priming with 50µg GMCs increase with each dose, as expected. Further conclusions seem unwarranted as the sample size of 46 is very small.

For the bivalent vaccine the prespecified success criteria for the primary immunogenicity objective were met, thus enabling the inference of vaccine effectiveness of a single 50 µg dose of mRNA-1273.222 in previously unvaccinated adolescents in Study 203 Part 3 from that observed in Study P301.

With the strain-adapted bivalent vaccine persistence of antibodies is also shown reliably over 180 days post vaccination. After the D29 datapoint antibodies decline but remain 5-fold (Omicron) or 3-fold (Ancestral) higher than at baseline.

3.4. Safety data

For Parts 1A and 1B, updated long-term safety data regarding unsolicited reactions are summarised (Table 10), and for Part 1C-1, updated cumulative long-term safety data regarding unsolicited reactions are presented in this CSR (Table 11). For Parts 1C-2 and 2 and 3, solicited ARs and unsolicited AE data are also presented below.

Table 10: Summary of Unsolicited TEAE by Age Group in Long-term Analysis Safety Set for primary dose (Long-term Analysis) (source: Table 23, CSR)

	Placebo-mRNA-1273 (N=96) n (%)	mRNA-1273 (N=2486) n (%)	Total (N=2582) n (%)
Unsolicited TEAEs related to study intervention			
All	7 (7.3)	378 (15.2)	385 (14.9)
Serious	0	0	0
Fatal	0	0	0
Medically attended	2 (2.1)	28 (1.1)	30 (1.2)
Leading to discontinuation from study intervention	0	1 (<0.1)	1 (<0.1)
Leading to discontinuation from participation in the study	0	0	0
Grade 3/severe	0	14 (0.6)	14 (0.5)
Grade 3 or higher	0	14 (0.6)	14 (0.5)
Non-serious [a]	7 (7.3)	378 (15.2)	385 (14.9)
Grade 3/severe	0	14 (0.6)	14 (0.5)
Grade 3 or higher	0	14 (0.6)	14 (0.5)
At least 1 non-serious [b]	7 (7.3)	378 (15.2)	385 (14.9)
Grade 3/severe	0	14 (0.6)	14 (0.5)
Grade 3 or higher	0	14 (0.6)	14 (0.5)
AESI	0	0	0
MIS-C	0	0	0
Other	0	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BD = booster dose; MIS-C = multisystem inflammatory syndrome in children; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

A TEAE was defined as any event not present before exposure to intervention or any event already present that worsened in intensity or frequency after exposure.

For placebo-mRNA-1273 group, only AEs occurring after the crossover mRNA-1273 first dose and before BD if applicable are included; for mRNA-1273 group, any AEs occurring after mRNA-1273 first dose and before BD if applicable are included.

Percentages were based on the number of participants in the Safety Set (Long-term Analysis).

a. Participants without any SAE and with any non-serious TEAE.

b. Participants with at least one non-serious TEAE regardless of reporting any SAE or not.

c. A participant in the placebo-mRNA-1273 group discontinued study intervention after Dose 1 because of an AE. This discontinuation was not included in Table 14.3.1.7.4.1 due to a data entry error.

Source: Table 14.3.1.7.4.1

Table 11: Summary of Unsolicited TEAE After Booster Dose (Part 1C-1 Safety Set) (source: Table 24, CSR)

	Placebo-mRNA-1273-Booster (N=51) n (%)	mRNA-1273-Booster (N=1357) n (%)	Total (N=1408) n (%)
Unsolicited TEAEs related to study intervention			
All	2 (3.9)	64 (4.7)	66 (4.7)
Serious	0	0	0
Fatal	0	0	0
Medically attended	0	4 (0.3)	4 (0.3)
Leading to discontinuation from study intervention	0	0	0
Leading to discontinuation from participation in the study	0	0	0
Grade 3/severe	1 (2.0)	3 (0.2)	4 (0.3)
Grade 3 or higher	1 (2.0)	3 (0.2)	4 (0.3)
Non-serious [a]	2 (3.9)	64 (4.7)	66 (4.7)
Grade 3/severe	1 (2.0)	3 (0.2)	4 (0.3)
Grade 3 or higher	1 (2.0)	3 (0.2)	4 (0.3)
At least 1 non-serious [b]	2 (3.9)	64 (4.7)	66 (4.7)
Grade 3/severe	1 (2.0)	3 (0.2)	4 (0.3)
Grade 3 or higher	1 (2.0)	3 (0.2)	4 (0.3)
AESI	0	1 (<0.1)	1 (<0.1)
MIS-C	0	0	0
Other	0	1 (<0.1)	1 (<0.1)

Abbreviations: AESI = adverse event of special interest; MIS-C = multisystem inflammatory syndrome in children; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
A TEAE was defined as any event not present before exposure to intervention or any event already present that worsened in intensity or frequency after exposure.
Percentages were based on the number of safety participants in Part 1C-1.
a. Participants without any SAE and with any non-serious TEAE.
b. Participants with at least one non-serious TEAE regardless of reporting any SAE or not.
Source: Table 14.3.1.7.5.2.1.

The only adverse event of special interest (AESI) considered related to study intervention was urticaria which occurred in 1 participant who developed ascending swelling of legs, hands, then face with associated itching 15 days after BD. The participant was evaluated by an allergist who felt the urticaria was most likely related to the study intervention. The participant was treated with diphenhydramine and ibuprofen. The event was resolved on relative Day 40 after BD. There were no cases of myocarditis or pericarditis reported and review of cases within the Cardiomyopathy Standardised MedDRA Queries (SMQ) were not suggestive of events of myocarditis or pericarditis. There were no reports of anaphylaxis.

Solicited adverse reactions of 1C-2

Within 7 days after the BD, solicited local ARs were reported by 89/124 (71.8%) participants and solicited systemic ARs were reported by 82/120 (68.3%) participants. The most frequently reported (>20% participants) solicited ARs included:

- Pain: 88/124 (71.0%) participants
- Headache: 59/119 (49.6%) participants
- Fatigue: 59/119 (49.6%) participants
- Myalgia: 48/119 (40.3%) participants
- Axillary swelling or tenderness: 37/117 (31.6%) participants
- Chills: 37/119 (31.1%) participants
- Arthralgia: 28/118 (23.7%) participants

The majority of local and systemic solicited ARs after the BD were Grade 1 or Grade 2 in severity. Grade 3 solicited local ARs were reported by 6/124 (4.8%) participants; pain (5/124 [4.0%] participants) was the most frequently reported Grade 3 solicited local AR. Grade 3 solicited systemic ARs were reported by 7/120 (5.8%) participants; fatigue (6/119 [5.0%] participants) was the most frequently reported Grade 3 solicited systemic AR. No Grade 4 solicited ARs were reported.

Unsolicited adverse reactions of 1C-2

Up to 18 days after the BP, unsolicited AE were reported for 19/155 (12.3%) participants. Only 4 unsolicited adverse events were considered related to the study intervention: all of the non-serious: 1 event each of dizziness, urticaria and arthralgia and 2 events of fatigue. No AESIs were reported as related up to 28 days after the BD.

Solicited Adverse Reactions of Part 2

Within 7 days **after Dose 1**, solicited local ARs were reported by 35/52 (67.3%) participants and solicited systemic ARs were reported by 38/52 (73.1%) participants. The most frequently reported (>20% participants) solicited ARs included:

- Pain: 35/52 (67.3%) participants
- Headache: 25/52 (48.1%) participants
- Myalgia: 21/52 (41.2%) participants
- Fatigue: 17/52 (32.7%) participants
- Arthralgia: 16/52 (31.4%) participants

The majority of local and systemic solicited ARs after Dose 1 were Grade 1 or Grade 2 in severity. No Grade 3 solicited local ARs were reported. Grade 3 solicited systemic ARs of fever, fatigue, myalgia, nausea/vomiting, and chills were reported by 1 participant. No Grade 4 solicited ARs were reported.

Within 7 days **after Dose 2**, solicited local ARs were reported by 27/46 (58.7%) participants and solicited systemic ARs were reported by 19/46 (41.3%) participants. The most frequently reported (>20% participants) solicited ARs included:

- Pain: 25/46 (54.3%) participants
- Fatigue: 14/46 (30.4%) participants
- Headache: 13/46 (28.3%) participants

The majority of local and systemic solicited ARs after Dose 2 were Grade 1 or Grade 2 in severity. Grade 3 solicited local ARs were reported by 2/46 (4.3%) participants – pain and erythema. Grade 3 solicited systemic ARs were reported by 2/46 (4.3%) participants – headache and fatigue. No Grade 4 solicited ARs were reported.

Within 7 days **after the BD**, solicited local ARs were reported by 8/19 (42.1%) participants and solicited systemic ARs were reported by 2/19 (10.5%) participants. The most frequently reported (>20% participants) solicited AR was pain in 8/19 (42.1%) participants. All solicited local SARs after the BD were Grade 1 in severity. All systemic SARs after the BD, except for a Grade 3 solicited systemic AR of fatigue, were Grade 1 or Grade 2 in severity.

Unsolicited ARs in Part 2

Two (3.8%) participants experienced unsolicited non-serious AEs assessed as related to study intervention by the Investigator – headache in 1 participant and injection site lymphadenopathy in 1 participant.

No SAEs, AESIs, or AEs leading to discontinuation from study intervention or study participation were reported throughout Part 2 **up until the BD**.

No severe AEs, SAEs, AESIs, AEs were assessed as related to study intervention by the Investigator or AEs leading to discontinuation from study participation were reported throughout Part 2 **after the BD**.

Part 3

Following an interim analysis of available Study P203 Part 3 data and authorization of the single dose regimen in the US, the protocol was amended (PA7) to discontinue administration of Dose 2 in the US. However, given that the single dose regimen had not been authorised in the DR, participants in the DR continued to receive 2 doses under the previous protocol amendment.

After Dose 1, participants were followed for a median of 351 days (range 4 to 419 days). After Dose 2, those participants who received a second injection were followed for a median of 170 days (range: 79 to 234 days).

Within 7 days after Dose 1, solicited local ARs were reported by 171/387 (44.2%) participants and solicited systemic ARs were reported by 153/387 (39.5%) participants. The most frequently reported (>20% participants) solicited ARs after Dose 1 included:

- Pain: 162/387 (41.9%) participants
- Headache: 105/386 (27.2%) participants

The majority of local and systemic SARs after Dose 1 were Grade 1 or Grade 2 in severity. Grade 3 solicited local ARs were reported by 10/387 (2.6%) participants; injection site erythema (6 [1.6%] participants) was the most frequently reported Grade 3 solicited local AR. There were no Grade 4 solicited local ARs reported.

Grade 3 solicited systemic ARs were reported by 16/387 (4.1%) participants; fever was the most frequently reported Grade 3 solicited systemic AR (10/387 [2.6%] participants). A Grade 4 solicited systemic AR of fever was reported by 1/387 (0.3%) participant. The participant reported temperature of 40.5°C (Grade 4 fever) on Day 5 and had a concurrent AE of lower respiratory tract infection. After Dose 1, 77/387 (19.9%) participants reported taking medication for pain or fever. Most reported use of medication to treat pain or fever (66/387 [17.1%] participants) compared to 21/387 (5.4%) participants who reported use of medication to prevent pain or fever.

One (0.3%) participant reported an unsolicited AE (a non-serious MAAE) that was assessed as related to study intervention by the Investigator.

SAEs were reported for 2 (0.5%) participants. Both SAEs were severe and were assessed as not related to study intervention by the Investigator. **There were no deaths, no AESIs, including cases of myocarditis, pericarditis, or multisystem inflammatory syndrome in children (MIS-C) reported within 28 days after Dose 1**. No participants discontinued from study intervention or study participation due to an AE.

Within 7 days **after Dose 2**, solicited local ARs were reported by 205/334 (61.4%) participants and solicited systemic ARs were reported by 155/334 (46.4%) participants. The most frequently reported (>20% participants) solicited ARs after Dose 2 included:

- Pain: 196/334 (58.7%) participants
- Headache: 96/334 (28.7%) participants

The majority of local and systemic SARs after Dose 2 were Grade 1 or Grade 2 in severity. Grade 3 solicited local ARs were reported by 19/334 (5.7%) participants; pain (9 [2.7%] participants) was the most frequently reported Grade 3 solicited local AR. Grade 3 solicited systemic ARs were reported by 32/334 (9.6%) participants; fever (17/333 [5.1%] participants) was the most frequently reported Grade 3 solicited systemic AR. There were no Grade 4 solicited local or systemic SARs reported after Dose 2. After Dose 2, 75/334 (22.5%) participants reported taking medication for pain or fever. Most reported use of medication to treat pain or fever (66/334 [19.8%] participants) compared to 18/334 (5.4%) participants who reported use of medication to prevent pain or fever.

One (0.3%) participant reported an unsolicited AE (a non-serious MAAE) that was assessed as related to study intervention by the Investigator**. There were no deaths, no SAEs, and no AESIs reported within 28 days after Dose 2.** No participants discontinued from study intervention or study participation due to an unsolicited AE.

3.5. Discussion

No safety issues are reported regardless of the number of doses or antigen strain. The safety profile of the vaccine is unchanged.