25 July 2024
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Spikevax

COVID-19 mRNA vaccine

Procedure no: EMEA/H/C/005791/P46/136

Note

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

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Status of this report and steps taken for the assessment				
PAM number				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	27/05/2024	27/05/2024	☐
☐	Rapporteur's preliminary Assessment Report	01/07/2024	08/07/2024	☐
☐	CHMP Members comments:	15/07/2024	18/07/2024	☐
☐	Updated Rapporteur's Assessment Report	18/07/2024	19/07/2024	☐
☒	CHMP adoption of conclusions:	25/07/2024	25/07/2024	☐

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration (score)
AR	adverse reaction
bAb	binding antibody
CDC	US Centers for Disease Control and Prevention
CEAC	Clinical Events Adjudication Committee
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMQ	customized MedDRA query
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTPA	computed tomography pulmonary angiogram
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
EOS	end of study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLSM	geometric least square mean
GMC	geometric mean concentration
GMFR	geometric mean fold-rise
GMR	geometric mean ratio
ICF	informed consent form
ICH	International Council for Harmonisation
ICD	implantable cardio-defibrillator
IEC	International Agency for Research on Cancer Ethics Committee
IRT	interactive response technology
IR	incidence rate
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LTFU	lost to follow-up
MAAE	medically attended adverse event
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
min	minimum
mITT	Modified Intent-to-Treat
MMRM	mixed effects model repeated measure
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
n	number of participants

nAb	neutralizing antibody
NP	nasopharyngeal
PCR	polymerase chain reaction
PPSE	Per-Protocol Set for Efficacy
PPSI	Per-Protocol Set for Immunogenicity
PT	preferred term
RBD	receptor-binding domain
RT-PCR	reverse transcription polymerase chain reaction
S	spike
S-2P	prefusion stabilized spike glycoprotein

1. Introduction

On 19 April 2024, the MAH submitted a completed paediatric study for mRNA-1273- P305, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1 Information on the development program

The MAH stated that Phase 2/3, Randomized, Observer-Blind, Active-Controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine (mRNA-1273- P305) is a stand-alone study.

2.2 Information on the pharmaceutical formulation used in the study

Omicron BA.1 monovalent vaccine, bivalent vaccine (original and Omicron BA.1), and mRNA-1273 (the active comparator) were administered as a single injection into the deltoid muscle on Day 1.

Vaccination	Dosage Level	Route of Administration	Physical Description	Lot Numbers
Part 1				
mRNA-1273.529 (Omicron BA.1 monovalent vaccine)	50 µg	Intramuscular	Sterile liquid for injection, white-to-off-white dispersion	8523100101 8523100102
mRNA-1273	50 µg			000074A, 000075A, 000076A, 000081A, 000084A, 000088A
Part 2				
mRNA-1273.214 (bivalent vaccine [original and Omicron BA.1])	50 µg	Intramuscular	Sterile liquid for injection, white-to-off-white dispersion	8523400101 8523400102
mRNA-1273	50 µg			000074A, 000075A, 000076A, 000081A, 000084A, 000088A

2.3 Clinical aspects

2.3.1 Introduction

The MAH submitted a final report for:

- Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine (mRNA-1273- P305).

2.3.2 Clinical study

Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine (mRNA-1273- P305)

Description

This was a Phase 2/3, 2-part, randomized, observer-blind, active-controlled, multicentre study to evaluate the immunogenicity and safety of the Omicron BA.1 monovalent vaccine, bivalent vaccine (original and Omicron BA.1), and the original mRNA-1273 vaccine in medically stable individuals 16 years and older.

Methods

Study design

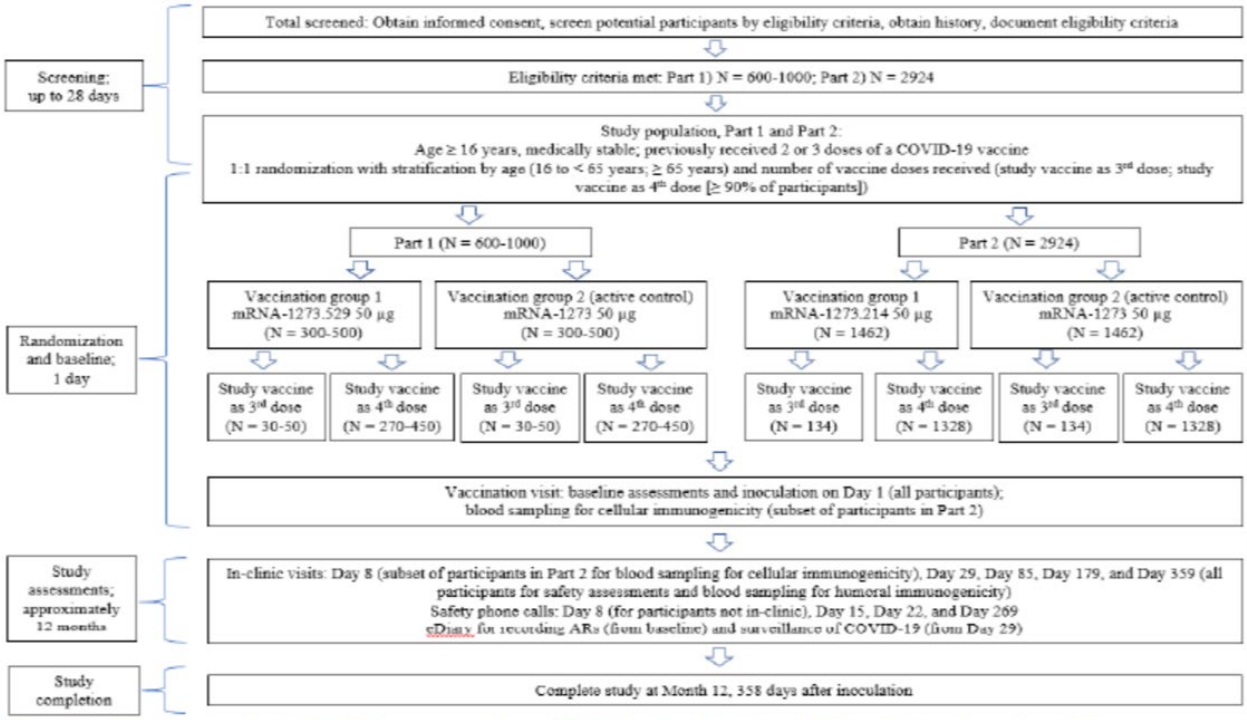
The study consisted of 2 parts each with 2 phases. Both Part 1 and Part 2 had a randomized blinded phase (Phase A) and an exploratory open-label observational phase (Phase B).

In Part 1, participants were randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 µg of the Omicron BA.1 monovalent vaccine or 50 µg of mRNA-1273 (active control).

In Part 2, participants were randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 µg of the bivalent vaccine (original and Omicron BA.1) or 50 µg of mRNA-1273 (active control).

Randomization in Part 1 and Part 2 was stratified by age groups (16 to <65 years or ≥65 years) and number of COVID-19 vaccine doses received (study vaccine received as either the fourth dose or third dose). At least 90% of participants received the study vaccine as the fourth dose.

Figure 1: Study Schema



Abbreviations: AR = adverse reaction; COVID-19 = coronavirus disease 2019; CSR = clinical study report; eDiary = electronic diary; N = number.
Note: The mRNA-1273.529 study vaccine is referred to as the "Omicron BA.1 monovalent vaccine" and the mRNA-1273.214 study vaccine is referred to as the "bivalent vaccine (original and Omicron BA.1)" in this CSR.

Following the randomized blinded phase (Phase A), the study transitioned to the open-label observational phase (Phase B). Phase B was designed to offer eligible participants in either vaccine arm the option to receive an additional COVID-19 vaccine outside of the study (as part of the 2022 autumn COVID-19 vaccination campaign) after their Month 6 assessment in Part 1 and after their Day 85 assessment in Part 2.

All participants had previously received 2 or 3 doses of an authorized/approved COVID-19 vaccine. Participants who had previously received 2 doses of a COVID-19 vaccine as a primary series received Omicron BA.1 monovalent vaccine, bivalent vaccine (original and Omicron BA.1), or mRNA-1273 as the third dose. Participants who had previously received a primary series and 1 study vaccine dose received the Omicron BA.1 monovalent vaccine, bivalent vaccine (original and Omicron BA.1), or mRNA-1273 as the fourth dose.

Participants who received the fourth dose as part of the study should have previously received a mRNA vaccine as the third dose of a COVID-19 vaccine. Participants who received the third dose as part of the study could have previously received 2 doses of a mRNA or a non-mRNA COVID-19 vaccine (a mixed approach was acceptable).

Study visits consisted of a Screening Visit (up to 28 days before the Day 1 visit or on Day 1), Vaccination Visit at Day 1, and subsequent study visits on Day 8 (for a subset of participants in Part 2), Day 29 (Month 1), Day 85, Day 179 (Month 6), and Day 359 (Month 12), with up to 13 months of study participation. Unscheduled visits for potential symptoms of COVID-19 included PCR testing. The EOS was defined as completion of the last visit of the last participant in each part of the study or last scheduled procedure for the last participant, as shown in the SoE of the mRNA-1273-P305 Clinical Study Protocol.

Discussion of Study Design

The scientific rationale for features of the study design, including chosen control groups, doses, and endpoints, as applicable, are discussed in the designated sections of the protocol provided in Appendix 16.1.1 (Scientific Rationale for Study Design and Justification for Dose and Control Product; not included in this AR).

Changes in Study Conduct

The original protocol was dated 26 Jan 2022, and there were 2 protocol amendments. Protocol Amendment 2 (26 Aug 2022) was used for this CSR. Changes in the conduct of the study that were implemented by protocol amendments are provided in Appendix 16.1.1 (not included in this AR). Substantial changes in the conduct of the study are described below.

Amendment 1 (03 Mar 2022)

The main rationale for this amendment was to modify the study design to include 2 parts: Part 1) Omicron BA.1 monovalent vaccine with a reduced sample size, and Part 2) Bivalent vaccine (original and Omicron BA.1) with a similar study design to Part 1.

Amendment 2 (26 Aug 2022)

Following authorization of the bivalent vaccine (original and Omicron BA.1) in the United Kingdom, this amendment incorporated an optional unblinding for participants who were eligible to receive an additional COVID-19 vaccination outside of the study.

Study participants

Inclusion Criteria

Each participant was to have met all of the following criteria to be enrolled in this study.

1. Male or female, at least 16 years of age at the time of consent (Screening Visit).
2. Investigator's assessment that the participant understood and was willing and physically able to comply with protocol-mandated follow-up, including all procedures.
3. Participant provided written informed consent for participation in this study, including all evaluations and procedures as specified in the mRNA-1273-P305 Clinical Study Protocol (Appendix 16.1.1).
4. Female participants of non-childbearing potential could be enrolled in the study. Non-childbearing potential was defined as postmenopausal or permanently sterilized. Levels of FSH were measured at the discretion of the Investigator to confirm postmenopausal status, if necessary.
5. Female participants of childbearing potential could have been enrolled in the study if the participant fulfilled all the following criteria:
    a. A negative pregnancy test at the Screening Visit and on the day of vaccination prior to vaccine dose being administered on Day 1.
    b. Practiced adequate contraception or had abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose (Day 1). Adequate female contraception was defined as consistent and correct use of a local health authority approved contraceptive method in accordance with the product label.
    c. Agreed to continue adequate contraception through 90 days following vaccine administration.
6. Received 2 prior doses of one of the following approved/authorized COVID-19 vaccines: Moderna, Pfizer/BioNTech, Oxford/AstraZeneca, Janssen. A heterologous vaccine regimen was acceptable.
7. Participants who received the fourth dose as part of the study must have previously received a mRNA vaccine (Moderna or Pfizer/BioNTech) as the third dose of a COVID-19 vaccine. Participants who received the third dose as part of the study could have previously received 2 doses of an approved/authorized mRNA or a non-mRNA COVID-19 vaccine (a heterologous vaccine regimen was acceptable).

Exclusion Criteria

Participants who met any of the following criteria, unless noted otherwise, were excluded from the study.

1. Had close contact (without personal protective equipment) as defined by the CDC in the past 14 days to someone diagnosed with SARS-CoV-2 infection or COVID-19 within 10 days of the close contact. Participants could have been rescreened after 14 days provided that they remain asymptomatic.

2. Participant was acutely ill or febrile (temperature ≥38.0° C/100.4° F) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion could have been rescheduled within the 28-day screening window and retained their initially assigned participant number.
3. Tested positive for SARS-CoV-2 by an authorized/approved lateral flow/rapid antigen or PCR test within 90 days of screening.
4. Received a COVID-19 vaccine within 90 days of the Screening Visit.
5. Received a total of 4 doses or more of COVID-19 vaccine.
6. Received a COVID-19 vaccine at a dose different from the authorized/approved dose.
7. History of a diagnosis or condition that, in the judgment of the Investigator, was clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable was defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to screening and included ongoing work-up of an undiagnosed illness that could lead to a new diagnosis or condition.
8. Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease requiring immunosuppressive treatment or other immunosuppressive condition.
9. Dermatologic conditions that could affect local solicited AR assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).
10. Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any components of mRNA vaccine.
11. Reported history of bleeding disorder that was considered a contraindication to intramuscular injection or phlebotomy.
12. Any medical, psychiatric, or occupational condition, including reported history of substance abuse, that, in the opinion of the Investigator, could pose additional risk due to participation in the study or could interfere with the interpretation of study results.
13. Received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 181 days prior to screening (for corticosteroids ≥10 mg/day of prednisone or equivalent) or was anticipating the need for immunosuppressive treatment at any time during participation in the study.
14. Received or planned to receive any licensed vaccine ≤28 days prior to the study injection (Day 1) or planned to receive a licensed vaccine within 28 days after the study injection (with the exception that approved seasonal influenza vaccine could be received by at least 7 days and preferably 14 days apart from the study injection).
15. Received systemic immunoglobulins or blood products within 90 days prior to the Screening Visit or planned to receive during the study.
16. Diagnosis of malignancy within the previous 10 years (excluding non-melanoma skin cancer).
17. Donated ≥450 mL of blood products within 28 days prior to the Screening Visit or planned to donate blood products during the study.
18. Participated in an interventional clinical study within 28 days prior to the Screening Visit based on the medical history interview or plans to do so while participating in this study.

19. Was an immediate family member or household member of study personnel, study site staff, or Sponsor personnel.

Assessor's comment:

The study aimed to enroll healthy participants at the age of 16 years or older. Immunocompromised participants were excluded.

Participant Discontinuation/Withdrawal From the Study

Participants who withdrew or were withdrawn from the study were not replaced. A "withdrawal" from the study referred to a situation wherein a participant did not return for the final visit planned in the protocol.

Participants could withdraw consent and withdraw from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive. The Investigator requested that the participant complete all study procedures pending at the time of withdrawal.

If a participant desired to withdraw from the study because of an AE, the Investigator attempted to obtain agreement to follow up with the participant until the event was considered resolved or stable and then completed the EOS eCRF.

Information related to the withdrawal was documented in the eCRF. The Investigator documented whether the decision to withdraw a participant from the study was made by the participant or by the Investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE (specify).
- SAE (specify).
- Solicited AR or reactogenicity event (specify).
- Death.
- Lost to follow-up.
- Physician decision (specify).
- Pregnancy.
- Protocol deviation.
- Study terminated by Sponsor.
- Withdrawal of consent by participant (specify).
- Other (specify).

Participants who were withdrawn from the study because of AEs (including SAEs, solicited ARs, or reactogenicity events) could be clearly distinguished from participants who were withdrawn for other reasons. Investigators followed up with participants who were withdrawn from the study as result of an AE, SAE, solicited AR, or reactogenicity event until resolution of the event.

A participant withdrawing from the study could request destruction of any samples taken and not tested, and the Investigator documented this in the site study records. Details regarding withdrawal of

consent for disclosure of future information are described in the mRNA-1273-P305 Clinical Study Protocol.

A participant was considered LTFU if he or she repeatedly failed to return for scheduled visits without stating an intention to withdraw consent and was unable to be contacted by the clinic. The sites pursued multiple follow-up actions if a participant failed to return to the study site for a required study visit.

Treatments

Omicron BA.1 monovalent vaccine, bivalent vaccine (original and Omicron BA.1), and mRNA-1273 (the active comparator) were administered as a single injection into the deltoid muscle on Day 1. The participants were observed closely (via clinical assessment including measurement of vital signs) for at least 15 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis or other hypersensitivity reactions. The study interventions in Part 1 and Part 2 of the study are outlined in section "Information on the pharmaceutical formulation used in the study" of this report.

mRNA-1273 is an LNP dispersion of an mRNA encoding the prefusion stabilized S-protein of SARS-CoV-2.

The Omicron BA.1 monovalent vaccine contains mRNA CX-031302 encoding for the S-2P of the SARS CoV-2 Omicron variant (Omicron BA.1). mRNA-1273 contains mRNA CX-024414 encoding for the S-2P of Wuhan-Hu-1.

The bivalent vaccine (original and Omicron BA.1) is a bivalent vaccine containing the Omicron BA.1 monovalent vaccine and mRNA-1273 co-formulated at a 1:1 ratio. The Omicron BA.1 monovalent vaccine, the bivalent vaccine (original and Omicron BA.1), and mRNA-1273 each consists of mRNAs formulated in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG 2000 DMG.

All study vaccines used in this study were prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or those of its designee, Code of Federal Regulations Title 21, Good Manufacturing Practice guidelines, ICH GCP Guidelines, guidelines for Quality System Regulations, and applicable regulations. The justification for the doses selected is described in the Justification for Dose section of the mRNA-1273-P305 Clinical Study Protocol.

Study Intervention Compliance

All vaccinations were administered by qualified and trained study personnel to ensure that all vaccine doses administered complied with those planned. Study vaccine doses administered were to be recorded in the eCRF. Administration data were reconciled with site accountability records to assess compliance.

Prior and Concomitant Medications and Therapies

Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) were recorded in the participant's eCRF.

Concomitant Medications and Therapies

At the study site, study staff questioned the participant regarding any concomitant medications taken and non-study vaccinations received by the participant and recorded the information in the eCRF. The information recorded for concomitant medications, non-study vaccination, and treatment medication is described in the mRNA-1273-P305 Clinical Study Protocol. Concomitant medications (including vaccinations) were coded using the WHO Drug Global.

Concomitant medications and/or vaccines that did not require withdrawal of the participant from the study but may have determined a participant's evaluability in the Per-Protocol analysis are listed in Appendix 16.1.1 (not included in this AR).

If a participant took a prohibited drug therapy, the Investigator and the CRO's Medical Monitor made a joint decision whether use of the medication compromised the participant's safety or interpretation of the data. The Investigator was responsible for ensuring that details regarding the concomitant medications were adequately recorded in the eCRF.

Objectives, endpoints

Table 1: Part 1: Omicron BA.1 Monovalent Vaccine and mRNA-1273

Objectives	Endpoints
Primary	
To demonstrate non-inferiority of the immune response of the Omicron BA.1 monovalent vaccine compared to mRNA-1273 booster administered as a fourth dose against the Omicron BA.1 strain at Day 29 or Day 85.	• Geometric mean concentrations (GMC) of Omicron BA.1 monovalent vaccine and mRNA-1273 against the Omicron BA.1 strain at Day 29 and Day 85 after study vaccine administration. • Ratio of $GMC_{\text{Omicron BA.1 monovalent vaccine}}$ /$GMC_{\text{mRNA-1273}}$ against the Omicron BA.1 strain at Day 29 and Day 85 after study vaccine administration.
To evaluate the safety and reactogenicity of the Omicron BA.1 monovalent vaccine and mRNA-1273 administered as a booster dose.	• Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after vaccination. • Unsolicited AEs during the 28-day follow-up period after vaccination. • SAEs, MAAEs, AEs leading to withdrawal, and AESIs from Day 1 to end of study.
Secondary	
Key Secondary	
To demonstrate superiority of the immune response of the Omicron BA.1 monovalent vaccine compared to mRNA-1273 administered as a fourth dose against the Omicron BA.1 strain at Day 29 or Day 85.	• GMC of Omicron BA.1 monovalent vaccine and mRNA-1273 against the Omicron BA.1 strain at Day 29 and Day 85 after study vaccine administration. • Ratio of $GMC_{\text{Omicron BA.1 monovalent vaccine}}$ /$GMC_{\text{mRNA-1273}}$ against the Omicron BA.1 strain at Day 29 and Day 85 after study vaccine administration.

Objectives	Endpoints
Other Secondary	
To demonstrate non-inferiority of the immune response of the Omicron BA.1 monovalent vaccine compared to mRNA-1273 booster administered as a fourth dose against both the Omicron BA.1 and the ancestral strain at all evaluable timepoints.	• GMC of Omicron BA.1 monovalent vaccine and mRNA-1273 against both the Omicron BA.1 and ancestral strains at all evaluable timepoints after study vaccine administration. • Ratio of $GMC_{\text{Omicron BA.1 monovalent vaccine}}$ /$GMC_{\text{mRNA-1273}}$ against both the Omicron BA.1 and ancestral strains at all evaluable timepoints after study vaccine administration.
To evaluate the SRR of the Omicron BA.1 monovalent vaccine and mRNA-1273 boosters administered as a fourth dose.	• SRR against the Omicron BA.1 strain. • SRR against the ancestral strain.
Exploratory Objectives	
To assess for symptomatic and asymptomatic SARS-CoV-2 infection after vaccination with the Omicron BA.1 monovalent vaccine booster or mRNA-1273 booster.	RT-PCR–confirmed symptomatic or asymptomatic SARS-CoV-2 infection were defined in participants based on the following criteria: • Protocol-defined COVID-19 case definition – The participant must have experienced at least 2 of the following systemic symptoms: fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), or – The participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath, or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND – The participant must have had at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. • CDC-defined COVID-19 definition based on the CDC criteria: presence of one of the CDC-listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and positive RT-PCR test on a respiratory sample. • Asymptomatic SARS-CoV-2 infection was defined as a positive RT-PCR test on a respiratory sample in the absence of symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test at time of enrollment.

Objectives	Endpoints
To evaluate the immunogenicity of the Omicron BA.1 monovalent vaccine booster against other variant strains.	• GMC of Omicron BA.1 monovalent vaccine against other variant strains (eg, Alpha, Beta, Delta) after study vaccine administration. • Ratio of $GMC_{\text{Omicron BA.1 monovalent vaccine}}$ /$GMC_{\text{mRNA-1273}}$ against other variant strains after study vaccine administration. • GMFR of Omicron BA.1 monovalent vaccine against other variant strains after study vaccine administration. • SRR against other variant strains.
To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.	• Characterize the SARS-CoV-2 spike genetic sequence of viral isolates and compare with the vaccine sequence. • Characterize the immune responses to vaccine breakthrough isolates.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; MAAE = medically attended adverse event; NP = nasopharyngeal; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

Note: "B.1.1.529" is referred to as "Omicron BA.1." The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

Table 2: Part 2: The Bivalent Vaccine (Original and Omicron BA.1) and mRNA-1273

Objectives	Endpoints
Primary	
To demonstrate non-inferiority of the immune response of the bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 booster administered as a fourth dose against the Omicron BA.1 strain at Day 29 or Day 85.	• GMC of the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 against the Omicron BA.1 strain at Day 29 or Day 85 after study vaccine administration. • Ratio of $GMC_{\text{bivalent vaccine (original and Omicron BA.1)}}$/$GMC_{\text{mRNA-1273}}$ against the Omicron BA.1 strain at Day 29 or Day 85 after study vaccine administration.
To demonstrate non-inferiority of the immune response of the bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 booster administered as a fourth dose against the ancestral strain at Day 29 or Day 85.	• GMC of the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 against the ancestral strain at Day 29 or Day 85 after study vaccine administration. • Ratio of $GMC_{\text{bivalent vaccine (original and Omicron BA.1)}}$/$GMC_{\text{mRNA-1273}}$ against the ancestral strain at Day 29 or Day 85 after study vaccine administration.
To demonstrate superiority of the immune response of the bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 booster administered as a fourth	• GMC of the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 against the Omicron BA.1 strain at Day 29 or Day 85 after study vaccine administration.

Objectives	Endpoints
dose against the Omicron BA.1 strain at Day 29 or Day 85.	• Ratio of GMC $_{\text{bivalent vaccine (original and Omicron BA.1)}}$/GMC$_{\text{mRNA-1273}}$ against the Omicron BA.1 strain at Day 29 or Day 85 after study vaccine administration.
To evaluate the safety and reactogenicity of the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 administered as a booster dose.	• Solicited local and systemic reactogenicity ARs during a 7-day follow-up period after vaccination. • Unsolicited AEs during the 28-day follow-up period after vaccination. • SAEs, MAAEs, AEs leading to withdrawal, and AESIs from Day 1 to end of study.
Secondary	
To evaluate the SRR of the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 boosters administered as a fourth dose.	• SRR against the Omicron BA.1 strain. • SRR against the ancestral strain.
To evaluate the immune response of the bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 booster administered as a fourth dose against other variant strains at Day 29 or Day 85.	• GMC of the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 against other variant strains at Day 29 or Day 85. • Ratio of GMC $_{\text{bivalent vaccine (original and Omicron BA.1)}}$/GMC$_{\text{mRNA-1273}}$ against other variant strains at Day 29 or Day 85. • SRR against other variant strains.
To assess for symptomatic and asymptomatic SARS-CoV-2 infection after vaccination with the bivalent vaccine (original and Omicron BA.1) booster or mRNA-1273 booster.	RT-PCR-confirmed symptomatic or asymptomatic SARS-CoV-2 infection was defined in participants based on the following criteria: • Protocol-defined COVID-19 case definition – The participant must have experienced at least 2 of the following systemic symptoms: fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR – The participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath, or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND – The participant must have at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. • CDC-defined COVID-19 definition based on the CDC criteria: the presence of one of the CDC listed symptoms (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and a positive RT-PCR test on a respiratory sample. • Asymptomatic SARS-CoV-2 infection was defined as a positive RT-PCR test on a respiratory sample in the absence

Objectives	Endpoints
	of symptoms or a positive serologic test for anti-nucleocapsid antibody after a negative test at time of enrollment.
Exploratory Objectives	
To evaluate cellular immunogenicity in a subset of participants.	• Frequency, magnitude, and phenotype of virus-specific T-cell and B-cell responses measured by flow cytometry or other methods, and to perform targeted repertoire analysis of T-cells and B-cells after vaccination.
To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.	• Characterize the SARS-CoV-2 spike genetic sequence of viral isolates and compare with the vaccine sequence. • Characterize the immune responses to vaccine breakthrough isolates.
To evaluate the immunogenicity of the bivalent vaccine (original and Omicron BA.1) booster compared to mRNA-1273 booster administered as a fourth dose study vaccine in participants at Month 6.	• GMC of the bivalent vaccine (original and Omicron BA.1) against both the Omicron BA.1 and the ancestral strain at Month 6 after study vaccine administration. • Ratio of $GMC_{\text{bivalent vaccine (original and Omicron BA.1)}}/GMC_{\text{mRNA-1273}}$ against the Omicron BA.1 strain at Month 6 after study vaccine administration. • Ratio of $GMC_{\text{bivalent vaccine (original and Omicron BA.1)}}/GMC_{\text{mRNA-1273}}$ against the ancestral strain at Month 6 after study vaccine administration. • GMFR of the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 against the Omicron BA.1 and ancestral strain at all evaluable timepoints after study vaccine administration. • SRR against both the Omicron BA.1 and ancestral strain at Month 6.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; MAAE = medically attended adverse event; NP = nasopharyngeal; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.
Note: "B.1.1.529" is referred to as "Omicron BA.1." The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

Assessor's comment:

The objectives and endpoints are well reflected in the study design.

Study Assessments and Procedures

Planned Measurements and Timing of Assessments

The specific immunogenicity, efficacy, and safety assessments, their schedules and measurement/collection methods are provided in the SoE (Parts 1 and 2) and described in the Study Assessments and Procedures sections of the mRNA-1273-P305 Clinical Study Protocol.

Immunogenicity Assessments

Blood samples for immunogenicity assessments were collected at the time points indicated in the SoE of the protocol for the following parameters:

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus neutralization assays.

- Serum bAb level against SARS-CoV-2 as measured by ligand binding assay specific to the SARS-CoV-2 S protein and the S protein RBD.
- Testing for serologic markers for SARS-CoV-2 infection as measured by anti-nucleocapsid antibodies detected by immunoassay.

SARS-CoV-2/COVID-19 Incidence and Surveillance for COVID-19 Symptoms

Relative vaccine efficacy was assessed as an exploratory endpoint in Part 1 and as a secondary endpoint in Part 2 of this study. Active surveillance for COVID-19 and SARS-CoV-2 infections were performed in both parts of the study.

Safety Assessments

Safety assessments included the recording and monitoring of the following:

- Solicited local and systemic ARs that occurred during the 7 days following vaccination (i.e., the day of injection and 6 subsequent days). Solicited ARs were recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following vaccination. Unsolicited AEs were AEs that were not included in the protocol-defined solicited ARs.
- AEs leading to withdrawal from the study.
- MAAEs from vaccination on Day 1 through EOS or withdrawal from the study.
- AESIs from vaccination on Day 1 through EOS or withdrawal from the study.
- SAEs from vaccination on Day 1 through EOS or withdrawal from the study.
- Vital sign measurements before and after vaccination.
- Physical examination findings (if performed).
- Assessments for SARS-CoV-2 infection from Day 1 through study completion.
- Details of all pregnancies in female participants were collected after the start of study vaccine and until the end of their participation in the study.

Solicited Adverse Reactions

The term "reactogenicity" referred to the occurrence and intensity of selected signs and symptoms (ARs) occurring after study vaccine injection. Participants recorded such occurrences in an eDiary on the day of study vaccine injection and for the 6 days after the day of dosing.

Solicited local ARs were injection site pain, injection site erythema (redness), injection site swelling/induration (hardness), and axillary (underarm) swelling or tenderness ipsilateral to the side of the injection. Solicited systemic ARs were headache, fatigue, myalgia (muscle aches all over the body), arthralgia (joint aches in several joints), nausea/vomiting, chills, and fever (oral temperature).

Severity grading of reactogenicity occurred automatically based on participant entries into the eDiary. The grading scales that were listed in the solicited AR section of the protocol were modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR starts beyond 7 days after dosing, it was to be captured on the AE page until resolution, not to exceed 28 days after vaccination.

If a solicited local or systemic AR continues beyond 7 days after dosing, the participant was to notify the site to provide an end date and close out the event. ARs beyond Day 7 were reviewed by the clinic

staff either during the next scheduled telephone call or at the next clinic visit, or during an unscheduled visit.

Adverse Events, Serious Adverse Events, Medically Attended Adverse Events and Adverse Events of Special Interest

The Investigator was responsible for reporting all AEs that were observed or reported during the study, regardless of their relationship to the study vaccine or their clinical significance. If there was any doubt as to whether a clinical observation is an AE, the event was reported.

The AE and SAE definitions are provided in the mRNA-1273-P305 Clinical Study Protocol.

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

An unsolicited AE was any AE reported by the participant that was not specified as a solicited AR in the protocol or was specified as a solicited AR but started outside the protocol-defined period for reporting solicited ARs (i.e., 7 days after vaccination).

A MAAE was an AE that led to an unscheduled visit to a healthcare practitioner. This included visits to a clinic for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, COVID-19) and visits to health care professionals external to the clinic (eg, urgent care, primary care physician). All PCR-confirmed COVID-19 cases were recorded as MAAEs under the AE term of "COVID-19."

An AESI was an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor are required. A complete list of AESIs is included in the protocol.

Anaphylaxis is an acute hypersensitive reaction with multiorgan system involvement that could present as, or rapidly progress to, a severe life-threatening reaction. All suspected cases of anaphylaxis were to be recorded as MAAEs and AESIs and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. Details for reporting anaphylaxis are provided in the protocol.

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis were to be reported as an AESI, even if it does not meet criteria per the CDC Working Case Definitions. The event should also be reported as an SAE if it met seriousness criteria. Additional detailed case definitions for the AESIs of acute myocarditis, acute pericarditis, and myopericarditis are provided in protocol.

The collection and assessment of safety information during the study (evaluation, definitions, recording, and reporting of solicited ARs, AEs, SAEs, and other reportable safety events, AE intensity and causality, and recording and follow-up of pregnancy) are detailed in the Safety Assessments and Safety Definition sections of the mRNA-1273-P305 Clinical Study Protocol.

Safety monitoring for this study included the blinded study team members, inclusive of at a minimum, the Sponsor Medical Monitor and CRO Medical Monitor, as well as safety reviews by an unblinded DSMB. Additionally, safety reviews are described in the Safety Oversight section of the protocol.

Vital Sign Measurements

Vitals signs were measured at the timepoints indicated in the SoE in the mRNA-1273-P305 Clinical Study Protocol. Vital sign measurements included systolic and diastolic BP, heart rate, respiratory rate, and body temperature (preferred route was oral). On the day of vaccination, vital signs were collected once prior to vaccination and once 15 minutes after vaccination. Vital signs may have been collected at other clinic visits in conjunction with a symptom-directed physical examination. Vital sign information was recorded in the eCRF.

Physical Examinations

A full physical examination, including height and weight, was performed at the Screening Visit and Day 1; symptom-directed physical examinations were performed at specified study visits including unscheduled visits according to the SoE. Interim physical examinations were performed at the discretion of the Investigator.

Assessment for SARS-CoV-2 Infection

Nasopharyngeal swab samples were collected for SARS-CoV-2 testing as specified in the SoE in Appendix 16.1.1. For the duration of the study, participants were directed as soon as possible and within 24 hours to obtain an approved/authorized PCR test for SARS-CoV-2 locally outside of the study per prior NHS guidance if they experienced symptoms of COVID-19 as previously defined by the NHS:

- High temperature (feel hot to touch on the chest or back).
- A new, continuous cough (coughing a lot for more than an hour, or more coughing episodes in 24 hours, or worse than usual cough).
- A loss or change to sense of smell or taste.

If a PCR test was unavailable locally, participants were requested to come in for a study visit or take an approved/authorized lateral flow/rapid antigen test for SARS-CoV-2.

Participants were also directed as soon as possible and within 24 hours to take an approved/authorized lateral flow/rapid antigen test for SARS-CoV-2 if they experienced any of the following (but did not meet the symptoms of COVID-19 as previously defined by the NHS and described above):

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) with modifications:
    - Chills
    - Cough (not meeting COVID-19 symptoms defined by the NHS)
    - Shortness of breath or difficulty breathing
    - Fatigue
    - Muscle or body aches
    - Headache
    - Sore throat
    - Congestion or runny nose
    - Nausea or vomiting
    - Diarrhea

Lateral flow/rapid antigen test for SARS-CoV-2 could be repeated every 24-48 hours if participants continued to have symptoms above.

Participants were directed to take an approved/authorized lateral flow/rapid antigen test for SARS CoV-2 within 4 to 6 days after last exposure* (see definition of last exposure below) if a participant experienced the following:

- Known close contact with someone who has known COVID-19 or SARS-CoV-2 infection. Examples include:
    - Being within 2 meters (without personal protective equipment) for a total of 15 minutes or more.
    - Providing care at home.
    - Having direct physical contact (hugged or kissed them).
    - Sharing eating or drinking utensils.
    - Being sneezed or coughed upon or getting respiratory droplets on the participant.

**Last exposure is defined as the last day a participant was in close contact with a symptomatic person in the household (if the participant was then isolated from that person) or the last day of the quarantine of the person the participant was exposed to, if that person was asymptomatic and/or the participant was unable to isolate from that person.*

A study illness visit (study site visit) was arranged as soon as possible and within 72 hours for participants who tested positive or equivocal for SARS-CoV-2 using an authorized/approved lateral flow/rapid antigen or local PCR testing. If a test for SARS-CoV-2 was unavailable or if there was uncertainty on the test result, a study site visit could be arranged as soon as possible and within 72 hours. At this visit, an NP swab was collected to evaluate for the presence of SARS-CoV-2 infection.

Active surveillance for COVID-19 were conducted throughout the study. Details for assessments for SARS-CoV-2 infection are provided in mRNA-1273-P305 Clinical Study Protocol.

Pregnancy Screen and Testing

A point-of-care urine pregnancy test was performed for all female participants of childbearing potential at the Screening Visit and before the vaccine dose on Day 1, if Day 1 was not on the same day as the Screening Visit. At any time, a pregnancy test either via blood or point-of-care urine could be performed, at the discretion of the Investigator. Levels of FSH could be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.

Appropriateness of Measurements

The endpoints used in this study (immunogenicity, safety, and efficacy) were standard, considered to be reliable, and relevant to the objectives set forth in the protocol.

Assessor's comment:

The view that endpoints used in this study (immunogenicity, safety, and efficacy) were standard, considered to be reliable, and relevant to the objectives set forth in the protocol, is agreed.

Additional Summary of Specific Assessments

Safety Telephone Calls

A safety telephone call was a telephone call made to the participant by trained site personnel. This call followed a script, which facilitated the collection of relevant safety information. Safety telephone calls followed a schedule for each participant, as shown in the SoE.

Use of Electronic Diaries

The eDiary was the primary source document allowed for solicited systemic or local Ars (including body temperature measurements) up to Day 7 post-vaccination. Participants recorded data into the eDiary

starting approximately 15 minutes after dosing under supervision of the study staff to ensure successful entry of assessments. Participants were instructed to complete eDiary entries daily. Clinic staff reviewed eDiary data with participants at a visit 7 days after the injection.

Sample size

Part 1 (50 µg Omicron BA.1 monovalent vaccine and 50 µg mRNA-1273 in 1:1 ratio)

The target enrollment was approximately 500 participants (minimum 300 participants) in each vaccine arm (1:1). The assumptions were: 1) at least 90% participants were in the fourth dose subgroup; and 2) 25% of participants were excluded from the Per-Protocol Set for Immunogenicity, SARS-CoV-2 negative (eg, due to infection with the SARS-CoV-2 Omicron variant).

Statistical power for hypotheses testing at Day 29 (alpha=0.01, 2-sided):

With approximately 200 to 337 evaluable participants per arm, there was at least 95% power to demonstrate non-inferiority of Omicron BA.1 monovalent vaccine against the Omicron BA.1 strain. With this range of sample sizes, the power to demonstrate superiority of Omicron BA.1 monovalent vaccine against the Omicron BA.1 variant strain at a 2-sided alpha of 1% at Day 29 ranged from 14% to 82%.

Statistical power for hypotheses testing at Day 85 (alpha=0.04, 2-sided):

With approximately 200 to 337 evaluable participants per arm, there was more than 95% power to demonstrate non-inferiority of Omicron BA.1 monovalent vaccine against the Omicron BA.1 strain. With this range of sample sizes, the power to demonstrate superiority of Omicron BA.1 monovalent vaccine against the Omicron BA.1 variant strain at a 2-sided alpha of 4% at Day 85 ranged from 28% to 93%. At both time points (Day 29 and Day 85), the assumptions were the true GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273) ranged from 1.25 to 1.5, the SD of the natural log-transformed concentration was 1.5, with a non-inferiority margin of 1.5.

Specific operating characteristics and power for the primary and key secondary objectives under various GMRs for Part 1 of the study are provided in the SAP (Appendix 16.1.9, not included in this AR). With approximately 270 to 450 participants receiving the fourth dose in each study vaccine arm, there was at least 90% probability to observe 1 participant reporting an AE in each study vaccine arm if the true incidence of AEs was 1%.

Part 2 (50 µg Bivalent vaccine [original and Omicron BA.1] and 50 µg mRNA-1273 in 1:1 ratio)

The sample size in Part 2 was driven by the subgroup of participants who received the bivalent vaccine (original and Omicron BA.1) (or mRNA-1273) as the fourth dose.

Statistical power for hypotheses testing at Day 29 (alpha=0.01, 2-sided):

For the fourth dose subgroup, the target enrollment was approximately 1328 participants in each study vaccine arm (1:1). Assuming 25% of participants were excluded from the Per-Protocol Set for Immunogenicity, SARS-CoV-2 negative, with approximately 996 evaluable participants in each arm, there was more than 95% power to demonstrate non-inferiority of bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 and against the original. With this sample size, there was approximately 77% to >95% power to demonstrate superiority of bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 variant strain at a 2-sided alpha of 1.0% at Day 29.

Statistical power for hypotheses testing at Day 85 (alpha=0.04, 2-sided):

With approximately 996 evaluable participants in each arm, there was more than 95% power to demonstrate non-inferiority of bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 and against original. With this sample size, there was approximately 90% to >95% power to demonstrate superiority of bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 strain at a 2-sided alpha of 4% at Day 85.At both time points (Day 29 and Day 85), the assumptions were the true GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273) against the Omicron BA.1 strain ranged from 1.25 to 1.5, and the true GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273) against the ancestral strain is 1, the SD of the natural log-transformed concentration is 1.5, with a non-inferiority margin of 1.5.

With approximately 1328 participants receiving the fourth dose in each study vaccine arm, there was at least 90% probability to observe 1 participant reporting an AE in each study vaccine arm if the true incidence of AEs was 1%.

Power and operating characteristics under various GMRs and 2 different scenarios for the number of evaluable participants with immunogenicity data for Part 2 of the study are provided in the SAP.

Randomisation and blinding (masking)

Method of Assigning Participants to Study Intervention

PPD's Biostatistics department generated the randomization schedules for study vaccine assignments. All participants were centrally randomized to investigational intervention using IRT during the blinded phase (Phase A) of the study. The method used to assign participants is further described in the mRNA-1273-P305 Clinical Study Protocol.

Blinding

The study participant, Investigator, clinical staff, site monitors, and Sponsor personnel (or its designees) were blinded to the study vaccine administered until unblinding occurred as described below. The laboratory personnel in charge of immunogenicity testing were blinded to the vaccine assignment of the samples tested throughout the study.

Pre-identified Sponsor team members and selected contract research organization team members were unblinded to conduct the analyses. Participants who reported eligibility to receive an additional vaccination outside of the mRNA-1273-P305 study had the option to be unblinded in Part 1 of the study after the completion of their scheduled Month 6 visit and in Part 2 after the completion of their scheduled Day 85 visit. Procedures for breaking the blind in case of medical necessity are described in Appendix 16.1.1.

Statistical Methods

Statistical Analysis Plan

All analyses were conducted using SAS software (SAS Institute, Inc, Cary North Carolina) Version 9.4 or higher. The mRNA-1273-P305 SAP (Version 5.0) dated 12 September 2023 is provided in Appendix 16.1.9 (not included in this AR).

General Considerations

Continuous variables were summarized using descriptive statistics: n, mean, SD, median, min, and max. Categorical variables were summarized using counts and percentages.

For the summary statistics of all numerical variables, unless otherwise specified, the display precision followed programming standards. For variable display standards, please refer to Appendix A of the SAP.

When count data were presented, the percentage was suppressed when the count was zero to draw attention to the non-zero counts. A row denoted "Missing" was included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages was the number of participants corresponding group, unless otherwise specified.

Baseline value, unless specified otherwise, was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the administration of study vaccine. Baseline or pre-vaccination SARS-CoV-2 status was determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1 (pre-vaccination).

Additional general statistical considerations including relative study day calculations, defined pre-vaccination SARS-CoV-2 status, unscheduled visits, and analysis visit windows are provided in the mRNA-1273-P305 SAP version 3.0.

The following analysis periods or stages for safety analyses were used in the study:

- Up to 28 days after vaccination: from the day of vaccination (Day 1) and continued through the earliest date of (Day 1 and 27 subsequent days, the day of study discontinuation). This period was used as the primary analysis period for safety analyses including unsolicited AEs, except for solicited ARs, unless specified otherwise.
- Throughout the study: from the day of vaccination (Day 1) and continued through the earliest date of study completion, discontinuation from the study, or death.

All analyses and data summaries/displays for disposition, baseline demographics and characteristics were provided by vaccine arm unless otherwise specified.

Vaccine Arms

Part 1

- Omicron BA.1 monovalent vaccine 50 µg, study vaccine as a fourth dose.
- mRNA-1273 50 µg, study vaccine as a fourth dose.
- Omicron BA.1 monovalent vaccine 50 µg, study vaccine as a third dose.
- mRNA-1273 50 µg, study vaccine as a third dose.

Part 2

- Bivalent vaccine (original and Omicron BA.1) 50 µg, study vaccine as a fourth dose.
- mRNA-1273 50 µg, study vaccine as a fourth dose.
- Bivalent vaccine (original and Omicron BA.1) 50 µg, study vaccine as a third dose.
- mRNA-1273 50 µg, study vaccine as a third dose.

All analyses and data summaries/display for efficacy were provided by study arm using the appropriate analysis population unless otherwise specified. Immunogenicity analyses were examined by subgroups.

Statistical Hypothesis

In Part 1, the primary objective on immune response was based on the participants who received the fourth dose in Part 1 of the study.

Primary Hypotheses

- Omicron BA.1 monovalent vaccine, as a single dose, was non-inferior to mRNA-1273 based on GMR against the Omicron BA.1 strain with a non-inferiority margin of 1.5 at Day 29.
- Omicron BA.1 monovalent vaccine, as a single dose, was non-inferior to mRNA-1273 based on GMR against the Omicron BA.1 strain with a non-inferiority margin of 1.5 at Day 85.

Key Secondary Hypothesis: Omicron BA.1 monovalent vaccine, as a single dose, was superior to mRNA-1273 based on GMR against the Omicron BA.1 strain at Day 29 or Day 85. For the primary objective of immune response in Part 1, hypotheses testing based on participants receiving the fourth dose, alpha of 0.05 (2-sided) was allocated between the 2 time points: alpha of 0.01 to Day 29 and alpha of 0.04 to Day 85.

Day 29: The non-inferiority of Omicron BA.1 monovalent vaccine as compared to mRNA-1273 against the Omicron BA.1 strain was assessed using a non-inferiority margin of 1.5 at 2-sided alpha of 0.01. The primary immunogenicity objective was considered met if non-inferiority against the Omicron BA.1 strain was demonstrated, i.e., the lower bound of the 99% CI of the GMR of Omicron BA.1 monovalent vaccine vs. mRNA-1273 against Omicron BA.1 strain was >0.667 (1/1.5).

Day 85: Using a non-inferiority margin of 1.5 at 2-sided alpha of 0.04, the primary immunogenicity objective was considered met if non-inferiority against the Omicron BA.1 strain was demonstrated, i.e., the lower bound of the 96% CI of the GMR of Omicron BA.1 monovalent vaccine vs. mRNA-1273 against Omicron BA.1 strain was >0.667 (1/1.5).

In Part 2, the primary objective on immune response was based on the participants who received the fourth dose in Part 2 of the study. The primary objective was considered to have met if (1) non-inferiority of bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 strain, (2) non-inferiority of bivalent vaccine (original and Omicron BA.1) against the ancestral strain, and (3) superiority of bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 strain were demonstrated as compared to mRNA-1273 at Day 29 or Day 85.

Primary Hypotheses

- Bivalent vaccine (original and Omicron BA.1), as a single dose, was non-inferior to mRNA-1273 based on GMR against the Omicron BA.1 strain with a non-inferiority margin of 1.5 at Day 29.
- Bivalent vaccine (original and Omicron BA.1), as a single dose, was non-inferior to mRNA-1273 based on GMR against the ancestral strain with a non-inferiority margin of 1.5 at Day 29.
- Bivalent vaccine (original and Omicron BA.1), as a single dose, was superior to mRNA-1273 based on GMR against the Omicron BA.1 strain at Day 29.
- Bivalent vaccine (original and Omicron BA.1), as a single dose, was non-inferior to mRNA-1273 based on GMR against the Omicron BA.1 strain with a non-inferiority margin of 1.5 at Day 85.
- Bivalent vaccine (original and Omicron BA.1), as a single dose, was non-inferior to mRNA-1273 based on GMR against the ancestral strain with a non-inferiority margin of 1.5 at Day 85.
- Bivalent vaccine (original and Omicron BA.1), as a single dose, was superior to mRNA-1273 based on GMR against the Omicron BA.1 strain at Day 85.

For the primary objective of immune response in Part 2, hypotheses testing based on participants receiving the fourth dose, alpha of 0.05 (2-sided) was allocated to the 2 time points: alpha of 0.01 to Day 29 and alpha of 0.04 to Day 85.

For the primary immunogenicity objective, the non-inferiority of bivalent vaccine (original and Omicron BA.1) as compared to mRNA-1273 against the Omicron BA.1 strain and the non-inferiority of bivalent vaccine (original and Omicron BA.1) as compared to mRNA-1273 against the ancestral strain at Day 29 were assessed using a non-inferiority margin of 1.5 at 2-sided alpha of 0.01.

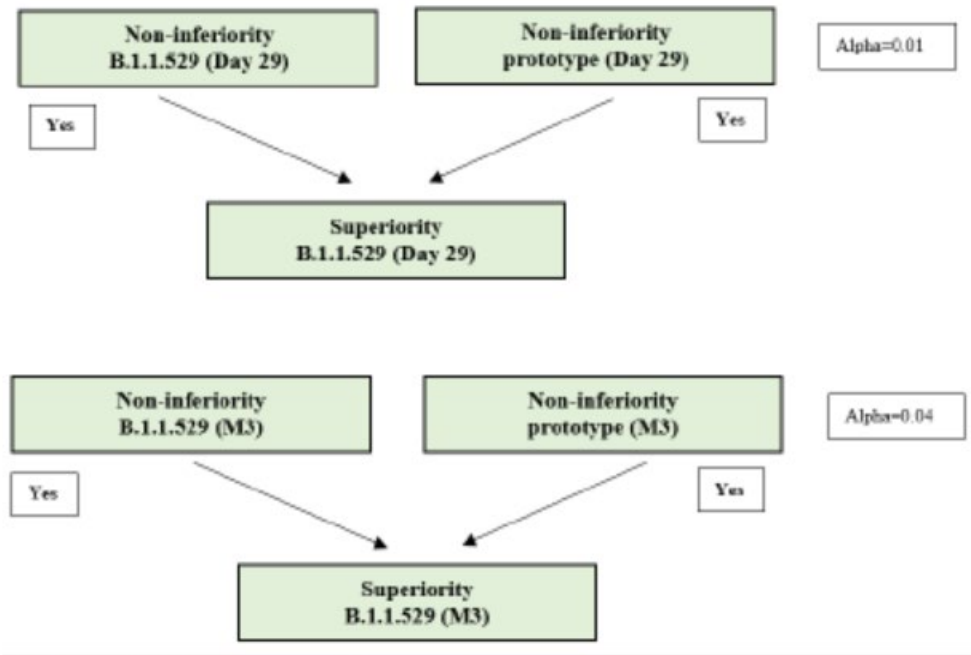
The primary immunogenicity objective was considered met if non-inferiority against the Omicron BA.1 strain and the ancestral strain were both demonstrated, i.e., the lower bound of the 99% CI of the GMR at Day 29 of bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 against Omicron BA.1 was >0.667 (1/1.5), and the lower bound of the 99% CI of the GMR of bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 against original was >0.667.

Once the non-inferiority of bivalent vaccine (original and Omicron BA.1) as compared to mRNA-1273 against the Omicron BA.1 strain and against the ancestral strain was demonstrated, the 99% CI of GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273) was used to assess superiority of bivalent vaccine (original and Omicron BA.1) as compared to mRNA-1273. If the lower bound of the GMR ruled out (>) 1 at Day 29, superiority of bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 against Omicron BA.1 strain was considered demonstrated.

Hypotheses testing at Day 85 was performed in the same manner, first testing 2 non-inferiority hypotheses (one against the Omicron BA.1 strain and one against the ancestral strain) at alpha of 0.04 level (2-sided). Once non-inferiority was demonstrated for both Omicron BA.1 and ancestral strains, then superiority testing against the Omicron BA.1 at alpha of 0.04 level (2-sided) was performed.

Figure 2 demonstrates the hypotheses testing strategy specific to Part 2.

Figure 2: Statistical hypothesis testing strategy of bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 (Part 2)



Abbreviations: CSR = clinical study report; M = month.
Note: For this CSR, B.1.1.529 is referred to as "Omicron BA.1." The mRNA-1273.214 study vaccine is referred to as the "bivalent vaccine (original and Omicron BA.1)," and "prototype" is referred to as "original."

Assessor's comment:

The primary immunogenicity objective was considered met if non-inferiority against the Omicron BA.1 strain and the ancestral strain were both demonstrated, i.e., the lower bound of the 99% CI of the GMR at Day 29 of bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 against Omicron BA.1 was >0.667 (1/1.5), and the lower bound of the 99% CI of the GMR of bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 against original was >0.667.

Once the non-inferiority of bivalent vaccine (original and Omicron BA.1) as compared to mRNA-1273 against the Omicron BA.1 strain and against the ancestral strain was demonstrated, the 99% CI of GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273) was used to assess superiority of bivalent vaccine (original and Omicron BA.1) as compared to mRNA-1273. If the lower bound of the GMR ruled out (>) 1 at Day 29, superiority of bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 against Omicron BA.1 strain was considered demonstrated.

The hypotheses reflect the endpoints. The sequential hypothesis testing strategy is deemed reasonable and adequate.

Analysis Sets

The following analysis sets are defined for each part.

Table 3: Definition of analysis set

Analysis Set	Description
Randomized Set	The Randomized Set consisted of all randomized participants. Participants were analyzed according to their randomized study vaccine arm.
Full Analysis Set	The FAS consisted of all randomized participants who received the study vaccine. Participants were analyzed according to their randomized study vaccine arm.
Modified Intent-to-Treat Set	The mITT Set consisted of all participants in FAS who had no immunologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on serum bAb specific to SARS-CoV-2 nucleocapsid) pre-vaccination, ie, all FAS participants with pre-vaccination/baseline SARS-CoV-2 negative status. Participants were analyzed according to their randomized study vaccine arm.
Per-Protocol Set for Immunogenicity	The PPSI consisted of all participants in the FAS who received the planned dose of study vaccination and had no major protocol deviations that had an impact on critical or key study data. Participants were analyzed according to their randomized study vaccine arm.
Per-Protocol Set for Immunogenicity – SARS-CoV-2 negative	The PPSI-Neg consisted of participants in the PPSI who had no serologic or virologic evidence of SARS-CoV-2 infection at Baseline and up to the day of analysis visit. This was defined by: • both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) on the day of analysis visit, AND • no prior positive RT-PCR test or positive test based on bAb specific to SARS-CoV-2 nucleocapsid at Baseline or between Baseline and the day of analysis visit. PPSI-Neg was the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants were analyzed according to their randomized study vaccine arm.

Analysis Set	Description
Modified Per-Protocol Set for Immunogenicity – SARS-CoV-2 negative	The Modified PPSI-Neg consisted of participants in the PPSI who had no serologic or virologic evidence of SARS-CoV-2 infection at Baseline. This was defined by both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at Baseline. Modified PPSI-Neg was used for sensitivity analysis of immunogenicity. Participants were analyzed according to their randomized study vaccine arm.
Solicited Safety Set	The Solicited Safety Set consisted of all randomized participants who received the study vaccine and contributed any solicited AR data within the first 7 days after study vaccine administration. The Solicited Safety Set was used for the analyses of solicited ARs within 7 days. Participants were included in the study vaccine arm that they actually received.
Safety Set	The Safety Set consisted of all randomized participants who received the study vaccine. The Safety Set was used for all analyses of safety except for the solicited ARs within 7 days. Participants were included in the study vaccine arm that they actually received.
Per-Protocol Set for Efficacy	The PPSE consisted of all participants in the mITT who received the planned dose of study vaccination and had no major protocol deviations that had an impact on key or critical data.

Abbreviations: AR = adverse reaction; bAb = binding antibody; FAS = Full Analysis Set; mITT = Modified Intent-to-Treat; PPSE = Per-Protocol Set for Efficacy; PPSI = Per-Protocol Set for Immunogenicity; PPSI-Neg = PPSI – SARS-CoV-2 negative; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Handling of Missing Data

Imputation rules for missing dates of prior/concomitant medications, non-study vaccinations and procedures, missing or incomplete AE dates, and laboratory results relative to LLOQ/ULOQ are provided in the SAP.

Interim Analyses

Two planned interim analyses of immunogenicity and safety were conducted after participants completed the Day 29 and Day 85 visit assessments in both Part 1 and Par 2 of the study. Analyses of the Month 6 and Month 12 visits including Phase B (open-label, observational) were exploratory. The final analysis of all endpoints was performed after all participants have completed or discontinued from the study.

Multiplicity Adjustments

Statistical testing in Part 1 was independent of testing in Part 2. In each Part, the family-wise alpha of 0.05 (2-sided) was preserved by allocating alpha across 2 time points: 0.01 (2-sided) at Day 29 and 0.04 (2-sided) at Day 85.

Multicenter Studies

No analyses were performed based on grouping or excluding any of the study sites.

Adjustments for Covariates

An ANCOVA model was performed to assess the difference in immune response between Omicron BA.1 monovalent vaccine and mRNA-1273 against the Omicron BA.1 strain at Day 29 in the subgroup of participants who received the fourth dose in Part 1 of the study. The same ANCOVA model described was used to assess immune response of Omicron BA.1 monovalent vaccine against the Omicron BA.1 strain at Day 85.

Age groups (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA or viral vector) and pre-vaccination antibody concentration level (if applicable) were adjusted in the ANCOVA model.

Supportive analyses of the primary and key secondary immunogenicity endpoints at Day 29 and Day 85 were also performed in the PPSI, and these analyses were based on the ANCOVA model and included the pre-vaccination/baseline SARS-CoV-2 status (negative, positive, or missing) as a factor.

The MMRM was used to analyze all post-vaccination measures including study vaccine arm, analysis visit, vaccine by visit interaction, age groups and pre-vaccination concentration levels (if available) as fixed effects and participant as a random effect. An unstructured covariance structure was used to model the within-participant errors. The compound symmetry structure was used when the model failed to converge.

The same ANCOVA model described for Part 1 was used to assess the difference in immune response between bivalent vaccine (original and Omicron BA.1) and mRNA-1273 in the subgroup of participants who received the fourth dose in Part 2 of the study. The same ANCOVA model was performed to assess the non-inferiority of immune response against the ancestral strain in the subgroup of participants who received bivalent vaccine (original and Omicron BA.1) and mRNA-1273 as the fourth dose (second primary hypothesis).

Examination of Subgroups

Immunogenicity was assessed in the following subgroups:

- Age (≥16 to <65, and ≥65 years).
- Sex (female, male).
- SARS-CoV-2 status (negative, positive) at the day of analysis visit (eg, for Day 29, subgroup analyses will be performed based on SARS-CoV-2 status up to Day 29 visit).
- Pre-vaccination SARS-CoV-2 status (negative, positive).
- Race and ethnicity group (White, Mixed or Multiple ethnic groups, Asian or Asian British, etc).
- In addition, Phase B in each study Part (analyses performed in 2 or 4 subsets):
  - Two subsets
    - Subset of participants in the fourth dose group who received an additional vaccination outside of the study.
    - Subset of participants in the fourth dose group who did not receive an additional vaccination outside of the study.
  - Four subsets
    - Subset of participants in the fourth dose group who were unblinded to the study vaccine and received an additional vaccination outside of the study.
    - Subset of participants in the fourth dose group who were unblinded to the study vaccine and did not receive an additional vaccination outside of the study.
    - Subset of participants in the fourth dose group who remained blinded to the study vaccine and received an additional vaccination outside of the study.
    - Subset of participants in the fourth dose group who remained blinded to the study vaccine and did not receive an additional vaccination outside of the study.

Safety and efficacy could have been assessed in the same subgroups.

Analyses Approach

All analyses and data summaries/displays were provided by study vaccine arm (Omicron BA.1 monovalent vaccine and mRNA-1273 for Part 1, and bivalent vaccine [original and Omicron BA.1] and mRNA-1273 for Part 2) and by vaccine subgroups (study vaccine administrated as third or fourth dose) using the appropriate analysis population, unless otherwise specified. Data summaries for participants disposition, baseline demographics, and safety data could also be provided by study vaccine arm.

All analyses were conducted using SAS Version 9.4 or higher unless otherwise specified.

Immunogenicity Measures

When referring to the immunogenicity measurement, concentration or level was used in this document as specified in the study TLFs.

Population, Immunogenicity, SARS-CoV-2/COVID-19 Incidence, and Safety Analyses

Study Population

Disposition

The number and percentage of participants who received the study vaccine and who completed the study were summarized based on the Randomization Set. This study vaccination only consists of a single dose, thus discontinuation from study vaccine is not applicable in this study.

The number and percentage of participants in the following analysis sets were summarized by study vaccine arm: FAS, mITT, PPSI, PPSI-Neg, Solicited Safety Set, Safety Set, and PPSE. The denominators of the percentages were based on participants in the FAS. For Solicited Safety Set and Safety Set, the percentage were based on the number of participants in the study vaccine arm within the Safety Set (as treated).

The number of participants in the following categories were summarized based on participants screened: number of participants screened and number and percentage of screen failure participants and the reason/s for screen failure. The percentage of participants who screen failed was based on the number of participants screened. The reason for screen failure was based on the number of participants who screen failed.

Summary of reasons for participants excluded from Per-Protocol Sets was provided.

Major Protocol Deviations

Major protocol deviations were a subset of protocol deviations that could have significantly impacted the completeness, accuracy, or reliability of the study data or that could have significantly affected a participant's rights, safety, or well-being. Major protocol deviations rules were developed and finalized before database lock.

The number and percentage of the participants with each major protocol deviation type were provided by study vaccine arm based on the Randomized Set.

Major protocol deviations were presented in a listing. Selected major protocol deviations deemed to impact critical data led to exclusion from the PPSI or PPSE.

Demographics and Baseline Characteristics

Descriptive statistics was calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), body mass index (kg/m2). The number and

percentage of participants were provided for categorical variables such as age group, sex, race, and ethnicity.

The summaries were provided separately based on the FAS, Safety Set, and PPSI-Neg Set.

Medical History

Medical history data were coded by System Organ class (SOC) and Preferred Term (PT) using MedDRA Version 23.0.

The number and percentage of participants with any medical history were summarized by SOC and PT based on the Safety Set. A participant was counted only once for multiple events within each SOC and PT. SOC was displayed in internationally agreed order. PT was displayed in descending order of frequency and then alphabetically within SOC.

Medical history data were presented in a listing.

Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccinations were coded using the WHO Drug Dictionary. The summary of concomitant medications was based on the Safety Set.

The number and percentage of participants using concomitant medications and non-study vaccinations during the 7-day follow-up period (i.e., on the day of vaccination and the 6 subsequent days) and during the 28-day follow-up period after the injection (i.e., on the day of injection and the 27 subsequent days) were summarized by study vaccine arm as follows:

- Any concomitant medications and non-study vaccination within 7 days postinjection.
- Any concomitant medications and non-study vaccination within 28 days postinjection.
- Seasonal influenza vaccine within 28 days postinjection.
- Medications to prevent pain or fever within 7 days postinjection.
- Medications to treat pain or fever within 7 days postinjection.

A summary table of concomitant medications and non-study vaccination that continued or newly received at or after the injection through 28 days was provided by PT in descending order of frequency and then alphabetically within SOC.

Prior and concomitant medications, non-study vaccination, and concomitant procedures were presented in listings.

Study Exposure

Study duration, defined as time on study from the injection to study discontinuation, study completion, last contact date, or data cut-off date, whichever occurs earlier, were summarized based on Safety Set.

Immunogenicity Analyses

The analyses of immunogenicity were based on the PPSI-Neg analysis population and performed by study vaccine arm.

Assessor's comment:

The analyses of immunogenicity were based on the PPSI-Neg analysis population which is reasonable to exclude effects from prior SARS-CoV-2 infections for which the infecting strain and timepoint is unknown.

Analysis of Immunogenicity Endpoints in Part 1 (Omicron BA.1 Monovalent Vaccine and mRNA-1273)

Primary and Key Secondary Analyses

Primary and key secondary hypotheses in Part 1 of the study are described earlier. The primary analysis set for immunogenicity objectives was based on PPSI-Neg.

Day 29 (alpha=0.01, 2-sided)

For the first primary hypothesis, an ANCOVA model was performed to assess the difference in immune response between the Omicron BA.1 monovalent vaccine and mRNA-1273 against the Omicron BA.1 strain at Day 29 in the subgroup of participants who received the fourth dose. Antibody concentrations at Day 29 post-vaccination against the Omicron BA.1 strain was a dependent variable, and a group variable (Omicron BA.1 monovalent vaccine and mRNA-1273) was the fixed effect, adjusting for age groups (≥16 to <65, ≥65 years), most recent COVID-19 vaccination type (mRNA or viral vector) and pre-vaccination antibody concentration level, if applicable. The GMC was estimated by the GLSM from the model, and the corresponding 99% CI was provided for each group. The GMR (ratio of GMCs) for Omicron BA.1 monovalent vaccine with respect to mRNA-1273 was estimated by the ratio of GLSM from the model with 99% CI. The 99% CI for GMR was used to assess the between-group difference in immune response against the Omicron BA.1 strain for Omicron BA.1 monovalent vaccine at Day 29 compared to mRNA-1273 as a study vaccine for non-inferiority testing.

Day 85 (alpha=0.04, 2-sided)

The same ANCOVA model described above was used to assess immune response of Omicron BA.1 monovalent vaccine against the Omicron BA.1 strain at Day 85. The 96% CI for GMR was used to assess the between-group difference in immune response against the Omicron BA.1 strain for non-inferiority.

The primary immunogenicity objective (against the Omicron BA.1 strain) was considered met if non-inferiority was demonstrated based on a GMR at either Day 29 or Day 85. Specifically, against the Omicron BA.1 strain, the non-inferiority of immune response of Omicron BA.1 monovalent vaccine as compared to mRNA-1273 was considered demonstrated if the lower bound of the corresponding 99% CI of the GMR was >0.667 (Day 29) based on a non-inferiority margin of 1.5 or the corresponding 96% CI of the GMR was >0.667 (Day 85).

Once non-inferiority against Omicron BA.1 was demonstrated, superiority of Omicron BA.1 monovalent vaccine as compared to mRNA-1273 against Omicron BA.1 was tested (key secondary hypothesis). Specifically, superiority of Omicron BA.1 monovalent vaccine as compared to mRNA-1273 was demonstrated if the lower bound of the 99% CI of the GMR was >1 (Day 29) or the lower bound of the 96% CI of the GMR was >1 (Day 85).

Supportive analyses of the primary and key secondary immunogenicity endpoints at Day 29 and Day 85 were also performed in the PPSI. These analyses were based on the ANCOVA model described above and included the pre-vaccination/baseline SARS-CoV-2 status (negative, positive, or missing) as a factor. The 99% CI for GMR was used to assess differences between groups at Day 29 and the 96% CI for GMR at Day 85.

Secondary Analyses

The ANCOVA model described above was used for secondary analyses to assess for immune response of Omicron BA.1 monovalent vaccine compared to mRNA-1273 vaccination administered as a third or fourth dose at all measured time points. The GMC was estimated by the GLSM from the model, and its corresponding 95% CIs was provided for each group. The GMR for Omicron BA.1 monovalent vaccine with respect to mRNA-1273 was estimated by the ratio of GLSM from the model and the corresponding 95% CIs were provided. No hypothesis tests were performed for these objectives.

For each antibody of interest, the GMC or level with corresponding 95% CI at each timepoint, and GMFR of post-baseline concentrations or levels over baseline with their corresponding 95% CIs at each post-baseline timepoint were provided. The 95% CIs were calculated based on the t-distribution of the log-transformed values then back-transformed to the original scale for presentation. The following descriptive statistics were also provided at each timepoint: n, median, minimum, and maximum.

The MMRM was used to analyze all post-vaccination measures including study vaccine arm, analysis visit, vaccine by visit interaction, age groups and pre-vaccination concentration levels (if available) as fixed effects and participant as a random effect.

PPSI was used as the analysis population to summarize the immune responses (antibodies of interest), and the above summary statistics including GMC and GMFR were provided by prevaccination/ study baseline SARS-CoV-2 status.

The SRR was summarized at all measured time points for each study vaccine arm with the 95% CI calculated using the Clopper-Pearson method. The difference of SRRs at all measured time points for Omicron BA.1 monovalent vaccine compared with mRNA-1273 was provided with 95% CI using Miettinen-Nurminen method. Analysis of the SRR was performed in the PPSINeg. A sensitivity analysis of SRR was performed in the PPSI by using stratified Miettinen-Nurminen method, with pre-vaccination positive, negative, and unknown SARS-CoV-2 status as strata.

Exploratory Analysis

Exploratory analyses using the same methods described above were used to assess for immune response of Omicron BA.1 monovalent vaccine compared to mRNA-1273 vaccination administered against other variant strains (eg, Alpha, Beta, etc) after study vaccination.

Similar analyses were used to assess for immune response of the Omicron BA.1 monovalent vaccine compared to the mRNA-1273 vaccine administered against the BA.4/BA.5 variant strains, conducted in the random sample of 200 participants. The exception was the sensitivity analysis of SRR performed in the PPSI using the stratified Miettinen-Nurminen method, where both SARS-CoV-2 status (positive, negative, and unknown) and age group (≥16 to <65, and ≥65 years) were included as strata.

Details of statistical methods used for exploratory analyses are provided in the SAP.

Analysis of Immunogenicity Endpoints in Part 2 (Bivalent Vaccine [Original and Omicron BA.1] and mRNA-1273)

Primary Analyses

Primary hypotheses in Part 2 of the study are described in Section 4.1.2. Serum nAb was used as the basis to assess non-inferiority and superiority in immune response. The primary analysis set for immunogenicity objectives was based on PPSI-Neg.

Day 29 (alpha=0.01, 2-sided)

The same ANCOVA model described for Part 1 was used to assess the difference in immune response against the Omicron BA.1 strain at Day 29 between the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 in the subgroup of participants who received the fourth dose.

The same ANCOVA model was performed to assess the non-inferiority of immune response against the ancestral strain in the subgroup of participants who received the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 as the fourth dose.

Day 85 (alpha=0.04, 2-sided)

The same ANCOVA model was used to assess immune response of the bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 strain at Day 85. The 96% CI for GMR was used to assess the between-group difference in immune response against the Omicron BA.1 strain for non-inferiority and superiority.

Part 2 of this study was considered to have met its primary objectives if non-inferiority of bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 strain, non-inferiority of bivalent vaccine (original and Omicron BA.1) against the ancestral strain, and superiority of bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1 strain were demonstrated as compared to mRNA-1273 at Day 29 or Day 85.

Secondary Analyses

The same ANCOVA model described above was used for secondary analyses to assess for immune response of bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 vaccination administered as a fourth dose against other variants at Day 29 or Day 85. The GMC was estimated by the GLSM from the model, and its corresponding 95% CIs were provided for each group.

SRR of the bivalent vaccine (original and Omicron BA.1) administered as a fourth dose against the Omicron BA.1 strain, ancestral strain and other VOC were analyzed in the PPSI-Neg using the methods as described for the Secondary Analyses in Part 1. MMRM (as described for the Secondary Analyses in Part 1) was used to assess immune response bivalent vaccine (original and Omicron BA.1) against the Omicron BA.1, the ancestral strain, and other VOC at all measured timepoints after study vaccine administration.

Exploratory Analyses

The same ANCOVA model described above could be used for exploratory analyses to assess for immune response of bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 vaccination administered as a fourth dose against both the Omicron BA.1 and the ancestral strain at Day 29, using a 95% CI for GLSM and GMR. Similar analyses conducted in Part 1 (Section 4.2.2.1) to assess for immune response of the study vaccine compared to the active comparator arm against the BA.4/BA.5 variant strains were also performed in Part 2 of the study.

Details of statistical methods used for sensitivity analyses on the primary immunogenicity endpoints using the Modified PPSI-Neg population are provided in the SAP.

SARS-CoV-2/COVID-19 Incidence Analyses

Number and IRs of symptomatic COVID-19 disease, asymptomatic SARS-CoV-2 infection, as well as SARS-CoV-2 infection regardless of symptoms were provided for each study vaccine arm. The primary analysis population for these assessments was the PPSE, unless otherwise specified. The mITT population could be used for supportive analyses. All results were summarized by study vaccine arm.

The IR of each type of event was calculated as the number of cases divided by the total person-time. Person-time was defined as the total time from randomization date to the date of event, last date of

study participation, censoring time, date of additional COVID-19 vaccine(s) received outside of the study during the study conduct, or efficacy data cut-off date, whichever was earlier. The 95% CI of the IR was calculated using the exact method (Poisson distribution) and adjusted by person-time.

Vaccine efficacy and the respective 95% CI were estimated.

Endpoint definitions/derivation for efficacy analyses are briefly described below. Additional information is provided in the SAP.

Derivation of SARS-CoV-2 Infection

SARS-CoV-2 infection was defined in participants with negative SARS-CoV-2 status prevaccination by either:

- bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that became positive (as measured by Roche Elecsys) post-baseline, OR
- Positive RT-PCR post-baseline.

The incidence of SARS-CoV-2 infection counted starting 14 days after randomization were summarized by study vaccine arm. Supportive analyses summarized incidence of SARS-CoV-2 infection in which a case was counted after randomization, i.e., date of documented infection - date of randomization ≥ 0.

Derivation of Asymptomatic SARS-CoV-2 Infection

This was an exploratory endpoint in Part 1 and a secondary endpoint in Part 2: the incidence of asymptomatic SARS-CoV-2 infection after study vaccination. Asymptomatic SARS-CoV-2 infection was identified by absence of symptoms and infections as detected by RT-PCR or serology tests. Specifically:

- Absence of COVID-19 symptoms +/- 14 days from the positive test below
- 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) post-baseline, or
    - Positive RT-PCR test post-baseline (at scheduled or unscheduled/illness visits).

Derivation of Symptomatic SARS-CoV-2 Infection (COVID-19)

The incidence of symptomatic SARS-CoV-2 infection was an exploratory endpoint in Part 1 and a secondary endpoint in Part 2.

Symptomatic SARS-CoV-2 infection was defined in the following 2 ways: protocol-defined COVID-19 case (primary case definition) and CDC Case Definition of COVID-19 (secondary case definition). COVID-19 primary and secondary case definitions are described below.

Table 4: COVID-19 (protocol-defined)

COVID-19 (Protocol-defined)	
Post-baseline PCR results	Positive, **AND**
Systemic symptoms	At least **2** of the following **systemic symptoms**: fever (≥ 38°C [≥ 100.4°F]), chills, muscle and/or body aches (not related to exercise), headache, sore throat, new loss of taste/smell; **OR**
Respiratory symptoms	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 Criteria)	
Post-baseline PCR results	Positive, **AND**
Systemic and respiratory symptoms	at least ONE of the following **systemic or respiratory symptoms**: Fever (≥38°C/≥ 100.4°F), chills, cough, shortness of breath, and/or difficulty breathing, fatigue, muscle and/or body aches (not related to exercise), headache, new loss of taste/smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhea.
Respiratory symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough, shortness of breath, or difficulty breathing.

Abbreviations: CDC = Center for Disease Control and Prevention: COVID-19 = coronavirus disease 2019; PCR = polymerase chain reaction.

Sensitivity Analysis of Efficacy Endpoints

Sensitivity analysis for the efficacy endpoints could be performed with the same methods described above based on the mITT Set and with cases counted starting at different time points.

A sensitivity analysis was performed based on a modified version of the primary and secondary definition substituting positive lateral flow test for PCR test.

A sensitivity analysis was performed based on a modified version of the primary and secondary definition including positive lateral flow test and positive PCR test.

SARS-CoV-2 Symptoms and COVID-19 Severity

Listings were provided for each of SARS-CoV-2-reported symptoms and COVID-19 severity. In addition, the following listings were provided for participants infected by SARS-CoV-2:

- Serum bAb level against SARS-CoV-2.
- Serum nAb concentration against SARS-CoV-2.
- Solicited ARs.
- Unsolicited AEs.

Safety Analyses

Safety analyses in the following sections are applicable for both Part 1 and Part 2 of the study.

Safety and reactogenicity were assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, treatment-related AEs, severe AEs, SAEs, MAAEs, AESIs, and AEs leading to withdrawal from study participation, vital signs, and physical examinations findings. Safety analyses were based on the Safety Set.

Unsolicited AEs were coded by SOC and PT according to the MedDRA. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) was used in this study for solicited ARs.

Safety analyses were based on the Safety Set.

Solicited Adverse Reactions

The solicited ARs were recorded by the participant in the eDiary on the day of vaccination and for the 6 days postinjection. Analyses of solicited ARs within 7 days were provided based on the Solicited Safety Set and analyses of solicited ARs with onset after Day 7 were provided based on the Safety Set. The following summaries were provided:

- Summary of solicited AR within 7 days (solicited AR eDiary and solicited AR eCRF) A 2-sided 95% exact CI using the Clopper-Pearson method was provided for the percentage of participants who reported any solicited local AR, solicited systemic AR, or any solicited AR.
- Summary of solicited AR with Grade 3 or higher.
- Summary of solicited AR duration (solicited AR eDiary and solicited AR eCRF).
- Summary of solicited AR persisting beyond 7 days (solicited AR eDiary and solicited AR eCRF). A 2 sided 95% exact CI using the Clopper-Pearson method was provided for the percentage of participants who reported any solicited local AR, solicited systemic AR, or any solicited AR persisting beyond 7 days after injection.
- Summary of solicited AR with onset after Day 7 (AE eCRF).
- Summary of onset day for local reactions (solicited AR eDiary and solicited AR eCRF).

Detailed descriptions of the above summaries are provided in the SAP.

Adverse Events

The collection and assessment of safety information during the study (evaluation, definitions, recording, and reporting of AEs, SAEs, and other reportable safety events) are detailed in the Safety Assessments and Safety Definition sections of the protocol.

Analyses of unsolicited AEs were summarized by stage, up to 28 days after vaccination and throughout the study and by study vaccine arm.

All summary tables (except for the overall summary of AEs) for unsolicited AEs were presented by SOC and PT for unsolicited AEs with counts of participants included. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE were counted once. Participants were presented according to the highest severity (the strongest causality) in the summaries by severity (of related AEs), if participants reported multiple events under the same SOC and/or PT.

Summary tables, including the number and percentages of participants by study vaccine arm, were presented for the following categories: any unsolicited AEs, SAEs, fatal AEs, unsolicited treatment emergent AESIs, unsolicited AEs that were MAAEs, unsolicited AEs leading to discontinuation from participation in the study, unsolicited severe AEs, unsolicited non-serious AEs, and unsolicited severe non-serious AEs.

Summary tables, including number and percentages, were also presented for participants with unsolicited AEs that were treatment-related in each of the above categories. In addition, separate

listings containing individual participant data for AEs leading to death, SAEs, AESIs, and a listing of AEs prior to death in the subset of deceased participants were provided separately.

Details on overall summary presentations of unsolicited AEs are provided in the SAP.

Pregnancy Tests

A participant listing was provided for pregnancy tests with positive results.

Vital Sign Measurements

Vital sign measurements for participants were presented in a listing. Abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement were also provided in the listing.

Shift from baseline in the toxicity grades at each timepoint and shift from baseline in the toxicity grades to the worst post-baseline result were also be summarized.

Changes in Planned Analyses Prior to Unblinding or Database Lock

There were no changes in the planned analyses for the study.

Changes Following Study Unblinding/Database Lock and Post-hoc Analyses

There were no changes to the planned analyses after unblinding.

Data Quality Assurance

Data collection was the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The Investigator was responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study were recorded in an eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator was responsible for verifying that data entries were accurate and correct by physically or electronically signing the eCRF.
- The Investigator was to maintain accurate documentation (source data) that supported the information entered in the eCRF.
- The Investigator was to permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical -Risk- Based Monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) were provided in the Clinical Monitoring Plan.
- The Sponsor or designee was responsible for the data management of this study including quality checking of the data.
- The Sponsor assumed accountability for actions delegated to other individuals (eg, CROs).
- Study monitors performed ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel were accurate, complete, and verifiable from source documents; that the safety and rights of participants were being protected; and that the study was being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study were to be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records were to be destroyed during the retention period without the written approval of the Sponsor. No records were to be transferred to another location or party without written notification to the Sponsor.

Quality assurance included all systematic actions established to ensure that the clinical study was performed, and the data were generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from the Sponsor or qualified designee, who was independent of and separated from routine monitoring, could periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections could include on-site inspections/audits and source data checks. Direct access to source documents was required for the purpose of these periodic inspections/audits.

Data Collection and Management

This study was conducted in compliance with ICH CGP guidelines. This study was also conducted in accordance with the most recent version of the Declaration of Helsinki.

This study used electronic data collection to collect data directly from the investigational site using eCRFs. The Investigator was responsible for ensuring that all sections of each eCRF were completed promptly and correctly and that entries could be verified against any source data.

Study monitors performed source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies were resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the clinical monitoring plan.

AEs were coded with MedDRA Version 23.0. Concomitant medications were coded using the WHO Drug Reference List.

Study Monitoring

Study sites were monitored by the Sponsor or its representatives. Sites were visited at regular intervals and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study specific CRFs. Additional details are provided in the Study Monitoring section of the protocol.

Audits and Inspections

The Sponsor, their designee(s), the IEC, or regulatory authorities were allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The Investigator agreed to allow the Sponsor, their designee(s), the IEC, or regulatory authorities to inspect the study vaccine storage area, study vaccine stocks, study vaccine records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and any IEC could have visited the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection was to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP (R2), and any applicable regulatory requirements.

The Principal Investigator had to obtain IEC approval for the investigation. Initial IEC approval and all materials approved by the IEC for this study, including the participant consent form and recruitment materials, were to be maintained by the Investigator and made available for inspection.

Two site audits were performed as part of the independent Sponsor quality assessment. The site audit certificates are provided in Appendix 16.1.8 (not included in this AR).

Laboratory Procedures

Where local laboratories were used (pregnancy testing), their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors. All other laboratory tests and assays were performed by PPD GCL Laboratory supplies and sample management (third party vendors/subcontracted by Moderna).

Quality Tolerance Limits

Quality tolerance limits were not defined for this study.

Results

Disposition of Participants

Part 1

A total of 720 randomized participants comprised the FAS in Part 1 of the study and included 363 participants in the Omicron BA.1 monovalent vaccine arm and 357 participants in the mRNA-1273 arm. Overall, 90.7% of participants completed Part 1 the study.

Reasons for study discontinuation included lost to follow-up (32 participants), withdrawal of consent (other) (26 participants), AEs (4 participants), "Other" reason (3 participants), and physician decision (1 participant). One death (due to an AE of small-cell lung cancer assessed by the Investigator as unrelated to study vaccine) was reported in the mRNA-1273 arm.

Details about participants who discontinued from the study are provided in Listing 16.2.1.1.1 (not included in this AR).

Details about randomized participants and their planned and actual study vaccine received are provided in Listing 16.1.7.1 (not included in this AR).

Table 5: Participant Disposition in Part 1 (Full Analysis Set)

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=1) n (%)	4th Dose (N=362) n (%)	Total (N=363) n (%)	3rd Dose (N=0) n (%)	4th Dose (N=357) n (%)	Total (N=357) n (%)	Overall (N=720) n (%)
Completed study[a]	0	333 (92.0)	333 (91.7)	–	320 (89.6)	320 (89.6)	653 (90.7)
Discontinued from study	1 (100)	29 (8.0)	30 (8.3)	–	37 (10.4)	37 (10.4)	67 (9.3)
Reason for discontinuation of study							
Adverse event (Other)	0	2 (0.6)	2 (0.6)	–	2 (0.6)	2 (0.6)	4 (0.6)
Adverse event (COVID-19 infection)	0	0	0	–	0	0	0
Death	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Lost to follow-up	1 (100)	15 (4.1)	16 (4.4)	–	16 (4.5)	16 (4.5)	32 (4.4)
Physician decision	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Pregnancy	0	0	0	–	0	0	0
Protocol deviation	0	0	0	–	0	0	0
Solicited AR/ reactogenicity event	0	0	0	–	0	0	0
Study terminated by Sponsor	0	0	0	–	0	0	0
Withdrawal of consent (COVID-19 non-infection related)	0	0	0	–	0	0	0
Withdrawal of consent (Other)	0	9 (2.5)	9 (2.5)	–	17 (4.8)	17 (4.8)	26 (3.6)
Other	0	2 (0.6)	2 (0.6)	–	1 (0.3)	1 (0.3)	3 (0.4)

Abbreviations: (–) = not applicable; AR = adverse reaction; COVID-19 = coronavirus disease 2019; EOS = end of study; IRT = interactive response technology.

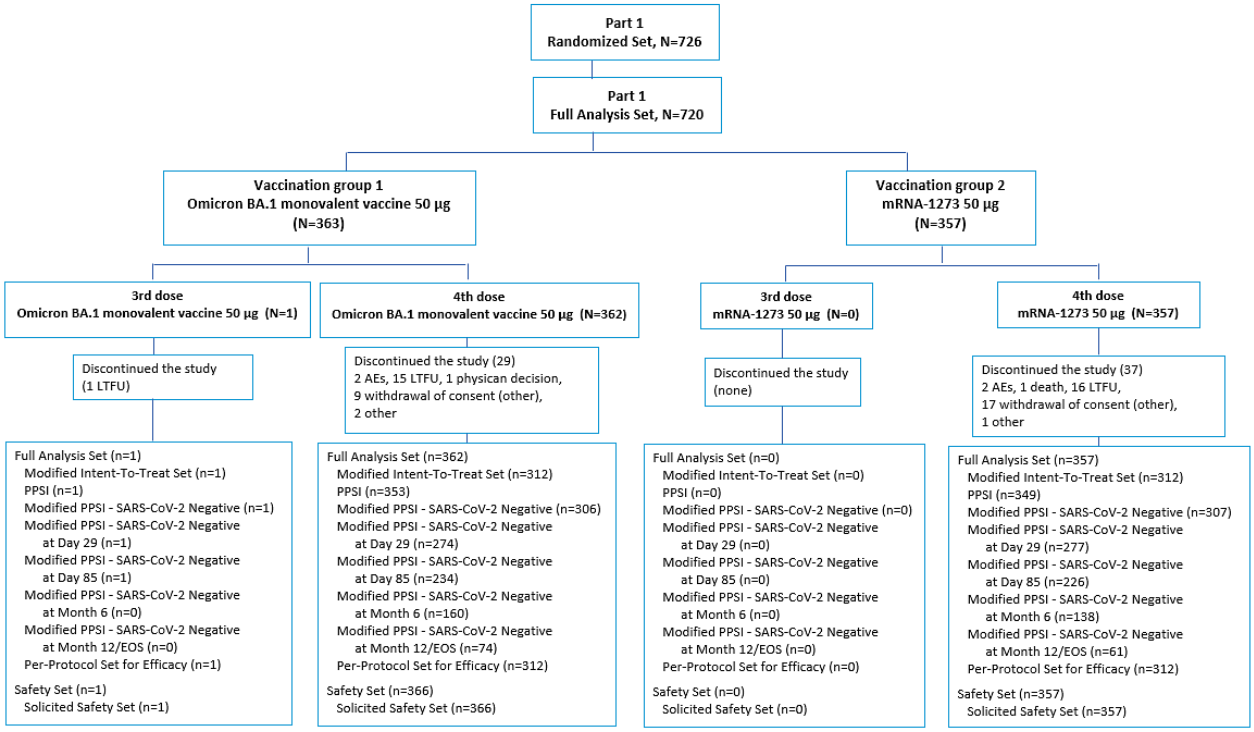
Notes: Due to an IRT system error, 4 participants were assigned to an inactive study arm instead of the planned 50 µg Omicron BA.1 monovalent study vaccine. For this reason, these 4 participants were not presented under Full Analysis Set. These 4 assignment errors were documented as dispensation errors. These 4 participants received the protocol-specified dose and were included in the 50 µg Omicron BA.1 monovalent vaccine arm based on actual study vaccine received under Safety Set. Please refer to Listing 16.2.5.2.1 for the full list of dispensation errors. Percentages were based on the number of participants in the Full Analysis Set.

The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

a. Study Completion was defined as a participant who completed last scheduled procedure (Day 359/EOS).

Source: Table 14.1.1.1.1

Figure 3: Participant Disposition in Part 1



Abbreviations: AE = adverse event; EOS = end of study; LTFU = lost to follow-up; PPSI = Per-Protocol Set for Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

Sources: Table 14.1.1.1.1 and Table 14.1.2.1.1

Part 2

A total of 2824 randomized participants comprised the FAS in Part 2 of the study and included 1422 participants in the bivalent vaccine (original and Omicron BA.1) arm and 1402 participants in the mRNA-1273 vaccine arm. Overall, 92.4% of participants completed Part 2 of the study (**Table 6**).

Reasons for study discontinuation included lost to follow-up (117 participants), withdrawal of consent (other) (75 participants), "Other" reasons (12 participants), AEs (4 participants with events assessed by the Investigator as unrelated to study vaccine), and withdrawal of consent ([COVID-19 non-infection related] 1 participant).

Two deaths (due to AEs assessed by the Investigator as unrelated to study vaccine: 1 completed suicide and 1 road traffic accident) were reported for the bivalent vaccine (original and Omicron BA.1) arm, and 4 deaths (due to AEs assessed by the Investigator as unrelated to study vaccine: 1 sudden unexplained death in epilepsy, 1 gastrointestinal carcinoma, 1 motor neurone disease, and 1 arrythmia) were reported for the mRNA-1273 active comparator arm.

Details about participants who discontinued from the study are provided in CSR Listing 16.2.1.1.2 (not included in this AR).

Details about randomized participants and their planned and actual study vaccine received are provided in CSR Listing 16.1.7.2 (not included in this AR).

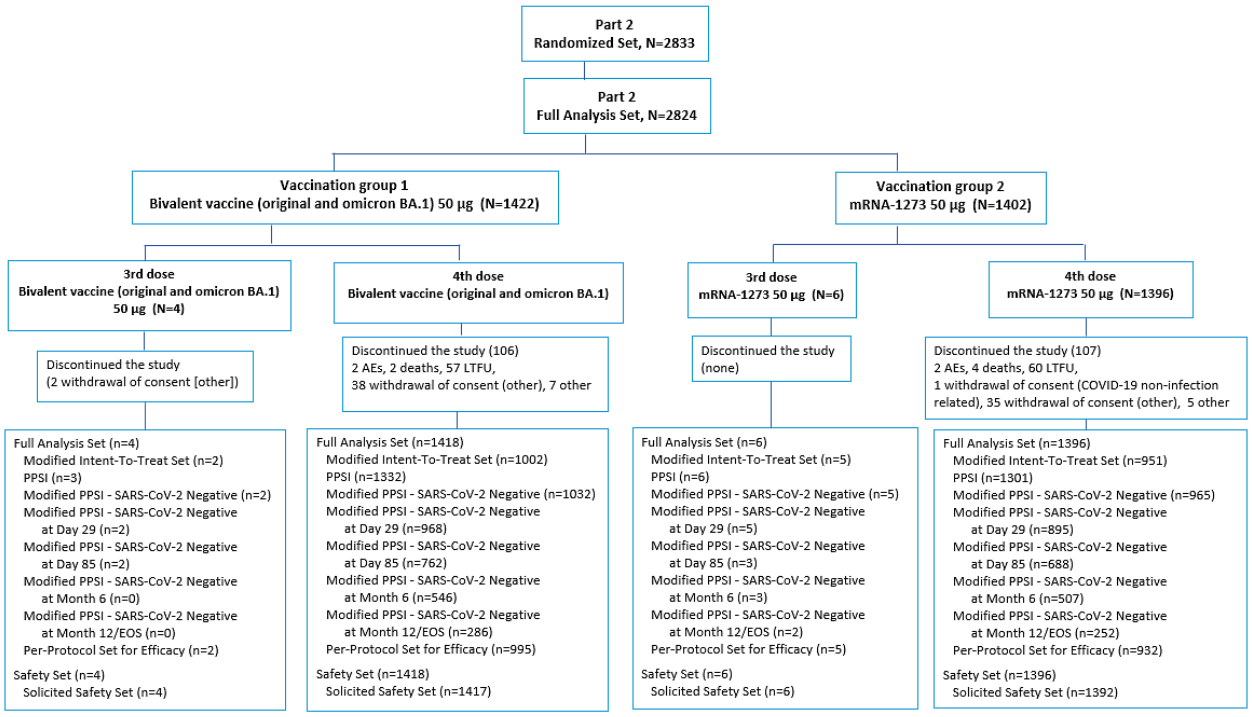
Table 6: Participant Disposition in Part 2 (Full Analysis Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4) n (%)	4th Dose (N=1418) n (%)	Total (N=1422) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1396) n (%)	Total (N=1402) n (%)	Overall (N=2824) n (%)
Completed study [a]	2 (50.0)	1312 (92.5)	1314 (92.4)	6 (100)	1289 (92.3)	1295 (92.4)	2609 (92.4)
Discontinued from study	2 (50.0)	106 (7.5)	108 (7.6)	0	107 (7.7)	107 (7.6)	215 (7.6)
Reason for discontinuation of study							
Adverse event (Other)	0	2 (0.1)	2 (0.1)	0	2 (0.1)	2 (0.1)	4 (0.1)
Adverse event (COVID-19 infection)	0	0	0	0	0	0	0
Death	0	2 (0.1)	2 (0.1)	0	4 (0.3)	4 (0.3)	6 (0.2)
Lost to follow-up	0	57 (4.0)	57 (4.0)	0	60 (4.3)	60 (4.3)	117 (4.1)
Physician decision	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0	0

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4) n (%)	4th Dose (N=1418) n (%)	Total (N=1422) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1396) n (%)	Total (N=1402) n (%)	Overall (N=2824) n (%)
Solicited AR/ reactogenicity event	0	0	0	0	0	0	0
Study terminated by Sponsor	0	0	0	0	0	0	0
Withdrawal of consent (COVID-19 non-infection related)	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Withdrawal of consent (Other)	2 (50.0)	38 (2.7)	40 (2.8)	0	35 (2.5)	35 (2.5)	75 (2.7)
Other	0	7 (0.5)	7 (0.5)	0	5 (0.4)	5 (0.4)	12 (0.4)

Abbreviations: AR = adverse reaction; COVID-19 = coronavirus disease 2019; EOS = end of study.
Notes: A total of 19 dosing errors occurred in Part 2 (3 participants in the bivalent vaccine [original and Omicron BA.1] arm received 25 µg instead of 50 µg, and 16 participants in the mRNA-1273 arm received 100 µg instead of 50 µg). The participants were included in the corresponding actual and planned study vaccine arms. Details of the dosing errors are provided in Listing 16.2.5.2.2.
Percentages were based on the number of participants in the Full Analysis Set.
The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.
a. Study Completion was defined as a participant who completed last scheduled procedure (Day 359/EOS).
Source: Table 14.1.1.1.2

Figure 4: Participant Disposition in Part 2



Abbreviations: AE = adverse event; EOS = end of study; LTFU = lost to follow-up; N = number of participants; PPSI = Per-Protocol Set for Immunogenicity; SARS-CoV-2 = severe acute. respiratory syndrome coronavirus 2.
Note: The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.
Sources: Table 14.1.1.1.2 and Table 14.1.2.1.2

Major Protocol Deviations

Part 1

Major protocol deviations in Part 1 of the study are summarized in Table below and included:

Administration of concomitant medication (immunosuppressants or other immune-modifying drugs) that was not permitted during the study (5 participants).

Administration of vaccine or medication (any investigational drug or vaccine other than the study vaccine) that was not permitted during the study (1 participant).

Randomization in the vaccine arm after participant met exclusion criterion (i.e., participant had participated in an interventional clinical trial within 28 days of screening).

A description of major protocol deviation is provided in CSR Listing 16.2.2.2.1.

Table 7: Major Protocol Deviations in Part 1 (Randomized Set)

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
Deviation Type	3rd Dose (N=1) n (%)	4th Dose (N=363) n (%)	Total (N=364) n (%)	3rd Dose (N=0) n (%)	4th Dose (N=358) n (%)	Total (N=358) n (%)	Overall (N=722) n (%)
Concomitant medication	0	4 (1.1)	4 (1.1)	–	2 (0.6)	2 (0.6)	6 (0.8)
Exclusion criteria	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)

Abbreviation: (–) = not applicable: IRT = interactive response technology.
Notes: Numbers were based on planned vaccine arm and percentages were based on the number of randomized participants.
A total of 726 participants comprised the Randomized Set in Part 1 of the study, but due to the IRT error where 4 participants were inadvertently assigned to the inactive study arm (100 µg dose), the "Overall" number of participants N=722 were included in Randomized Set for this table.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.
Source: Table 14.1.1.3.1

Part 2

Major protocol deviations in Part 2 of the study are summarized in Table below and included:

- Administration of incorrect dose of study vaccine (i.e., either full dose was not given or over the full dose was given to 19 participants).
- Administration of medication or vaccine (either immunosuppressants or other immune-modifying drugs, or any investigational drug or vaccine other than the study vaccine) that was not permitted during the study (17 participants overall).

Other deviations were reported for ≤5 participants. A description of all major protocol deviations is provided in CSR Listing 16.2.2.2.2.

Table 8: Major Protocol Deviations in Part 2 (Randomized Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
Deviation Type	3rd Dose (N=4) n (%)	4th Dose (N=1422) n (%)	Total (N=1426) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1401) n (%)	Total (N=1407) n (%)	Overall (N=2833) n (%)
Concomitant medication	0	6 (0.4)	6 (0.4)	0	11 (0.8)	11 (0.8)	17 (0.6)
Exclusion criteria	0	1 (0.1)	1 (0.1)	0	4 (0.3)	4 (0.3)	5 (0.2)
Inclusion criteria	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Inv randomization/ unblinding	0	2 (0.1)	2 (0.1)	0	2 (0.1)	2 (0.1)	4 (0.1)
Study vaccine admin/dispense	0	3 (0.2)	3 (0.2)	0	16 (1.1)	16 (1.1)	19 (0.7)
Study vaccine randomization	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)

Notes: Numbers were based on planned vaccine arm and percentages were based on the number of randomized participants.
The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.
Source: Table 14.1.1.3.2

Analysis Sets

Part 1

Analysis sets are summarized in the table below. A total of 726 participants were randomized in Part 1 of the study, and all but 1 participant received the study vaccine as the fourth dose. Two participants, one in each vaccine arm, did not receive a study vaccine.

The Safety Set and Solicited Safety Set included all 724 participants (n=367 for the Omicron BA.1 monovalent vaccine arm and n=357 for the mRNA-1273 vaccine arm). Four participants who received the Omicron BA.1 monovalent vaccine were excluded in the FAS due to assignment error in vaccine dose.

PPSI-Neg was the primary analysis set for analyses of immunogenicity and consisted of participants in the PPSI (see Section 4.1.4) who had no evidence of prior SARS-CoV-2 infection based on negative RT PCR and anti-nucleocapsid antibody testing up to the day of immunogenicity analysis.

The PPSI-Neg analysis set included n=275 in Omicron BA.1 monovalent vaccine arm and n=277 in the mRNA-1273 vaccine arm at Day 29. At Day 85, this analysis set included n=235 and n=226 in the Omicron BA.1 monovalent vaccine arm and mRNA-1273 vaccine arm, respectively.

The PPSE comprised all participants in the FAS who received the planned study vaccination, had no pre-vaccination immunologic or virologic evidence of SARS-CoV-2 infection, and had no major protocol deviations that impact key or critical data. This set included n=313 in the Omicron BA.1 monovalent vaccine arm and n=312 in the mRNA-1273 arm.

A list of participants included in each analysis set and the reasons for exclusion are provided in CSR Listing 16.2.3.1.

Table 9: Number of Participants in Each Analysis Set in Part 1 (Full Analysis Set)

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=1)	4th Dose (N=362)	Total (N=363)	3rd Dose (N=0)	4th Dose (N=357)	Total (N=357)	Overall (N=720)
FAS, n[a]	1	362	363	–	357	357	720
mITT, n (%)[b]	1 (100)	312 (86.2)	313 (86.2)	–	312 (87.4)	312 (87.4)	625 (86.8)
PPSI, n (%)[b]	1 (100)	353 (97.5)	354 (97.5)	–	349 (97.8)	349 (97.8)	703 (97.6)
Modified PPSI-Neg, n (%)[b]	1 (100)	306 (84.5)	307 (84.6)	–	307 (86.0)	307 (86.0)	614 (85.3)
PPSI-Neg at Day 29, n (%)[b]	1 (100)	274 (75.7)	275 (75.8)	–	277 (77.6)	277 (77.6)	552 (76.7)
PPSI–Neg at Day 85, n (%) [b]	1 (100)	234 (64.6)	235 (64.7)	–	226 (63.3)	226 (63.3)	461 (64.0)
PPSI–Neg at Month 6, n (%)[b]	0	160 (44.2)	160 (44.1)	–	138 (38.7)	138 (38.7)	298 (41.4)
PPSI-Neg at Month 12/EOS, n (%)[b]	0	74 (20.4)	74 (20.4)	–	61 (17.1)	61 (17.1)	135 (18.8)
PPSE, n (%)[b]	1 (100)	312 (86.2)	313 (86.2)	–	312 (87.4)	312 (87.4)	625 (86.8)
Safety Set, n[c]	1	366	367	–	357	357	724
Solicited Safety Set, n (%)[d]	1 (100)	366 (100)	367 (100)	–	357 (100)	357 (100)	724 (100)

Abbreviations: (–) = not applicable; EOS = end of study; FAS = Full Analysis Set; IRT = interactive response technology; mITT = Modified-Intent-to-Treat; PPSE = Per-Protocol Set for Efficacy; PPSI = Per-Protocol for Immunogenicity; PPSI-Neg = PPSI SARS-CoV-2 negative; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Notes: Due to an IRT system error, 4 participants were assigned to an inactive study arm, instead of the planned 50 µg Omicron BA.1 monovalent vaccine. For this reason, these 4 participants were not presented under Full Analysis Set. These 4 assignment errors were documented as dispensation errors. These 4 participants actually received the protocol-specified dose and were included in the 50 µg Omicron BA.1 monovalent vaccine arm based on actual vaccine received under Safety Set. Please refer to Listing 16.2.5.2.1 for the full list of dispensation errors.

The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

a. Numbers were based on planned vaccine arm.
b. Numbers were based on planned vaccine arm and percentages were based on the number of participants in the Full Analysis Set.
c. Numbers were based on actual vaccine arm.
d. Numbers were based on actual vaccine arm and percentages were based on the number of participants in the Safety Set.

Source: Table 14.1.2.1.1

Part 2

Analysis sets are summarized in the table below. A total of 2824 randomized participants received the study vaccine and were analyzed according to their randomized arm, and all but 10 participants received the study vaccine as the fourth dose.

The FAS and Safety Set included all 2824 participants (n=1422 for the bivalent vaccine [original and Omicron BA.1] arm and n=1402 for the mRNA-1273 arm). Overall, 5 participants did not contribute any solicited AR data and were excluded from the Solicited Safety Set.

Dosing errors, which were reported as major protocol deviations, occurred in 19 participants in the Safety Set. The planned study vaccine dose and actual dose received by each participant are provided in CSR Listing 16.2.5.2.2.

PPSI-Neg was the primary analysis set for analyses of immunogenicity and consisted of participants in the PPSI who had no evidence of prior SARS-CoV-2 infection based on negative RT PCR and anti-nucleocapsid antibody testing up to the day of immunogenicity analysis.

The PPSI-Neg analysis set included n=970 in the bivalent vaccine (original and Omicron BA.1) arm and n=900 in the mRNA-1273 arm at Day 29. At Day 85, this analysis set included n=764 and n=691 in the study vaccine and active control arm, respectively.

The PPSE comprised all participants in the FAS who received the planned study vaccination, had no pre-vaccination immunologic or virologic evidence of SARS-CoV-2 infection, and had no major protocol deviations that impact key or critical data. This set included n=997 in the bivalent vaccine (original and Omicron BA.1) arm and n=937 in the mRNA-1273 arm.

A list of participants included in each analysis set and the reasons for exclusion are provided in CSR Listing 16.2.3.2.

Table 10: Number of Participants in Each Analysis Set in Part 2 (Full Analysis Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4)	4th Dose (N=1418)	Total (N=1422)	3rd Dose (N=6)	4th Dose (N=1396)	Total (N=1402)	Overall (N=2824)
FAS, n[a]	4	1418	1422	6	1396	1402	2824
mITT, n (%)[b]	2 (50.0)	1002 (70.7)	1004 (70.6)	5 (83.3)	951 (68.1)	956 (68.2)	1960 (69.4)
PPSI, n (%)[b]	3 (75.0)	1332 (93.9)	1335 (93.9)	6 (100)	1301 (93.2)	1307 (93.2)	2642 (93.6)
Modified PPSI-Neg, n (%)[b]	2 (50.0)	1032 (72.8)	1034 (72.7)	5 (83.3)	965 (69.1)	970 (69.2)	2004 (71.0)
PPSI-Neg at Day 29, n (%)[b]	2 (50.0)	968 (68.3)	970 (68.2)	5 (83.3)	895 (64.1)	900 (64.2)	1870 (66.2)
PPSI-Neg at Day 85, n (%)[b]	2 (50.0)	762 (53.7)	764 (53.7)	3 (50.0)	688 (49.3)	691 (49.3)	1455 (51.5)
PPSI-Neg at Month 6, n (%)[b]	0	546 (38.5)	546 (38.4)	3 (50.0)	507 (36.3)	510 (36.4)	1056 (37.4)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4)	4th Dose (N=1418)	Total (N=1422)	3rd Dose (N=6)	4th Dose (N=1396)	Total (N=1402)	Overall (N=2824)
PPSI-Neg at Month 12/EOS, n (%)[b]	0	286 (20.2)	286 (20.1)	2 (33.3)	252 (18.1)	254 (18.1)	540 (19.1)
PPSE, n (%)[b]	2 (50.0)	995 (70.2)	997 (70.1)	5 (83.3)	932 (66.8)	937 (66.8)	1934 (68.5)
Safety Set, n[c]	4	1418	1422	6	1396	1402	2824
Solicited Safety Set, n (%)[d]	4 (100)	1417 (99.9)	1421 (99.9)	6 (100)	1392 (99.7)	1398 (99.7)	2819 (99.8)

Abbreviations: EOS = end of study; FAS = Full Analysis Set; mITT = Modified-Intent-to-Treat; PPSE = Per-Protocol Set for Efficacy; PPSI = Per-Protocol for Immunogenicity; PPSI-Neg = PPSI SARS-CoV-2 negative; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Notes: A total of 19 dosing errors occurred in Part 2 (3 participants in the bivalent vaccine (original and Omicron BA.1) arm received 25 µg instead of 50 µg and 16 participants in the mRNA-1273 arm received 100 µg instead of 50 µg). The participants were included in the corresponding actual and planned vaccine arms. Details of the dosing errors are provided in Listing 16.2.5.2.2.

The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

a. Numbers were based on planned vaccine arm.

b. Numbers were based on planned vaccine arm and percentages were based on the number of participants in the Full Analysis Set.

c. Numbers were based on actual vaccine arm.

d. Numbers were based on actual vaccine arm and percentages were based on the number of participants in the Safety Set.

Source: Table 14.1.2.1.2

Baseline data

Part 1

Demographics

The baseline characteristics (age, sex, race, interval since last COVID-19 vaccine, and prior SARS-CoV-2 infection at Baseline) between the 2 vaccine arms, the Omicron BA.1 monovalent vaccine and mRNA 1273, were balanced. The average age of participants was approximately 57 years in both arms, with an age range from 19 to 87 years. About one-third of participants was ≥65 years and sex was balanced between vaccine arms. The majority of participants were White, reflecting that of the UK population where this study was conducted. The proportion of participants with evidence of SARS-CoV- 2 infection at Baseline was 12.9% and 12.0% in the Omicron BA.1 monovalent vaccine and mRNA 1273 arms, respectively. The mean time from most recent COVID-19 vaccine in the fourth dose arm was similar (4.16 months and 4.12 months in the Omicron BA.1 monovalent vaccine and mRNA-1273 arms, respectively).

Demographic and baseline characteristics were also balanced in the Safety Analysis Set (N=724) and in the PPSI-Neg analysis set up to Day 29 (N=552) in Part 1 of the study.

Table 11: Participant Demographics and Characteristics in Part 1 (Full Analysis Set)

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=1)	4th Dose (N=362)	Total (N=363)	3rd Dose (N=0)	4th Dose (N=357)	Total (N=357)	Overall (N=720)
Age (years)							
n	1	362	363	–	357	357	720
Mean (SD)	19.0 (NA)	57.7 (12.83)	57.6 (12.97)	–	57.3 (13.22)	57.3 (13.22)	57.4 (13.09)
Median	19.0	60.5	60.0	–	60.0	60.0	60.0
Min, Max	19, 19	22, 87	19, 87	–	21, 87	21, 87	19, 87
Age group (stratification for randomization), n (%)							
≥16 and <65 years	1 (100)	237 (65.5)	238 (65.6)	–	235 (65.8)	235 (65.8)	473 (65.7)
≥65 years	0	125 (34.5)	125 (34.4)	–	122 (34.2)	122 (34.2)	247 (34.3)
Sex, n (%)							
Male	1 (100)	163 (45.0)	164 (45.2)	–	155 (43.4)	155 (43.4)	319 (44.3)
Female	0	199 (55.0)	199 (54.8)	–	202 (56.6)	202 (56.6)	401 (55.7)
Race, n (%)							
White	1 (100)	348 (96.1)	349 (96.1)	–	335 (93.8)	335 (93.8)	684 (95.0)
English, Welsh, Scottish, Northern Irish, or British	1 (100)	286 (79.0)	287 (79.1)	–	277 (77.6)	277 (77.6)	564 (78.3)
Irish	0	5 (1.4)	5 (1.4)	–	3 (0.8)	3 (0.8)	8 (1.1)
Gypsy or Irish Traveller	0	0	0	–	0	0	0
Any Other White Background	0	17 (4.7)	17 (4.7)	–	17 (4.8)	17 (4.8)	34 (4.7)
Unknown	0	40 (11.0)	40 (11.0)	–	40 (11.2)	40 (11.2)	80 (11.1)
Mixed or Multiple Ethnic Groups	0	3 (0.8)	3 (0.8)	–	5 (1.4)	5 (1.4)	8 (1.1)
White and Black Caribbean	0	0	0	–	0	0	0
White and Black African	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
White and Asian	0	2 (0.6)	2 (0.6)	–	2 (0.6)	2 (0.6)	4 (0.6)
Any other mixed or multiple ethnic background	0	1 (0.3)	1 (0.3)	–	2 (0.6)	2 (0.6)	3 (0.4)
Unknown	0	0	0	–	0	0	0

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=1)	4th Dose (N=362)	Total (N=363)	3rd Dose (N=0)	4th Dose (N=357)	Total (N=357)	Overall (N=720)
Asian or Asian British	0	10 (2.8)	10 (2.8)	–	10 (2.8)	10 (2.8)	20 (2.8)
Indian	0	6 (1.7)	6 (1.7)	–	0	0	6 (0.8)
Pakistani	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Bangladeshi	0	0	0	–	0	0	0
Chinese	0	1 (0.3)	1 (0.3)	–	4 (1.1)	4 (1.1)	5 (0.7)
Any Other Asian Background	0	3 (0.8)	3 (0.8)	–	5 (1.4)	5 (1.4)	8 (1.1)
Unknown	0	0	0	–	0	0	0
Black, African, Caribbean, or Black British	0	0	0	–	0	0	0
African	0	0	0	–	0	0	0
Caribbean	0	0	0	–	0	0	0
Any Other Black, African, or Caribbean Background	0	0	0	–	0	0	0
Unknown	0	0	0	–	0	0	0
Other ethnic group	0	1 (0.3)	1 (0.3)	–	5 (1.4)	5 (1.4)	6 (0.8)
Arab	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Any other ethnic group	0	1 (0.3)	1 (0.3)	–	4 (1.1)	4 (1.1)	5 (0.7)
Unknown	0	0	0	–	0	0	0
Not Reported	0	0	0	–	2 (0.6)	2 (0.6)	2 (0.3)
Unknown	0	0	0	–	0	0	0
Weight (kg)							
n	1	359	360	–	356	356	716
Mean (SD)	54.2 (NA)	79.8 (17.70)	79.7 (17.72)	–	82.0 (18.44)	82.0 (18.44)	80.9 (18.10)
Median	54.2	77.5	77.4	–	80.2	80.2	79.0
Min, Max	54, 54	42, 139	42, 139	–	38, 164	38, 164	38, 164
Height (cm)							
n	1	359	360	–	356	356	716
Mean (SD)	162.0 (NA)	169.5 (9.80)	169.5 (9.79)	–	170.0 (9.57)	170.0 (9.57)	169.7 (9.68)
Median	162.0	169.0	169.0	–	170.0	170.0	169.8
Min, Max	162, 162	134, 195	134, 195	–	146, 200	146, 200	134, 200

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=1)	4th Dose (N=362)	Total (N=363)	3rd Dose (N=0)	4th Dose (N=357)	Total (N=357)	Overall (N=720)
Body mass index (kg/m²)							
n	1	359	360	–	356	356	716
Mean (SD)	20.7 (NA)	27.7 (5.67)	27.7 (5.67)	–	28.3 (5.83)	28.3 (5.83)	28.0 (5.76)
Median	20.7	26.7	26.7	–	27.1	27.1	26.9
Min, Max	21, 21	17, 55	17, 55	–	18, 56	18, 56	17, 56
Pre-booster/baseline RT-PCR results, n (%)							
Negative	1 (100)	358 (98.9)	359 (98.9)	–	351 (98.3)	351 (98.3)	710 (98.6)
Positive	0	4 (1.1)	4 (1.1)	–	6 (1.7)	6 (1.7)	10 (1.4)
Missing	0	0	0	–	0	0	0
Pre-booster/baseline Elecsys anti-SARS-CoV-2 results, n (%)							
Negative	1 (100)	315 (87.0)	316 (87.1)	–	318 (89.1)	318 (89.1)	634 (88.1)
Positive	0	44 (12.2)	44 (12.1)	–	37 (10.4)	37 (10.4)	81 (11.3)
Missing	0	3 (0.8)	3 (0.8)	–	2 (0.6)	2 (0.6)	5 (0.7)
Pre-booster/baseline SARS-CoV-2 status, n (%) [a]							
Negative	1 (100)	312 (86.2)	313 (86.2)	–	312 (87.4)	312 (87.4)	625 (86.8)
Positive	0	47 (13.0)	47 (12.9)	–	43 (12.0)	43 (12.0)	90 (12.5)
Missing	0	3 (0.8)	3 (0.8)	–	2 (0.6)	2 (0.6)	5 (0.7)
Time duration from most recent COVID-19 vaccine to booster dose (months) [b]							
n	1	362	363	–	357	357	720
Mean (SD)	7.56 (NA)	4.16 (0.737)	4.17 (0.757)	–	4.12 (0.681)	4.12 (0.681)	4.15 (0.720)
Median	7.56	4.06	4.07	–	4.07	4.07	4.07
Min, Max	7.6, 7.6	3.0, 8.9	3.0, 8.9	–	3.0, 5.6	3.0, 5.6	3.0, 8.9

Abbreviations: (–) = not applicable; COVID-19 = coronavirus disease 2019; Max = maximum; Min = minimum; NA = not applicable; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

Notes: Percentages were based on the number of participants in Full Analysis Set.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

[a] Pre-booster/Baseline SARS-CoV-2 Status was positive if there was immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative was defined as negative RT-PCR test and negative Elecsys result at Day 1. Missing was defined as missing in both tests, or with one test was missing and one test negative.

[b] Time Duration from most recent COVID-19 vaccine to booster dose (months)=(booster dose day — most recent COVID-19 vaccine + 1) / 30.4375.

Source: Table 14.1.3.1.1

Medical History

Overall, 89.2% participants had at least 1 medical history event in Part 1 of the study.

The most commonly reported medical history event by SOC was surgical and medical procedures (26.8%), followed by musculoskeletal and connective tissue disorders (24.7%), vascular disorders (24.6%), respiratory/thoracic/mediastinal disorders and GI disorders (19.8% each), and metabolism and nutrition disorders (19.2%). Medical history events by PTs that occurred in ≥10% of participants in any vaccine arm included hypertension (~19% in each arm), asthma (12.5% to 16.2%), osteoarthritis (10.6% in the active comparator arm), and seasonal allergy (10.9% in the active comparator arm).

A listing of each participant's medical history is provided in CSR Listing 16.2.4.2.1 (not included in this AR).

Part 2

Demographics

The baseline characteristics (age, sex, race, interval since last COVID-19 vaccine, and prior SARS-CoV 2 infection at Baseline) between the 2 vaccine arms, bivalent vaccine (original and Omicron BA.1) and mRNA-1273, were balanced. The average age of participants was approximately 57 years in both arms, with an age range from 17 to 89 years. About one-third of participants was ≥65 years and sex was balanced between vaccine arms. The majority of participants were White, reflecting that of the UK population where this study was conducted. The proportion of participants with evidence of SARS-CoV-2 infection at Baseline was 22.6% and 26.0% in the bivalent vaccine (original and Omicron BA.1) arm and mRNA-1273 vaccine arm, respectively. The mean time from most recent COVID-19 vaccine in the fourth dose arm was similar in both vaccine arms (5.5 months).

Table 12: Participant Demographics and Characteristics in Part 2 (Full Analysis Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4)	4th Dose (N=1418)	Total (N=1422)	3rd Dose (N=6)	4th Dose (N=1396)	Total (N=1402)	Overall (N=2824)
Age (years)							
n	4	1418	1422	6	1396	1402	2824
Mean (SD)	43.5 (14.62)	57.5 (12.50)	57.5 (12.52)	46.5 (20.54)	57.0 (12.77)	57.0 (12.82)	57.2 (12.67)
Median	45.5	60.0	60.0	44.5	60.0	60.0	60.0

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4)	4th Dose (N=1418)	Total (N=1422)	3rd Dose (N=6)	4th Dose (N=1396)	Total (N=1402)	Overall (N=2824)
Min, Max	24, 59	18, 89	18, 89	17, 70	18, 81	17, 81	17, 89
Age group (stratification for randomization), n (%)							
≥16 and <65 years	4 (100)	941 (66.4)	945 (66.5)	4 (66.7)	931 (66.7)	935 (66.7)	1880 (66.6)
≥65 years	0	477 (33.6)	477 (33.5)	2 (33.3)	465 (33.3)	467 (33.3)	944 (33.4)
Sex, n (%)							
Male	2 (50.0)	727 (51.3)	729 (51.3)	3 (50.0)	703 (50.4)	706 (50.4)	1435 (50.8)
Female	2 (50.0)	691 (48.7)	693 (48.7)	3 (50.0)	693 (49.6)	696 (49.6)	1389 (49.2)
Race, n (%)							
White	4 (100)	1341 (94.6)	1345 (94.6)	4 (66.7)	1311 (93.9)	1315 (93.8)	2660 (94.2)
English, Welsh, Scottish, Northern Irish, or British	2 (50.0)	1153 (81.3)	1155 (81.2)	3 (50.0)	1114 (79.8)	1117 (79.7)	2272 (80.5)
Irish	0	15 (1.1)	15 (1.1)	0	10 (0.7)	10 (0.7)	25 (0.9)
Gypsy or Irish Traveller	0	2 (0.1)	2 (0.1)	0	0	0	2 (0.1)
Any Other White Background	0	56 (3.9)	56 (3.9)	0	75 (5.4)	75 (5.3)	131 (4.6)
Unknown	2 (50.0)	118 (8.3)	120 (8.4)	1 (16.7)	116 (8.3)	117 (8.3)	237 (8.4)
Mixed or Multiple Ethnic Groups	0	22 (1.6)	22 (1.5)	0	26 (1.9)	26 (1.9)	48 (1.7)
White and Black Caribbean	0	3 (0.2)	3 (0.2)	0	1 (0.1)	1 (0.1)	4 (0.1)
White and Black African	0	2 (0.1)	2 (0.1)	0	0	0	2 (0.1)
White and Asian	0	11 (0.8)	11 (0.8)	0	13 (0.9)	13 (0.9)	24 (0.8)
Any other mixed or multiple ethnic background	0	5 (0.4)	5 (0.4)	0	7 (0.5)	7 (0.5)	12 (0.4)
Unknown	0	1 (0.1)	1 (0.1)	0	5 (0.4)	5 (0.4)	6 (0.2)
Asian or Asian British	0	32 (2.3)	32 (2.3)	1 (16.7)	39 (2.8)	40 (2.9)	72 (2.5)
Indian	0	10 (0.7)	10 (0.7)	0	14 (1.0)	14 (1.0)	24 (0.8)
Pakistani	0	0	0	0	3 (0.2)	3 (0.2)	3 (0.1)
Bangladeshi	0	0	0	0	0	0	0
Chinese	0	10 (0.7)	10 (0.7)	1 (16.7)	7 (0.5)	8 (0.6)	18 (0.6)
Any Other Asian Background	0	10 (0.7)	10 (0.7)	0	13 (0.9)	13 (0.9)	23 (0.8)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4)	4th Dose (N=1418)	Total (N=1422)	3rd Dose (N=6)	4th Dose (N=1396)	Total (N=1402)	Overall (N=2824)
Unknown	0	3 (0.2)	3 (0.2)	0	2 (0.1)	2 (0.1)	5 (0.2)
Black, African, Caribbean, or Black British	0	6 (0.4)	6 (0.4)	0	6 (0.4)	6 (0.4)	12 (0.4)
African	0	3 (0.2)	3 (0.2)	0	4 (0.3)	4 (0.3)	7 (0.2)
Caribbean	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Any Other Black, African, or Caribbean Background	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Unknown	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Missing	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Other ethnic group	0	4 (0.3)	4 (0.3)	0	7 (0.5)	7 (0.5)	11 (0.4)
Arab	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Any other ethnic group	0	2 (0.1)	2 (0.1)	0	5 (0.4)	5 (0.4)	7 (0.2)
Unknown	0	2 (0.1)	2 (0.1)	0	0	0	2 (0.1)
Not Reported	0	11 (0.8)	11 (0.8)	1 (16.7)	6 (0.4)	7 (0.5)	18 (0.6)
Unknown	0	2 (0.1)	2 (0.1)	0	1 (0.1)	1 (0.1)	3 (0.1)
Weight (kg)							
n	4	1408	1412	6	1381	1387	2799
Mean (SD)	80.0 (16.91)	80.9 (17.87)	80.9 (17.86)	75.8 (13.02)	81.2 (18.86)	81.2 (18.83)	81.0 (18.35)
Median	75.5	79.1	79.1	77.0	79.0	79.0	79.0
Min, Max	66, 103	44, 179	44, 179	54, 91	39, 190	39, 190	39, 190
Height (cm)							
n	4	1404	1408	6	1373	1379	2787
Mean (SD)	168.7 (14.23)	170.7 (9.30)	170.7 (9.31)	165.3 (3.43)	171.1 (9.77)	171.1 (9.76)	170.9 (9.54)
Median	169.8	171.0	171.0	165.0	171.0	171.0	171.0
Min, Max	152, 183	141, 198	141, 198	161, 170	142, 202	142, 202	141, 202
Body mass index (kg/m^2)							
n	4	1403	1407	6	1373	1379	2786
Mean (SD)	28.2 (4.93)	27.7 (5.55)	27.7 (5.55)	27.7 (4.73)	27.6 (5.76)	27.6 (5.75)	27.7 (5.65)
Median	30.4	26.8	26.8	29.0	26.8	26.8	26.8

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4)	4th Dose (N=1418)	Total (N=1422)	3rd Dose (N=6)	4th Dose (N=1396)	Total (N=1402)	Overall (N=2824)
Min, Max	21, 31	17, 60	17, 60	20, 32	15, 71	15, 71	15, 71
Pre-booster/baseline RT-PCR results, n (%)							
Negative	3 (75.0)	1299 (91.6)	1302 (91.6)	6 (100)	1284 (92.0)	1290 (92.0)	2592 (91.8)
Positive	0	19 (1.3)	19 (1.3)	0	15 (1.1)	15 (1.1)	34 (1.2)
Missing	1 (25.0)	100 (7.1)	101 (7.1)	0	97 (6.9)	97 (6.9)	198 (7.0)
Pre-booster/baseline Elecsys anti-SARS-CoV-2 results, n (%)							
Negative	2 (50.0)	1091 (76.9)	1093 (76.9)	5 (83.3)	1028 (73.6)	1033 (73.7)	2126 (75.3)
Positive	2 (50.0)	311 (21.9)	313 (22.0)	1 (16.7)	356 (25.5)	357 (25.5)	670 (23.7)
Missing	0	16 (1.1)	16 (1.1)	0	12 (0.9)	12 (0.9)	28 (1.0)
Pre-booster/baseline SARS-CoV-2 status, n (%) [a]							
Negative	2 (50.0)	1002 (70.7)	1004 (70.6)	5 (83.3)	951 (68.1)	956 (68.2)	1960 (69.4)
Positive	2 (50.0)	320 (22.6)	322 (22.6)	1 (16.7)	363 (26.0)	364 (26.0)	686 (24.3)
Missing	0	96 (6.8)	96 (6.8)	0	82 (5.9)	82 (5.8)	178 (6.3)
Time duration from most recent COVID-19 vaccine to booster dose (months) [b]							
n	4	1418	1422	6	1396	1402	2824
Mean (SD)	9.96 (2.787)	5.52 (1.019)	5.54 (1.053)	5.22 (2.706)	5.53 (1.013)	5.53 (1.024)	5.53 (1.038)
Median	9.48	5.45	5.45	4.35	5.42	5.42	5.45
Min, Max	7.5, 13.4	3.1, 11.2	3.1, 13.4	3.4, 10.6	2.8, 9.9	2.8, 10.6	2.8, 13.4

Abbreviations: COVID-19 = coronavirus disease 2019; Max = maximum; Min = minimum; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

Notes: Percentages were based on the number of participants in Full Analysis Set.

The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

[a] Pre-booster/Baseline SARS-CoV-2 Status was positive if there was immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative was defined as negative RT-PCR test and negative Elecsys result at Day 1. Missing was defined as missing in both tests, or with one test was missing and one test negative.

[b] Time Duration from most recent COVID-19 vaccine to booster dose (months) = (booster dose day — most recent COVID-19 vaccine + 1) / 30.4375.

Source: Table 14.1.3.1.2

Assessor's comment:

Participant demographics are overall well balanced in part 1 and part 2 with regards to age, sex and ethnicity. Also rates of prior SARS-CoV-2 infections and duration since last booster vaccination are well balanced.

Medical History

Overall, 84.5% participants had at least 1 medical history event in Part 2 of the study.

The most commonly reported medical history event by SOC was vascular disorders (21.2%), followed by musculoskeletal and connective tissue disorders and GI disorders (20.6%), surgical and medical procedures (17.4%), respiratory/thoracic/mediastinal disorders (17.0%), metabolism and nutrition disorders (16.6%), and immune system disorders (15.8%). Medical history events by PTs that occurred in ≥10% of participants in any vaccine arm included hypertension (18.3% to 18.9%), seasonal allergy (12.8% to 14.8%%), and asthma (10.6% to 12.2%).

A listing of each participant's medical history is provided in CSR Listing 16.2.4.2.2 (not included in this AR).

Prior and Concomitant Therapy

Part 1

Overall, concomitant medications or non-study vaccines were reported for 43.1% and 51.2% of participants within 7 days and within 28 days after vaccination, respectively.

A total of 87.7% (635/724) of participants reported at least 1 concomitant medication through 28 days after vaccination. Between the vaccine arms, the most frequently used concomitant medication was paracetamol (41.4% and 43.1%). All other medications were reported for ≤15% of participants in at least one of the vaccine arms.

Use of concomitant medications or non-study vaccines in Part 1 of the study are summarized in Table 14.1.5.1.1 (not included in this AR). Concomitant medications reported by PT through 28 days after vaccination are summarized in Table 14.1.5.2.1 (not included in this AR).

Part 2

Overall, concomitant medications or non-study vaccines were reported for 37.7% and 47.2% of participants within 7 days and within 28 days after vaccination, respectively.

A total of 84.9% (2397/2824) of participants reported at least 1 concomitant medication through 28 days after vaccination. Between the vaccine arms, the most frequently used concomitant medication was paracetamol (33.5% and 37.2%). All other medications were reported for <15% of participants in at least one of the vaccine arms.

Use of concomitant medications or non-study vaccines in Part 2 of the study are summarized in Table 14.1.5.1.2. Concomitant medications reported by PT through 28 days after vaccination are summarized in Table 14.1.5.2.2 (not included in this AR).

Study Duration

Part 1

Between 16 February 2022 and 24 March 2022, 726 participants were randomized in Part 1 of the study. Two participants were randomized but did not receive the study vaccine. The median time on study was 357 days (range: 29 to 441 days) and 357 days (range: 29 to 440 days) in the Omicron BA.1 monovalent vaccine and mRNA-1273 arms, respectively.

Table 13: Summary of Study Duration in Part 1 (Safety Set)

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=1) n (%)	4th Dose (N=366) n (%)	Total (N=367) n (%)	3rd Dose (N=0) n (%)	4th Dose (N=357) n (%)	Total (N=357) n (%)	Overall (N=724) n (%)
Study duration from randomization (days)							
n	1	366	367	–	357	357	724
Mean (SD)	249.0 (N/A)	349.8 (46.12)	349.5 (46.35)	–	345.8 (52.12)	345.8 (52.12)	347.7 (49.28)
Median	249.0	357.0	357.0	–	357.0	357.0	357.0
Min, Max	249, 249	29, 441	29, 441	–	29, 440	29, 440	29, 441
Study duration from study injection (days)							
n	1	366	367	–	357	357	724
Mean (SD)	249.0 (N/A)	349.8 (46.12)	349.5 (46.35)	–	345.8 (52.12)	345.8 (52.12)	347.7 (49.28)
Median	249.0	357.0	357.0	–	357.0	357.0	357.0
Min, Max	249, 249	29, 441	29, 441	–	29, 440	29, 440	29, 441

Abbreviations: (–) = not applicable; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation.
Notes: Numbers were based on actual vaccine arm, and percentages were based on the number of participants in Safety Set.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.
Source: Table 14.1.6.1

Part 2

Between 02 April 2022 and 17 June 2022, 2833 participants were randomized in Part 2 of the study. Nine participants were randomized but did not receive the study vaccine. A total of 2824 participants were included in the FAS, which comprised all randomized participants who received the study vaccine and were analyzed according to their randomized arm. The median time on study was 359 days (range: 22 to 434 days) and 359 days (range: 6 to 439 days) in the bivalent vaccine (original and Omicron BA.1) arm and mRNA-1273 vaccine arm, respectively.

Table 14: Summary of Study Duration in Part 2 (Safety Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4) n (%)	4th Dose (N=1418) n (%)	Total (N=1422) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1396) n (%)	Total (N=1402) n (%)	Overall (N=2824) n (%)
Study duration from randomization (days)							
n	4	1418	1422	6	1396	1402	2824
Mean (SD)	290.0 (103.04)	350.1 (50.37)	349.9 (50.62)	358.5 (7.23)	351.9 (47.54)	351.9 (47.44)	350.9 (49.07)
Median	313.5	359.0	359.0	357.0	359.0	359.0	359.0
Min, Max	151, 382	22, 434	22, 434	349, 367	6, 439	6, 439	6, 439
Study duration from study injection (days)							
n	4	1418	1422	6	1396	1402	2824
Mean (SD)	290.0 (103.04)	350.1 (50.37)	349.9 (50.62)	358.5 (7.23)	351.9 (47.54)	351.9 (47.44)	350.9 (49.07)
Median	313.5	359.0	359.0	357.0	359.0	359.0	359.0
Min, Max	151, 382	22, 434	22, 434	349, 367	6, 439	6, 439	6, 439

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation.
Notes: Numbers were based on actual vaccine arm, and percentages were based on the number of participants in Safety Set.
The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.
Source: Table 14.1.6.2

Immunogenicity results

Blood was collected from study participants for measurement of SARS-CoV-2 specific antibody responses at timepoints specified in mRNA-1273 P305 Clinical Study Protocol Table 1 (not included in this AR). The assays used for the assessment of the immunogenicity endpoints are presented in Section 8.6.1 of the mRNA-1273 P305 Clinical Study Protocol Table 1 (not included in this AR).

In Part 1, the primary immunogenicity objective was to demonstrate the non-inferiority of the immune response of the Omicron BA.1 monovalent vaccine compared to the original mRNA-1273 vaccine administered as a fourth dose against the Omicron BA.1 strain at Day 29 or Day 85. Superior immune responses of the Omicron BA.1 monovalent vaccine compared with mRNA-1273 vaccination against the Omicron BA.1 strain was a key secondary endpoint. Non-inferior immune response of the Omicron BA.1 monovalent vaccine compared with mRNA-1273 vaccination against both Omicron BA.1 and the ancestral strain, as well as the evaluation of the SRR against both strains were all secondary endpoints. The SRR was defined by an increase of GMC from pre-study vaccination (booster) below the LLOQ to at least 4 x LLOQ, or a 4-fold or greater rise if pre-study vaccination was ≥LLOQ.

In Part 2, the primary immunogenicity objectives include demonstration of non-inferior and superior immune responses against Omicron BA.1 and non-inferior immune response against the ancestral strain for the bivalent vaccine (original and Omicron BA.1) compared with the mRNA- 1273 vaccination at Day 29 or Day 85. The evaluation of the SRR against the Omicron BA.1 was a secondary endpoint in Part 2.

PPSI-NEG, the primary immunogenicity analysis sets in Part 1 and Part 2 of this study were based on participants who received the fourth dose and had no evidence of SARS-CoV-2 infection up until the analysis visit.

SARS-CoV-2 Specific Neutralizing Antibodies

Part 1

Omicron BA.1

PPSI-Neg (Primary Immunogenicity Set)

The summary of the nAb responses against the Omicron BA.1 strain in the PPSI-Neg primary immunogenicity set for Part 1 is presented in Table 14.

At Baseline (prior to study vaccination), the observed GMC was 70.1 (95% CI: 62.6, 78.3) in the Omicron BA.1 monovalent vaccine arm and 67.3 (95% CI: 60.0, 75.4) in the mRNA-1273 vaccine arm (Table 14).

At Day 29, the observed GMC was 537.7 (95% CI: 478.2, 604.6) for the Omicron BA.1 monovalent vaccine arm and 302.8 (95% CI: 274.8, 333.6) for the mRNA-1273 vaccine arm, which represent 7.7-fold and 4.5-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 7.7 [7.0, 8.4] and 4.5 [4.1, 4.9]), respectively (Table 14). The Day 29 GMR was 1.73 (99% CI: 1.49, 2.01), which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI $\geq$0.67). Additionally, superiority of the immune response of Omicron BA.1 monovalent vaccine compared with the mRNA-1273 vaccine against Omicron BA.1 (key secondary objective) was demonstrated based on the lower bound of the 99% CI >1 (Table 16). The SRR was 83.2% (95% CI: 78.2%, 87.4%) and 55.2% (95% CI: 49.2%, 61.2%) after the Omicron BA.1 monovalent and mRNA-1273 vaccines, respectively, with an SRR difference of 28.0% (95% CI: 20.5%, 35.2%).

At Day 85, the observed GMC was 284.7 (95% CI: 248.0, 326.7) for the Omicron BA.1 monovalent vaccine arm and 152.6 (95% CI: 135.1, 172.3) for the mRNA-1273 vaccine arm, which represent 4.0-fold and 2.3-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 4.0 [3.6, 4.4] and 2.3 [2.1, 2.5], respectively (Table 14). The Day 85 GMR was 1.763 (96% CI: 1.546, 2.001), which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 96% CI $\geq$0.67) (Table 16). Additionally, superiority of the immune response of the Omicron BA.1 monovalent vaccine compared with the mRNA-1273 vaccine against the Omicron BA.1 (key secondary objective) was demonstrated based on the lower bound of the 96% CI >1.0 (Table 16). The SRR was 48.3% (95% CI: 41.7%, 54.9%) and 15.9% (95% CI: 11.4%, 21.4%) after the Omicron BA.1 monovalent and mRNA-1273 vaccines, respectively (Table 14), with an SRR difference of 32.4% (95% CI: 24.2%, 40.2%).

For Day 179 results, refer to Table 14 and Table 16.

For results at Day 359 from participants who did and did not receive an additional vaccination outside of this study refer to Table 14 and Table 16.

PPSI (Supportive Analysis)

The summary of the nAb responses against the Omicron BA.1 strain in the PPSI set is presented in Table 15.

As expected, GMC values in the PPSI set were generally higher than that of the PPSI-Neg Set as PPSI includes participants who were SARS-CoV-2 positive at Baseline or during the study (Table 15).

At Baseline (prior to study vaccination), the observed GMC was 81.7 (95% CI: 73.1, 91.4) in the Omicron BA. 1 monovalent vaccine arm and 79.6 (95% CI: 70.9, 89.4) in the mRNA-1273 vaccine arm (Table 15).

At Day 29, the observed GMC was 655.0 (95% CI: 587.5, 732.1) for the Omicron BA.1 monovalent vaccine arm and 381.5 (95% CI: 343.8, 423.3) for the mRNA-1273 vaccine arm, which represent 8.0-fold and 4.8-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 8.0 [7.3, 8.8] and 4.8 [4.4, 5.2], respectively) (Table 15). The Day 29 GMR was 1.69 (99% CI: 1.46, 1.96), which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67) (Table 17). Additionally, superiority of the immune response of the Omicron BA.1 monovalent vaccine compared with the mRNA-1273 vaccine against the Omicron BA.1 (key secondary objective) was demonstrated based on the lower bound of the 99% CI >1.0 (Table 17). The SRR was 82.4% (95% CI: 78.1%, 86.3%) and 55.9% (95% CI: 50.5%, 61.2%) after the Omicron BA.1 monovalent and the mRNA-1273 vaccines, respectively, with an SRR difference of 26.3% (95% CI: 19.9%, 32.8%).

At Day 85, the observed GMC was 457.2 (95% CI: 397.9, 525.4) for the Omicron BA 1 monovalent vaccine arm and 268.4 (95% CI: 232.5, 309.8) for the mRNA-1273 arm, which represent 5.6-fold and 3.4-fold increases respectively, over the baseline (observed GMFR [95% CI] values of 5.6 [5.0, 6.4] and 3.4 [3.0, 3.9], respectively) (Table 15). The Day 85 GMR was 1.67 (96% CI: 1.40, 1.99), which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 96% CI > 0.67) (Table 17). Additionally, superiority of the immune response of the Omicron BA.1 monovalent vaccine compared with the mRNA-1273 vaccine against the Omicron BA.1 (key secondary objective) was demonstrated based on the lower bound of the 96% CI >1.0 (Table 17). The SRR was 55.6% (95% CI: 50.1%, 60.9%) and 30.8% (95% CI: 25.9%, 36.1%) after the Omicron BA.1 monovalent and mRNA-1273 vaccines, respectively (Table 15), with an SRR difference of 24.4% (CI: 17.2%, 31.5%).

For Day 179 results, refer to Table 15 and Table 17.

For Day 359 results, refer to Table 15.

Ancestral Strain

PPSI-Neg (Primary Immunogenicity Set)

The summary of the nAb responses against the ancestral strain in the PPSI-Neg primary immunogenicity set is presented in Table 18.

At Baseline (prior to study vaccination), the observed GMC was 731.7 (95% CI: 662.2, 808.5) in the Omicron BA.1 monovalent vaccine arm and 634.3 (95% CI: 575.6, 699.0) in the mRNA-1273 vaccine arm (Table 18).

At Day 29, the observed GMC was 2699.7 (95% CI: 2431.3, 2997.7) for the Omicron BA.1 monovalent vaccine arm and 3020.6 (95% CI: 2776.5, 3286.2) for the mRNA-1273 vaccine arm, which represent 3.7-fold and 4.8-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 3.7 [3.4, 4.0] and 4.8 [4.4, 5.2], respectively) (Table 18). The Day 29 GMR was 0.82 (95% CI: 0.74. 0.91) (Table 20), which met the pre-specified secondary immunogenicity criterion of non-inferiority (the lower bound of 95% CI ≥0.67). The SRR was 43.1% (95% CI: 37.1%, 49.2%) and 59.0% (95% CI: 52.9%, 65.0%) (Table 18) after the Omicron BA.1 monovalent and the mRNA-1273 vaccines, respectively, with an SRR difference of -16.0% (95% CI: -24.2%, -7.5%).

At Day 85, the observed GMC was 1401.2 (95% CI: 1236.9, 1587.4) for the Omicron BA 1 monovalent vaccine arm and 1559.4 (95% CI: 1401.2, 1735.5) for the mRNA-1273 vaccine arm, which represent

1.9-fold and 2.5-fold increases respectively, over the baseline (observed GMFR [95% CI] values of 1.9 [1.7, 2.1] and 2.5 [2.3, 2.7], respectively) (Table 18). The Day 85 GMR was 0.80 (95% CI: 0.71, 0.90), which met the pre-specified secondary immunogenicity criterion of non-inferiority (the lower bound of 95% CI ≥0.67) (Table 20). The SRR was 14.3% (95% CI: 10.0%, 19.5%) and 21.8% (95% CI: 16.6%, 27.7%) after the Omicron BA.1 monovalent and mRNA-1273 vaccines, respectively (Table 18), with an SRR difference of -7.5% (CI: -14.6%, -0.4%).

For Day 179 and Day 359 results refer to Table 18 and Table 20.

PPSI (Supportive Analysis)

The summary of the nAb responses against the ancestral strain in the PPSI set is presented in Table 19.

At Baseline (prior to study vaccination), the observed GMC was 849.8 (95% CI: 768.3, 939.9) in the Omicron BA. 1 monovalent vaccine arm and 743.3 (95% CI: 674.1, 819.7) in the mRNA-1273 vaccine arm (Table 19).

At Day 29, the observed GMC was 3265.4 (95% CI: 2954.7, 3608.7) for the Omicron BA.1 monovalent vaccine arm and 3628.3 (95% CI: 3327.8, 3956.0) for the mRNA-1273 vaccine arm, which represent 3.8-fold and 4.9-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 3.8 [3.5, 4.2] and 4.9 [4.5, 5.3], respectively) (Table 19). The Day 29 GMR was 0.83 (95% CI: 0.75, 0.91), (Table 21). The SRR was 43.7% (95% CI: 38.4%, 49.2%) and 58.3% (95% CI: 52.8%, 63.6%) after the Omicron BA.1 monovalent and mRNA-1273 vaccines, respectively, with a SRR difference of -13.7% (95% CI: -21.0%, -6.4%).

At Day 85, the observed GMC was 2202.9 (95% CI: 1943.7, 2496.6) for the Omicron BA.1 monovalent vaccine arm and 2440.6 (95% CI: 2168.5, 2746.8) for the mRNA-1273 vaccine arm, which represent 2.6-fold and 3.3-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 2.6 [2.3, 2.9] and 3.3 [2.9,3.7], respectively) (Table 19). The Day 85 GMR was 0.82 (95% CI: 0.71, 0.95), (Table 21). The SRR was 26.5% (95% CI: 21.8%, 31.5%) and 32.5% (95% CI: 27.5%, 37.9%) after the Omicron BA.1 monovalent and mRNA-1273 vaccines, respectively, with a SRR difference of 5.1% (95% CI: -11.8%, 1.6%) (Table 14.2.2.2.4.2.1).

For Day 179 and Day 359 results refer to Table 19 and Table 21.

Table 15: Summary of Neutralizing Antibody Concentrations Against Omicron BA.1 Strain (PPSI - SARS-CoV-2 Negative) in Part 1

	Omicron BA.1 Monovalent Vaccine 50 µg		mRNA-1273 50 µg	
Timepoint Data Category Statistic	3rd Dose	4th Dose	3rd Dose	4th Dose
Baseline (Day 1)				
n [a]	1	274	0	277
GMC	62.0	70.1	–	67.3
95% CI [b]	(NE, NE)	(62.6, 78.3)	–	(60.0, 75.4)
Day 29				
n [a]	1	274	0	277

Timepoint Data Category Statistic	Omicron BA.1 Monovalent Vaccine 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
GMC	2117.0	537.7	–	302.8
95% CI [b]	(NE, NE)	(478.2, 604.6)	–	(274.8, 333.6)
GMC fold-rise	34.1	7.7	–	4.5
95% CI [b]	(NE, NE)	(7.0, 8.4)	–	(4.1, 4.9)
Seroresponse [c]				
n (%) [d]	1 (100)	228 (83.2)	0	153 (55.2)
95% CI [e]	(2.5, 100.0)	(78.2, 87.4)	–	(49.2, 61.2)
Day 85 (Month 3)				
n [a]	1	234	0	226
GMC	1364.0	284.7	–	152.6
95% CI [b]	(NE, NE)	(248.0, 326.7)	–	(135.1, 172.3)
GMC fold-rise	22.0	4.0	–	2.3
95% CI [b]	(NE, NE)	(3.6, 4.4)	–	(2.1, 2.5)
Seroresponse [c]				
n (%) [d]	1 (100)	113 (48.3)	0	36 (15.9)
95% CI [e]	(2.5, 100.0)	(41.7, 54.9)	–	(11.4, 21.4)
Day 179 (Month 6)				
n [a]	0	160	0	138
GMC	–	144.3	–	70.1
95% CI [b]	–	(119.4, 174.5)	–	(59.0, 83.4)
GMC fold-rise	–	2.0	–	1.0
95% CI [b]	–	(1.7, 2.3)	–	(0.9, 1.1)
Seroresponse [c]				
n (%) [d]	0	29 (18.1)	0	4 (2.9)
95% CI [e]	–	(12.5, 25.0)	–	(0.8, 7.3)
Day 359/EOS (Month 12)[f]				
n [a]	0	19	0	17
GMC	–	230.0	–	121.4
95% CI [b]	–	(106.9, 494.9)	–	(52.0, 283.4)
GMC fold-rise	–	3.0	–	1.6
95% CI [b]	–	(1.6, 5.5)	–	(0.9, 2.6)
Seroresponse [c]				

Timepoint Data Category Statistic	Omicron BA.1 Monovalent Vaccine 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
n (%) [d]	0	8 (42.1)	0	3 (17.6)
95% CI [e]	–	(20.3, 66.5)	–	(3.8, 43.4)
Day 359/EOS (Month 12)[f]				
n [a]	0	55	0	44
GMC	–	267.9	–	180.5
95% CI [b]	–	(197.3, 363.8)	–	(131.1, 248.3)
GMC fold-rise	–	3.3	–	2.6
95% CI [b]	–	(2.6, 4.2)	–	(2.0, 3.3)
Seroresponse [c]				
n (%) [d]	0	19 (34.5)	0	13 (29.5)
95% CI [e]	–	(22.2, 48.6)	–	(16.8, 45.2)

Abbreviations: (–) = not applicable; CI = confidence interval; EOS = end of study; GM = geometric mean; GMC = geometric mean concentration; LLOQ = lower limit of quantification; NE = not evaluable; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: n = Number of participants with non-missing data at Baseline and the corresponding post-baseline timepoint.
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.
B.1.1.529 is referred to as Omicron BA.1 in this table. The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

a. Number of participants with non-missing data at the timepoint (baseline or post-baseline).
b. 95% CI is calculated based on the t-distribution of the log-transformed values or the differences in the log-transformed values for GM value and GM fold-rise, respectively, then back-transformed to the original scale for presentation.
c. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ or at least a 4-fold-rise if baseline is ≥LLOQ.
d. Number of participants meeting the criterion at the timepoint. Percentages are based on n.
e. 95% CI is calculated using the Clopper-Pearson method.
f. Phase B Subgroup: Participants did not receive an additional booster outside of the study.
g. Phase B Subgroup: Participants received an additional booster outside of the study.

Sources: Table 14.2.1.2.1.2.1 and Table 14.2.1.2.1.3.1

Table 16: Summary of Neutralizing Antibody Concentrations against Omicron BA. 1 Strain (PPSI) in Part 1

	Omicron BA.1 Monovalent Vaccine 50 µg		mRNA-1273 50 µg	
Timepoint Data Category Statistic	3rd Dose	4th Dose	3rd Dose	4th Dose
Baseline (Day 1)				
n [a]	1	353	0	349
GMC	62.0	81.7	–	79.6
95% CI [b]	(NE, NE)	(73.1, 91.4)	–	(70.9, 89.4)
Day 29				
n [a]	1	353	0	349
GMC	2117.0	655.9	–	381.5
95% CI [b]	(NE, NE)	(587.5, 732.1)	–	(343.8, 423.3)
GMC fold-rise	34.1	8.0	–	4.8
95% CI [b]	(NE, NE)	(7.3, 8.8)	–	(4.4, 5.2)
Seroresponse [c]				
n (%) [d]	1 (100)	291 (82.4)	0	195 (55.9)
95% CI [e]	(2.5, 100.0)	(78.1, 86.3)	–	(50.5, 61.2)
Day 85 (Month 3)				
n [a]	1	342	0	331
GMC	1364.0	457.2	–	268.4
95% CI [b]	(NE, NE)	(397.9, 525.4)	–	(232.5, 309.8)
GMC fold-rise	22.0	5.6	–	3.4
95% CI [b]	(NE, NE)	(5.0, 6.4)	–	(3.0, 3.9)
Seroresponse [c]				
n (%) [d]	1 (100)	190 (55.6)	0	102 (30.8)
95% CI [e]	(2.5, 100.0)	(50.1, 60.9)	NA	(25.9, 36.1)
Day 179 (Month 6)				
n [a]	0	333	0	322
GMC	–	419.8	–	297.3
95% CI [b]	–	(354.8, 496.7)	–	(247.8, 356.7)
GMC fold-rise	–	5.2	–	3.8
95% CI [b]	–	(4.4, 6.1)	–	(3.2, 4.5)
Seroresponse [c]				
n (%) [d]	0	162 (48.6)	0	139 (43.2)

Timepoint Data Category Statistic	Omicron BA.1 Monovalent Vaccine 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
95% CI [e]	–	(43.2, 54.2)	–	(37.7, 48.8)
Day 359/EOS (Month 12)				
n [a]	0	323	0	306
GMC	–	1020.6	–	702.9
95% CI [b]	–	(884.6, 1177.6)	–	(609.6, 810.4)
GMC fold-rise	–	12.8	–	8.9
95% CI [b]	–	(10.9, 15.1)	–	(7.7, 10.4)
Seroresponse [c]				
n (%) [d]	0	240 (74.3)	0	219 (71.6)
95% CI [e]	–	(69.2, 79.0)	–	(66.2, 76.6)

Abbreviations: (–) = not applicable; CI = confidence interval; EOS = end of study; GM = geometric mean; GMC = geometric mean concentration; LLOQ = lower limit of quantification; NE = not evaluable; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: n=Number of participants with non-missing data at Baseline and the corresponding post-baseline timepoint. 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.
B.1.1.529 is referred to as Omicron BA.1 in this table. The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

a. Number of participants with non-missing data at the timepoint (baseline or post-baseline).
b. 95% CI is calculated based on the t-distribution of the log-transformed values for GM value and GM fold-rise, respectively, then back-transformed to the original scale for presentation.
c. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold-rise if baseline is ≥LLOQ.
d. Number of participants meeting the criterion at the timepoint. Percentages are based on n.
e. 95% CI is calculated using the Clopper-Pearson method.

Source: Table 14.2.1.2.1.1.1

Table 17: Analysis of Neutralizing Antibody Concentrations against Omicron BA.1 Strain After Study Vaccination as the 4th Dose in Part 1 ANCOVA Model (PPSI SARS-CoV-2 Negative)

Timepoint Statistic	4th Dose	
	Omicron BA.1 monovalent vaccine 50 µg	mRNA-1273 50 µg
Day 29		
N1	274	277
GLSM	529.6	306.1
99% CI	(476.1, 589.0)	(275.5, 340.2)

Timepoint Statistic	4th Dose	
	Omicron BA.1 monovalent vaccine 50 µg	mRNA-1273 50 µg
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	1.730	–
99% CI	(1.493, 2.005)	–
Day 85 (Month 3)		
N1	234	226
GLSM	274.8	155.9
96% CI	(250.3, 301.8)	(141.9, 171.4)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	1.763	–
96% CI	(1.546, 2.010)	–
Day 179 (Month 6)		
N1	160	138
GLSM	140.7	71.4
95% CI	(124.7, 158.6)	(62.8, 81.2)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	1.970	–
95% CI	(1.655, 2.345)	–
Day 359/EOS (Month 12)[a]		
N1	55	44
GLSM	267.3	196.9
95% CI	(211.5, 337.7)	(152.6, 254.1)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	1.358	–
95% CI	(0.967, 1.906)	–
Day 359/EOS (Month 12)[b]		
N1	19	17
GLSM	234.1	119.0
95% CI	(134.9, 406.5)	(66.4, 213.3)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	1.967	–
95% CI	(0.881, 4.393)	–

Abbreviations: (–) = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; EOS = end of study; GLSM = geometric least squares mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least square; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: n = Number of participants with non-missing data at Baseline and the corresponding timepoint.

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 concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

[a] Phase B Subgroup: Participants received an additional booster outside of the study.
[b] Phase B Subgroup: Participants did not receive an additional booster outside of the study.

Sources: Table 14.2.2.2.1.1.1, Table 14.2.2.2.1.2.1, Table 14.2.2.2.1.2.3, and Table 14.2.2.2.1.7.1

Table 18: Analysis of Neutralizing Antibody Concentrations Against Omicron BA.1 Strain after Study Vaccination as the 4th Dose in Part 1 – ANCOVA Model (PPSI)

	4th Dose	
Timepoint Statistic	Omicron BA.1 monovalent vaccine 50 µg	mRNA-1273 50 µg
Day 29		
N1	353	349
GLSM	681.9	403.9
99% CI	(499.8, 930.4)	(295.2, 552.6)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	1.688	–
99% CI	(1.456, 1.957)	–
Day 85 (Month 3)		
N1	342	331
GLSM	359.6	215.2
96% CI	(250.9, 515.4)	(149.6, 309.6)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	1.671	–
96% CI	(1.403, 1.989)	–
Day 179 (Month 6)		
N1	333	322
GLSM	392.5	281.5
95% CI	(245.7, 627.2)	(175.3, 452.1)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	1.395	–
95% CI	(1.108, 1.755)	–

Abbreviations: (–) = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; GLSM = geometric least squares mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least square; MSD = meso scale discovery, PPSI = Per-Protocol Set Immunogenicity; ULOQ = upper limit of quantification.

Notes: N1 = Number of participants with non-missing data at Baseline and the corresponding timepoint.
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 concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

Sources: Table 14.2.2.2.1.3.1, Table 14.2.2.2.1.4.1, and Table 14.2.2.2.1.4.3

Table 19: Summary of Neutralizing Antibody Concentrations against Ancestral Strain in Part 1 (PPSI – SARS-CoV-2 Negative)

	Omicron BA.1 monovalent vaccine 50 µg		mRNA-1273 50 µg	
Timepoint Data Category Statistic	3rd Dose	4th Dose	3rd Dose	4th Dose
Baseline (Day 1)				
n [a]	1	271	0	276
GMC	424.0	731.7	–	634.3
95% CI [b]	(NE, NE)	(662.2, 808.5)	–	(575.6, 699.0)
Day 29				
n [a]	1	270	0	272
GMC	5196.0	2699.7	–	3020.6
95% CI [b]	(NE, NE)	(2431.3, 2997.7)	–	(2776.5, 3286.2)
GMC fold-rise	12.3	3.7	–	4.8
95% CI [b]	(NE, NE)	(3.4, 4.0)	–	(4.4, 5.2)
Seroresponse [c]				
n (%) [d]	1 (100)	115 (43.1)	0	160 (59.0)
95% CI [e]	(2.5, 100.0)	(37.1, 49.2)	–	(52.9, 65.0)
Day 85 (Month 3)				
n [a]	1	234	0	226
GMC	5091.0	1401.2	–	1559.4
95% CI [b]	(NE, NE)	(1236.9, 1587.4)	–	(1401.2, 1735.5)
GMC fold-rise	12.0	1.9	–	2.5
95% CI [b]	(NE, NE)	(1.7, 2.1)	–	(2.3, 2.7)
Seroresponse [c]				
n (%) [d]	1 (100)	33 (14.3)	0	49 (21.8)
95% CI [e]	(2.5, 100.0)	(10.0, 19.5)	–	(16.6, 27.7)
Day 179 (Month 6)				
n [a]	0	160	0	133
GMC	–	734.6	–	747.6
95% CI [b]	–	(621.8, 867.9)	–	(644.1, 867.7)

Timepoint Data Category Statistic	Omicron BA.1 monovalent vaccine 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
GMC fold-rise	–	0.9	–	1.1
95% CI [b]	–	(0.8, 1.0)	–	(1.0, 1.2)
Seroresponse [c]				
n (%) [d]	0	4 (2.5)	0	8 (6.1)
95% CI [e]	–	(0.7, 6.4)	–	(2.7, 11.6)
Day 359/EOS (Month 12)[f]				
n [a]	0	55	0	44
GMC	–	856.6	–	1079.5
95% CI [b]	–	(668.6, 1097.3)	–	(803.4, 1450.5)
GMC fold-rise	–	1.0	–	1.5
95% CI [b]	–	(0.8, 1.1)	–	(1.2, 1.9)
Seroresponse [c]				
n (%) [d]	0	1 (1.9)	0	5 (11.4)
95% CI [e]	–	(<0.05, 9.9)	–	(3.8, 24.6)
Day 359/EOS (Month 12)[g]				
n [a]	0	19	0	17
GMC	–	1029.3	–	920.3
95% CI [b]	–	(526.1, 2013.5)	–	(480.5, 1762.7)
GMC fold-rise	–	1.0	–	1.2
95% CI [b]	–	(0.6, 1.6)	–	(0.7, 1.9)
Seroresponse [c]				
n (%) [d]	0	1 (5.3)	0	0
95% CI [e]	–	(0.1, 26.0)	–	(0.0, 19.5)

Abbreviations: (–) = not applicable; CI = confidence interval; EOS = end of study; GM = geometric mean; GMC = geometric mean concentration; LLOQ = lower limit of quantification; NE = not evaluable; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: Prototype was changed to Ancestral in table title.
n = Number of participants with non-missing data at Baseline and the corresponding post-baseline timepoint.
Antibody values are 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 Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

[a] Number of participants with non-missing data at the timepoint (baseline or post-baseline).
[b] 95% CI is calculated based on the t-distribution of the log-transformed values for GM value and GM fold-rise, respectively, then back-transformed to the original scale for presentation.
[c] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold-rise if baseline is ≥LLOQ.
[d] Number of participants meeting the criterion at the timepoint. Percentages are based on n.
[e] 95% CI is calculated using the Clopper-Pearson method.
[f] Phase B Subgroup: Participants received an additional booster outside of the study.
[g] Phase B Subgroup: Participants did not receive an additional booster outside of the study.

Sources: Table 14.2.1.2.2.2.1 and Table 14.2.1.2.2.3.1

Table 20: Summary of Neutralizing Antibody Concentrations against Ancestral Strain (PPSI) in Part 1

Timepoint Data Category Statistic	Omicron BA.1 monovalent vaccine 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
Baseline (Day 1)				
n [a]	1	347	0	347
GMC	424.0	849.8	–	743.3
95% CI [b]	(NE, NE)	(768.3, 939.9)	–	(674.1, 819.7)
Day 29				
n [a]	1	348	0	340
GMC	5196.0	3265.4	–	3628.3
95% CI [b]	(NE, NE)	(2954.7, 3608.7)	–	(3327.8, 3956.0)
GMC fold-rise	12.3	3.8	–	4.9
95% CI [b]	(NE, NE)	(3.5, 4.2)	–	(4.5, 5.3)
Seroresponse [c]				
n (%) [d]	1 (100)	150 (43.7)	0	197 (58.3)
95% CI [e]	(2.5, 100.0)	(38.4, 49.2)	–	(52.8, 63.6)
Day 85 (Month 3)				
n [a]	1	342	0	331
GMC	5091.0	2202.9	–	2440.6
95% CI [b]	(NE, NE)	(1943.7, 2496.6)	–	(2168.5, 2746.8)
GMC fold-rise	12.0	2.6	–	3.3
95% CI [b]	(NE, NE)	(2.3, 2.9)	–	(2.9, 3.7)
Seroresponse [c]				
n (%) [d]	1 (100)	89 (26.5)	0	107 (32.5)
95% CI [e]	(2.5, 100.0)	(21.8, 31.5)	–	(27.5, 37.9)

Timepoint Data Category Statistic	Omicron BA.1 monovalent vaccine 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
Day 179 (Month 6)				
n [a]	0	332	0	317
GMC	–	1843.6	–	2281.7
95% CI [b]	–	(1589.1, 2139.0)	–	(1974.0, 2637.2)
GMC fold-rise	–	2.2	–	3.0
95% CI [b]	–	(1.9, 2.5)	–	(2.6, 3.5)
Seroresponse [c]				
n (%) [d]	0	104 (31.9)	0	134 (42.5)
95% CI [e]	–	(26.9, 37.3)	–	(37.0, 48.2)
Day 359/EOS (Month 12)				
n [a]	0	323	0	306
GMC	–	2916.7	–	3280.8
95% CI [b]	–	(2579.9, 3297.6)	–	(2912.4, 3695.9)
GMC fold-rise	–	3.5	–	4.3
95% CI [b]	–	(3.1, 4.0)	–	(3.7, 4.8)
Seroresponse [c]				
n (%) [d]	0	153 (48.3)	0	167 (54.9)
95% CI [e]	–	(42.6, 53.9)	–	(49.2, 60.6)

Abbreviations: (–) = not applicable; CI = confidence interval; EOS = end of study; GM = geometric mean; GMC = geometric mean concentration; LLOQ = lower limit of quantification; NE = not evaluable; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: Prototype was changed to Ancestral in table title.
n = Number of participants with non-missing data at Baseline and the corresponding post-baseline timepoint. 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 Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

[a] Number of participants with non-missing data at the timepoint (baseline or post-baseline).
[b] 95% CI is calculated based on the t-distribution of the log-transformed values for GM value and GM fold-rise, respectively, then back-transformed to the original scale for presentation.
[c] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold-rise if baseline is ≥LLOQ.
[d] Number of participants meeting the criterion at the timepoint. Percentages are based on n.
[e] 95% CI is calculated using the Clopper-Pearson method.

Source: Table 14.2.1.2.2.1.1

Table 21: Analysis of Neutralizing Antibody Concentrations against Ancestral Strain by Visit after Study Vaccination as the 4th Dose in Part 1 – ANCOVA Model (PPSI – SARS-CoV-2 Negative)

	4th Dose	
Timepoint Statistic	Omicron BA.1 monovalent vaccine 50 µg	mRNA-1273 50 µg
Day 29		
N1	267	271
GLSM	2566.2	3129.9
95% CI	(2383.7, 2762.6)	(2909.2, 3367.4)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	0.820	–
99% CI	(0.740, 0.908)	–
Day 85 (Month 3)		
N1	231	225
GLSM	1315.5	1647.4
95% CI	(1209.0, 1431.4)	(1513.0, 1793.8)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	0.799	–
95% CI	(0.709, 0.899)	–
Day 179 (Month 6)		
N1	158	132
GLSM	680.6	792.4
95% CI	(611.5, 757.6)	(705.4, 890.2)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	0.859	–
95% CI	(0.734, 1.005)	–
Day 359/EOS (Month 12)		
N1	73	61
GLSM	844.2	1161.9
95% CI	(706.0, 1009.5)	(958.7, 1408.2)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	0.727	–
95% CI	(0.560, 0.943)	–

Abbreviations: (–) = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; EOS = end of study; GLSM = geometric least squares mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least square; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: Prototype was changed to Ancestral in table title.
n = Number of participants with non-missing data at Baseline and the corresponding timepoint.
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 concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

Source: Table 14.2.2.2.3.1.1

Table 22: Analysis of Neutralizing Antibody Concentrations against Ancestral Strain by Visit after Study Vaccination as the 4th Dose in Part 1 – ANCOVA Model (PPSI)

	4th Dose	
Timepoint Statistic	Omicron BA.1 monovalent vaccine 50 µg	mRNA-1273 50 µg
Day 29		
N1	343	338
GLSM	3019.9	3661.4
95% CI	(2451.9, 3719.4)	(2967.8, 4517.0)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	0.825	–
95% CI	(0.746, 0.912)	–
Day 85 (Month 3)		
N1	336	329
GLSM	1904.7	2321.2
95% CI	(1411.3, 2570.6)	(1716.1, 3139.6)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	0.821	–
95% CI	(0.709, 0.949)	–
Day 179 (Month 6)		
N1	326	315
GLSM	1722.4	2264.9
95% CI	(1154.5, 2569.7)	(1512.9, 3390.7)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	0.760	–
95% CI	(0.624, 0.927)	–
Day 359/EOS (Month 12)		
N1	317	304
GLSM	2613.5	3034.2
95% CI	(1893.3, 3607.8)	(2191.9, 4200.1)
GMR (Omicron BA.1 monovalent vaccine vs. mRNA-1273)	0.861	–

Timepoint Statistic	4th Dose Omicron BA.1 monovalent vaccine 50 µg	 mRNA-1273 50 µg
95% CI	(0.733, 1.012)	–

Abbreviations: (–) = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; EOS = end of study; GLSM = geometric least squares mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least square; PPSI = Per-Protocol Set Immunogenicity; ULOQ = upper limit of quantification.

Notes: Prototype was changed to Ancestral in table title.
N = Number of participants with non-missing data at Baseline and the corresponding timepoint.
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 concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

Source: Table 14.2.2.2.3.2.1

Part 2

Omicron BA.1

PPSI-Neg (Primary Immunogenicity Set)

The summary of the nAb responses Omicron BA.1 strain levels in the PPSI-Neg primary immunogenicity set for Part 2 is presented in Table 22.

At Baseline (prior to study vaccination), the observed GMC was 50.5 (95% CI: 47.4, 53.8) in the bivalent vaccine (original and Omicron BA.1) arm and 52.3 (95% CI: 48.8, 56.0) in the mRNA-1273 vaccine arm (Table 22).

At Day 29, the observed GMC was 465.7 (95% CI: 437.0, 496.3) and 311.0 (95% CI: 292.9, 330.1) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 9.2-fold and 5.9-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 9.2 [8.8, 9.7] and 5.9 [5.6, 6.3], respectively) (Table 22). The Day 29 GMR was 1.54 (99% CI: 1.41, 1.67) (Table 24), which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.667). Additionally, superiority of the immune response of the bivalent vaccine (original and Omicron BA.1) compared with the mRNA-1273 vaccine against Omicron BA.1 (primary objective) was demonstrated based on the lower bound of the 99% CI >1.0 (Table 24). The SRR was 84.7% (95% CI: 82.3, 86.9) and 70.4% (95% CI: 67.2, 73.3) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccines, respectively. The SRR difference and corresponding 95% CI was 14.4% (95% CI: 10.6%, 18.1%).

At Day 85, the observed GMC was 258.2 (95% CI: 239.3, 278.7) and 153.0 (95% CI: 142.2, 164.6) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 5.0-fold and 2.9-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 5.0 [4.7, 5.3] and 2.9 [2.7, 3.1], respectively) (Table 22). The Day 85 GMR was 1.71 (96% CI: 1.58, 1.85), which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 96% CI ≥0.67) and primary objective of superiority (Table 24). The SRR was 60.6% (95% CI: 57.0, 64.1) and 32.3% (95% CI: 28.8, 35.9) after the bivalent vaccine (original and Omicron BA.1) and the mRNA 1273, respectively. The SRR difference and corresponding 95% CI was 28.3% (23.3%, 33.2%).

For Day 179 and Day 359 results refer to Table 22 and Table 24.

PPSI (Supportive Analysis)

The summary of nAb responses against Omicron BA. 1 strain in the PPSI set is presented in Table 23.

At Baseline (prior to study vaccination), the observed GMC was 77.2 (95% CI: 71.8, 82.9) in the bivalent vaccine (original and Omicron BA.1) arm and 84.1 (95% CI: 78.1, 90.6) in the mRNA-1273 vaccine arm (Table 23).

At Day 29, the observed GMC was 644 (95% CI: 606.5, 684.6) and 431.9 (95% CI: 408.0, 457.2) after the bivalent vaccine (original and Omicron BA. 1) and the mRNA-1273 vaccine, which represent 8.3-fold and 5.1-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 8.3 [7.9, 8.8] and 5.1 [4.9, 5.4], respectively) (Table 23). The Day 29 GMR was 1.57 (99% CI: 1.46, 1.70) which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67). Additionally, superiority of the immune response of the bivalent vaccine (original and Omicron BA.1) compared with mRNA-1273 vaccination against Omicron BA.1 (key secondary objective) was demonstrated based on the lower bound of the 99% CI >1.0 (Table 25). The SRR was 78.3% (95% CI: 76.0%, 80.5%) and 58.9% (95% CI: 56.2%, 61.6%) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, respectively. The SRR difference and corresponding 95% CI was 17.2% (95% CI: 14.0%, 20.4%).

At Day 85, the observed GMC was 446.7 (95% CI: 417.0, 478.6) and 307.5 (95% CI: 286.4, 330.2) after the bivalent vaccine (original and Omicron BA. 1) and the mRNA-1273 vaccine, which represent 5.8-fold and 3.6-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 5.8 [5.4, 6.1] and 3.6 [3.4, 3.9], respectively) (Table 23).The Day 85 GMR was 1.52 (96% CI: 1.40, 1.66) which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 96% CI ≥0.67) (Table 25). The SRR was 60.6% (95% CI: 57.9%, 63.3%) and 36.8% (95% CI: 34.2%, 39.6%) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, respectively. The SRR difference and corresponding 95% CI was 22.8% (95% CI: 19.2%, 26.4%).

For Day 179 and Day 359 results refer to Table 23.

Ancestral Strain

PPSI-Neg (Primary Immunogenicity Set)

The summary of the nAb responses against the ancestral strain in the PPSI-Neg primary immunogenicity set is presented in Table 26.

At baseline (prior to study vaccination), the observed GMC was 502.7 (95% CI: 472.9, 534.4) in the bivalent vaccine (original and Omicron BA.1) arm and 521.2 (95% CI: 489.8, 554.7) in the mRNA-1273 vaccine arm (Table 26).

At Day 29, the observed GMC was 2998.8 (95% CI: 2825.4, 3182.8) for the bivalent vaccine (original and Omicron BA.1) arm and 2933.6 (95% CI: 2772.3, 3104.4) for the mRNA-1273 vaccine arm, which represent 6.0-fold and 5.6-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 6.0 [5.6, 6.3] and 5.6 [5.3, 5.9], respectively) (Table 26). The Day 29 GMR was 1.05 (99% CI: 0.96, 1.15) (Table 28), which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67). The SRR was 70.9% (95% CI: 67.9%, 73.8%) and 68.4% (95% CI: 65.2%, 71.5%) after the Omicron BA.1 monovalent and mRNA-1273 vaccines, respectively, with an SRR difference of 2.5% (95% CI: -1.7%, 6.7%) (Table 14.2.2.2.4.1.2).

At Day 85, the observed GMC was 1753.1 (95% CI: 1650.0, 1862.6) for the bivalent vaccine (original and Omicron BA.1) arm and 1610.2 (95% CI: 1519.6, 1706.2) for the mRNA-1273 vaccine arm, which represent 3.4-fold and 3.0-fold increases respectively, over the baseline (observed GMFR [95% CI] values of 3.4 [3.2, 3.6] and 3.0 [2.9, 3.2], respectively) (Table 26). The Day 85 GMR was 1.10 (96%

CI: 1.03, 1.18), which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 96% CI ≥0.67) (Table 28). The SRR was 38.8% (95% CI: 35.3%, 42.4%) and 33.4% (95% CI: 29.8%, 37.1%) after the Omicron BA.1 monovalent and mRNA-1273 vaccines, respectively, with an SRR difference of 5.4% (CI: 0.4%, 10.4%).

For Day 179 and at Day 359 results refer to Table 26 and Table 28.

PPSI (Supportive Analysis)

The summary of nAb responses against the ancestral strain in the PPSI set is presented in Table 27.

At Baseline (prior to study vaccination), the observed GMC was 737.4 (95% CI: 689.9, 788.2) in the bivalent vaccine (original and Omicron BA.1) arm and 798.7 (95% CI: 747.3, 853.6) in the mRNA-1273 vaccine arm (Table 27).

At Day 29, the observed GMC was 3831.4 (95% CI: 3628.8, 4045.3) and 3732.0 (95% CI: 3546.5, 3927.2) after the bivalent vaccine (original and Omicron BA. 1) and the mRNA-1273 vaccine, which represent 5.3-fold and 4.7-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 5.3 [5.0, 5.63] and 4.7 [4.4, 5.0], respectively) (Table 27).

The Day 29 GMR was 1.08 (99% CI: 0.10, 1.16) which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67) (Table 29). The SRR was 61.4% (95% CI: 58.7%, 64.0%) and 56.4% (95% CI: 53.6%, 59.1%) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccines, respectively. The SRR difference and corresponding 95% CI was 3.6% (95% CI: 0.1%, 7.0%).

At Day 85, the observed GMC was 2668.8 (95% CI: 2525.9, 2819.7) and 2693.9 (95% CI:2550.2, 2845.7) after the bivalent vaccine (original and Omicron BA. 1) and the mRNA-1273 vaccine, which represent 3.6-fold and 3.4-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 3.6 [3.4, 3.8] and 3.4 [3.2, 3.6], respectively) (Table 27). The Day 85 GMR was 1.03 (96% CI: 0.96, 1.10) which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 96% CI ≥0.67) (Table 29). The SRR was 39.3% (95% CI: 36.6%, 42.0%) and 36.6% (95% CI: 33.9%, 39.3%) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccines, respectively. The SRR difference and corresponding 95% CI was 1.8% (95% CI: -1.5%, 5.0%).

For Day 179 and at Day 359 results refer to tables below.

Table 23: Summary of Neutralizing Antibody Concentrations against Omicron BA.1 Strain in Part 2 (PPSI – SARS-CoV-2 Negative)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
Timepoint Data Category Statistic	3rd Dose	4th Dose	3rd Dose	4th Dose
Baseline (Day 1)				
n [a]	2	968	5	895
GMC	13.4	50.5	61.2	52.3
95% CI [b]	(3.3, 55.4)	(47.4, 53.8)	(14.1, 266.4)	(48.8, 56.0)
Day 29				
n [a]	2	968	5	894
GMC	99.4	465.7	423.8	311.0
95% CI [b]	(<0.05, 268931204.7)	(437.0, 496.3)	(152.9, 1174.6)	(292.9, 330.1)
GMC fold-rise	7.4	9.2	6.9	5.9
95% CI [b]	(<0.05, 82734029.7)	(8.8, 9.7)	(4.0, 12.0)	(5.6, 6.3)
Seroresponse [c]				
n (%) [d]	1 (50.0)	820 (84.7)	4 (80.0)	629 (70.4)
95% CI [e]	(1.3, 98.7)	(82.3, 86.9)	(28.4, 99.5)	(67.2, 73.3)
Day 85 (Month 3)				
n [a]	2	761	3	688
GMC	62.1	258.2	172.8	153.0
95% CI [b]	(<0.05, 111711133.4)	(239.3, 278.7)	(52.3, 570.9)	(142.2, 164.6)

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
GMC fold-rise	4.6	5.0	2.5	2.9
95% CI [b]	(<=0.05, 34366827.2)	(4.7, 5.3)	(0.4, 15.1)	(2.7, 3.1)
Seroresponse [c]				
n (%) [d]	1 (50.0)	461 (60.6)	1 (33.3)	222 (32.3)
95% CI [e]	(1.3, 98.7)	(57.0, 64.1)	(0.8, 90.6)	(28.8, 35.9)
Day 179 (Month 6)[f]				
n [a]	0	356	1	338
GMC	–	205.3	164.0	121.6
95% CI [b]	–	(180.0, 234.1)	(NE, NE)	(106.6, 138.7)
GMC fold-rise	–	3.9	1.1	2.3
95% CI [b]	–	(3.5, 4.4)	(NE, NE)	(2.1, 2.7)
Seroresponse [c]				
n (%) [d]	–	157 (44.1)	0	103 (30.5)
95% CI [e]	–	(38.9, 49.4)	(0.0, 97.5)	(25.6, 35.7)
Day 179 (Month 6)[g]				
n [a]	0	190	2	169
GMC	–	141.1	45.9	87.5
95% CI [b]	–	(120.2, 165.5)	(20.0, 105.3)	(72.9, 105.1)
GMC Fold-Rise	–	2.5	1.0	1.6
95% CI [b]	–	(2.2, 2.9)	(<=0.05, 2314.4)	(1.4, 1.9)
Seroresponse [c]				
n (%) [d]	0	48 (25.3)	0	28 (16.6)
95% CI [e]	–	(19.3, 32.1)	(0.0, 84.2)	(11.3, 23.0)
Day 359/EOS (Month 12)[f]				
n [a]	0	188	1	176
GMC	–	161.7	260.0	145.8
95% CI [b]	–	(136.8, 191.2)	(NE, NE)	(120.7, 176.2)
GMC fold-rise	–	3.1	1.7	2.6
95% CI [b]	–	(2.7, 3.5)	(NE, NE)	(2.3, 3.0)
Seroresponse [c]				
n (%) [d]	0	70 (37.2)	0	47 (26.7)

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
95% CI [e]	–	(30.3, 44.6)	(0.0, 97.5)	(20.3, 33.9)
Day 359/EOS (Month 12)[g]				
n [a]	0	98	1	75
GMC	–	127.8	120.0	74.2
95% CI [b]	–	(96.9, 168.5)	(NE, NE)	(54.2, 101.5)
GMC fold-rise	–	2.1	5.0	1.6
95% CI [b]	–	(1.7, 2.6)	(NE, NE)	(1.2, 2.0)
Seroresponse [c]				
n (%) [d]	0	23 (23.5)	1 (100)	16 (21.3)
95% CI [e]	–	(15.5, 33.1)	(2.5, 100.0)	(12.7, 32.3)

Abbreviations: CI = confidence interval; EOS = end of study; GM = geometric mean; GMC = geometric mean concentration; LLOQ = lower limit of quantification; NE = not evaluable; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: n = Number of participants with non-missing data at Baseline and the corresponding post-baseline timepoint. 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.

B.1.1.529 is referred to as Omicron BA.1 in this table. The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

a. Number of participants with non-missing data at the timepoint (baseline or post-baseline).
b. 95% CI is calculated based on the t-distribution of the log-transformed values for GM value and GM fold-rise, respectively, then back-transformed to the original scale for presentation.
c. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold-rise if baseline is ≥LLOQ.
d. Number of participants meeting the criterion at the timepoint. Percentages are based on n.
e. 95% CI is calculated using the Clopper-Pearson method.
f. Phase B Subgroup: Participants received an additional vaccination outside of the study.
g. Phase B Subgroup: Participants did not receive an additional vaccination outside of the study.

Sources: Table 14.2.1.2.1.2.2 and Table 14.2.1.2.1.3.2

Table 24: Summary of Neutralizing Antibody Concentrations Against Omicron BA.1 Strain by Pre-Booster SARS-CoV-2 Status in Part 2 (PPSI)

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
Baseline (Day 1)				
n [a]	3	1332	6	1301
GMC	55.9	77.2	111.9	84.1

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg 3rd Dose	Bivalent Vaccine (Original and Omicron BA.1) 50 µg 4th Dose	mRNA-1273 50 µg 3rd Dose	mRNA-1273 50 µg 4th Dose
95% CI [b]	(0.1, 26089.7)	(71.8, 82.9)	(16.6, 754.3)	(78.1, 90.6)
Day 29				
n [a]	3	1332	6	1300
GMC	272.2	644.0	520.9	431.9
95% CI [b]	(1.5, 49911.0)	(605.8, 684.6)	(204.5, 1327.0)	(408.0, 457.2)
GMC fold-rise	4.9	8.3	4.7	5.1
95% CI [b]	(0.1, 187.6)	(7.9, 8.8)	(1.5, 14.0)	(4.9, 5.4)
Seroresponse [c]				
n (%) [d]	1 (33.3)	1043 (78.3)	4 (66.7)	766 (58.9)
95% CI [e]	(0.8, 90.6)	(76.0, 80.5)	(22.3, 95.7)	(56.2, 61.6)
Day 85 (Month 3)				
n [a]	3	1305	5	1281
GMC	168.9	446.7	467.6	307.5
95% CI [b]	(1.0, 28895.3)	(417.0, 478.6)	(78.2, 2796.2)	(286.4, 330.2)
GMC fold-rise	3.0	5.8	2.7	3.6
95% CI [b]	(0.1, 110.3)	(5.4, 6.1)	(0.5, 13.8)	(3.4, 3.9)
Seroresponse [c]				
n (%) [d]	1 (33.3)	791 (60.6)	2 (40.0)	472 (36.8)
95% CI [e]	(0.8, 90.6)	(57.9, 63.3)	(5.3, 85.3)	(34.2, 39.6)
Day 179 (Month 6)				
n [a]	2	1263	6	1245
GMC	1123.6	477.3	252.9	339.2
95% CI [b]	(152.2, 8294.3)	(440.5, 517.3)	(31.3, 2043.5)	(311.4, 369.4)
GMC fold-rise	10.4	6.2	2.3	4.1
95% CI [b]	(<0.05, 1.0E14)	(5.7, 6.7)	(0.4, 13.5)	(3.7, 4.5)
Seroresponse [c]				
n (%) [d]	1 (50.0)	687 (54.4)	2 (33.3)	558 (44.8)
95% CI [e]	(1.3, 98.7)	(51.6, 57.2)	(4.3, 77.7)	(42.0, 47.6)
Day 359/EOS (Month 12)				
n [a]	2	1216	6	1163
GMC	862.2	680.9	373.4	547.4
95% CI [b]	(0.9, 791504.8)	(628.7, 737.4)	(61.7, 2258.8)	(505.2, 593.0)

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
GMC fold-rise	8.0	8.7	3.3	6.6
95% CI [b]	(<0.05, 11452760760.1)	(7.9, 9.5)	(0.8, 13.3)	(6.1, 7.3)
Seroresponse [c]				
n (%) [d]	1 (50.0)	810 (66.6)	3 (50.0)	694 (59.7)
95% CI [e]	(1.3, 98.7)	(63.9, 69.3)	(11.8, 88.2)	(56.8, 62.5)

Abbreviations: CI = confidence interval; EOS = end of study; GM = geometric mean; GMC = geometric mean concentration; LLOQ = lower limit of quantification; PPSI = per-protocol immunogenicity set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: n = Number of participants with non-missing data at Baseline and the corresponding post-baseline timepoint. Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
B.1.1.529 is referred to as Omicron BA.1 in this table. The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

[a] Number of participants with non-missing data at the timepoint (baseline or post-baseline).
[b] 95% CI is calculated based on the t-distribution of the log-transformed values for GM value and GM fold-rise, respectively, then back-transformed to the original scale for presentation.
[c] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold-rise if baseline is ≥ LLOQ.
[d] Number of participants meeting the criterion at the timepoint. Percentages are based on n.
[e] 95% CI is calculated using the Clopper-Pearson method.

Source: Table 14.2.1.2.1.1.2

Table 25: Analysis of Neutralizing Antibody Concentrations against Omicron BA1 Strain after Study Vaccination as the 4th Dose in Part 2 – ANCOVA Model (PPSI – SARS-CoV-2 Negative)

Timepoint Statistic	4th Dose	
	Bivalent Vaccine (Original and Omicron BA.1) 50 µg	mRNA-1273 50 µg
Day 29		
N1	968	894
GLSM	479.3	312.3
99% CI	(451.1, 509.3)	(293.3, 332.6)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.535	–
99% CI	(1.409, 1.672)	–
Day 85 (Month 3)		
N1	761	688
GLSM	265.5	155.0

Timepoint Statistic	4th Dose	
	Bivalent Vaccine (Original and Omicron BA.1) 50 µg	mRNA-1273 50 µg
96% CI	(251.3, 280.4)	(146.3, 164.2)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.713	–
96% CI	(1.583, 1.853)	–
Day 179 (Month 6) [a]		
N1	356	338
GLSM	206.1	123.8
95% CI	(184.2, 230.5)	(110.3, 138.9)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.665	–
95% CI	(1.418, 1.956)	–
Day 179 (Month 6) [b]		
N1	190	169
GLSM	146.5	93.2
95% CI	(128.4, 167.3)	(80.8, 107.4)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.573	–
95% CI	(1.306, 1.894)	–
Day 359/EOS (Month 12) [a]		
N1	188	176
GLSM	165.7	141.9
95% CI	(145.4, 188.9)	(124.0, 162.4)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.168	–
95% CI	(0.968, 1.410)	–
Day 359/EOS (Month 12) [b]		
N1	98	75
GLSM	125.6	93.6
95% CI	(101.5, 155.4)	(73.1, 119.8)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.342	–
95% CI	(0.975, 1.848)	–

Abbreviations: (–) = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; EOS = end of study; GLSM = geometric least squares mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least square; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

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

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 concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
B.1.1.529 is referred to as Omicron BA.1 in this table. The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

a. Phase B Subgroup: Participants received an additional vaccination outside of the study
b. Phase B Subgroup: Participants did not receive an additional vaccination outside of the study

Sources: Table 14.2.2.2.1.1.2, Table 14.2.2.2.1.2.2, and Table 14.2.2.2.1.7.2

Table 26: Analysis of Neutralizing Antibody Concentrations against Omicron BA1 Strain After Study Vaccination as the 4th Dose in Part 2 – ANCOVA Model (PPSI)

	4th Dose	
Timepoint Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg	mRNA-1273 50 µg
Day 29		
N1	1332	1300
GLSM	652.6	415.0
99% CI	(607.3, 701.2)	(385.9, 446.3)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.573	–
99% CI	(1.459, 1.695)	–
Day 85 (Month 3)		
N1	1305	1281
GLSM	430.6	282.7
96% CI	(397.6, 466.3)	(260.8, 306.3)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.523	–
96% CI	(1.401, 1.656)	–

Abbreviations: (–) = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; GLSM = geometric least squares mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least square; ULOQ = upper limit of quantification.
Notes: n = Number of participants with non-missing data at Baseline and the corresponding timepoint.
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.
B.1.1.529 is referred to as Omicron BA.1 in this table. The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.
The log-transformed antibody concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
Sources: Table 14.2.2.2.1.3.2 and Table 14.2.2.2.1.4.2.

Table 27: **Summary of Neutralizing Antibody Concentrations against Ancestral Strain in Part 2 (PPSI – SARS-CoV-2 Negative)**

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
Timepoint Data Category Statistic	3rd Dose	4th Dose	3rd Dose	4th Dose
Baseline (Day 1)				
n [a]	2	951	5	880
GMC	140.2	502.7	721.2	521.2
95% CI [b]	(<0.05, 799759.2)	(472.9, 534.4)	(207.9, 2501.4)	(489.8, 554.7)
Day 29				
n [a]	2	951	5	880
GMC	953.0	2998.8	3439.5	2933.6
95% CI [b]	(0.7, 1330303.6)	(2825.4, 3182.8)	(1276.9, 9264.9)	(2772.3, 3104.4)
GMC fold-rise	6.8	6.0	4.8	5.6
95% CI [b]	(<0.05, 54096843.8)	(5.6, 6.3)	(3.4, 6.7)	(5.3, 5.9)
Seroresponse [c]				
n (%) [d]	1 (50.0)	670 (70.9)	5 (100)	597 (68.4)
95% CI [e]	(1.3, 98.7)	(67.9, 73.8)	(47.8, 100.0)	(65.2, 71.5)
Day 85 (Month 3)				
n [a]	2	761	3	685
GMC	600.2	1753.1	1634.7	1610.2
95% CI [b]	(0.1, 4776269.3)	(1650.0, 1862.6)	(401.5, 6654.6)	(1519.6, 1706.2)
GMC fold-rise	4.3	3.4	2.1	3.0
95% CI [b]	(<0.05, 194227154.9)	(3.2, 3.6)	(0.9, 4.8)	(2.9, 3.2)
Seroresponse [c]				
n (%) [d]	1 (50.0)	290 (38.8)	0	224 (33.4)
95% CI [e]	(1.3, 98.7)	(35.3, 42.4)	(0.0, 70.8)	(29.8, 37.1)
Day 179 (Month 6)[f]				
n [a]	0	352	1	330
GMC	–	1149.5	1339.0	1175.4
95% CI [b]	–	(1036.6, 1274.7)	(NE, NE)	(1056.5, 1307.8)

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
GMC fold-rise	–	2.4	0.9	2.2
95% CI [b]	–	(2.1, 2.6)	(NE, NE)	(2.0, 2.5)
Seroresponse [c]				
n (%) [d]	–	110 (31.4)	0	95 (29.2)
95% CI [e]	–	(26.6, 36.6)	(0.0, 97.5)	(24.3, 34.5)
Day 179 (Month 6)[g]				
n [a]	0	189	2	168
GMC	–	918.8	453.2	911.9
95% CI [b]	–	(810.3, 1041.9)	(98.7, 2081.1)	(797.9, 1042.3)
GMC fold-rise	–	1.6	0.8	1.6
95% CI [b]	–	(1.4, 1.8)	(<0.05, 1516.3)	(1.4, 1.8)
Seroresponse [c]				
n (%) [d]	0	23 (12.7)	0	21 (13.0)
95% CI [e]	–	(8.2, 18.5)	(0.0, 84.2)	(8.2, 19.1)
Day 359/EOS (Month 12)[f]				
n [a]	0	188	1	176
GMC	–	742.8	1446.0	978.9
95% CI [b]	–	(653.7, 843.9)	(NE, NE)	(848.7, 1129.0)
GMC fold-rise	–	1.5	0.9	1.7
95% CI [b]	–	(1.3, 1.6)	(NE, NE)	(1.5, 1.9)
Seroresponse [c]				
n (%) [d]	–	19 (10.1)	0	24 (13.9)
95% CI [e]	–	(6.2, 15.3)	(0.0, 97.5)	(9.1, 19.9)
Day 359/EOS (Month 12)[g]				
n [a]	0	98	1	76
GMC	–	673.8	665.0	585.6
95% CI [b]	–	(552.9, 821.2)	(NE, NE)	(464.2, 738.7)
GMC fold-rise	–	1.1	1.9	1.1
95% CI [b]	–	(0.9, 1.3)	(NE, NE)	(0.9, 1.4)
Seroresponse [c]				
n (%) [d]	–	6 (6.5)	0	7 (9.5)

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg 3rd Dose	 4th Dose	mRNA-1273 50 µg 3rd Dose	 4th Dose
95% CI [a]	–	(2.4, 13.7)	(0.0, 97.5)	(3.9, 18.5)

Abbreviations: CI = confidence interval; EOS = end of study; GM = geometric mean; GMC = geometric mean concentration; LLOQ = lower limit of quantification; NE = not evaluable; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: 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.

Original changed to Ancestral in table title.

B.1.1.529 is referred to as Omicron BA.1 in this table. The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

[a] Number of participants with non-missing data at the timepoint (baseline or post-baseline).

[b] 95% CI is calculated based on the t-distribution of the log-transformed values for GM value and GM fold-rise, respectively, then back-transformed to the original scale for presentation.

[c] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold-rise if baseline is ≥LLOQ.

[d] Number of participants meeting the criterion at the timepoint. Percentages are based on n.

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

[f] Phase B Subgroup: Participants received an additional vaccination outside of the study.

[g] Phase B Subgroup: Participants did not receive an additional vaccination outside of the study.

Sources: Table 14.2.1.2.2.2.2 and Table 14.2.1.2.2.3.2

Table 28: Summary of Neutralizing Antibody Concentrations against Ancestral Strain by Pre-booster SARS-CoV-2 Status in Part 2 (PPSI)

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg 3rd Dose	 4th Dose	mRNA-1273 50 µg 3rd Dose	 4th Dose
Baseline (Day 1)				
n [a]	3	1313	6	1276
GMC	440.2	737.4	1215.8	798.7
95% CI [b]	(2.4, 80083.6)	(689.9, 788.2)	(236.1, 6260.9)	(747.3, 853.6)
Day 29				
n [a]	3	1305	6	1275
GMC	1945.4	3831.4	4103.6	3732.0
95% CI [b]	(66.2, 57203.3)	(3628.8, 4045.3)	(1709.3, 9852.1)	(3546.5, 3927.2)
GMC fold-rise	4.4	5.3	3.4	4.7
95% CI [b]	(0.1, 164.4)	(5.0, 5.6)	(1.3, 8.5)	(4.4, 5.0)
Seroresponse [c]				

Timepoint Data Category Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
	3rd Dose	4th Dose	3rd Dose	4th Dose
n (%) [d]	1 (33.3)	796 (61.4)	5 (83.3)	712 (56.4)
95% CI [a]	(0.8, 90.6)	(58.7, 64.0)	(35.9, 99.6)	(53.6, 59.1)
Day 85 (Month 3)				
n [a]	3	1304	5	1275
GMC	1253.9	2668.8	3601.8	2693.9
95% CI [b]	(33.5, 47004.1)	(2525.9, 2819.7)	(826.0, 15706.0)	(2550.2, 2845.7)
GMC fold-rise	2.8	3.6	2.1	3.4
95% CI [b]	(0.1, 136.1)	(3.4, 3.8)	(0.6, 7.4)	(3.2, 3.6)
Seroresponse [c]				
n (%) [d]	1 (33.3)	505 (39.3)	1 (20.0)	458 (36.6)
95% CI [a]	(0.8, 90.6)	(36.6, 42.0)	(0.5, 71.6)	(33.9, 39.3)
Day 179 (Month 6)				
n [a]	2	1253	6	1227
GMC	3685.6	2363.6	1950.1	2462.3
95% CI [b]	(634.4, 21411.7)	(2212.9, 2524.4)	(362.8, 10482.5)	(2305.5, 2629.7)
GMC fold-rise	6.6	3.2	1.6	3.1
95% CI [b]	(<0.05, 8.6E12)	(3.0, 3.5)	(0.3, 8.3)	(2.9, 3.4)
Seroresponse [c]				
n (%) [d]	1 (50.0)	510 (41.2)	2 (33.3)	491 (40.7)
95% CI [a]	(1.3, 98.7)	(38.5, 44.0)	(4.3, 77.7)	(38.0, 43.6)
Day 359/EOS (Month 12)				
n [a]	2	1219	6	1166
GMC	2219.3	2261.9	2013.9	2492.6
95% CI [b]	(21.7, 226663.5)	(2123.2, 2409.6)	(631.5, 6422.6)	(2342.6, 2652.1)
GMC fold-rise	4.0	3.1	1.7	3.1
95% CI [b]	(<0.05, 8678216222.7)	(2.8, 3.3)	(0.5, 5.5)	(2.9, 3.4)
Seroresponse [c]				
n (%) [d]	1 (50.0)	513 (42.6)	1 (16.7)	508 (44.3)
95% CI [a]	(1.3, 98.7)	(39.8, 45.4)	(0.4, 64.1)	(41.4, 47.2)

Abbreviations: CI = confidence interval; EOS = end of study; GM = geometric mean; GMC = geometric mean concentration; LLOQ = lower limit of quantification; NE = not evaluable; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: 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.
Original changed to Ancestral in table title.
B.1.1.529 is referred to as Omicron BA.1 in this table. The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

[a] Number of participants with non-missing data at the timepoint (baseline or post-baseline).
[b] 95% CI is calculated based on the t-distribution of the log-transformed values for GM value and GM fold-rise, respectively, then back-transformed to the original scale for presentation.
[c] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold-rise if baseline is ≥LLOQ.
[d] Number of participants meeting the criterion at the timepoint. Percentages are based on n.
[e] 95% CI is calculated using the Clopper-Pearson method.

Source: Table 14.2.1.2.2.1.2

Table 29: Analysis of Neutralizing Antibody Concentrations against Ancestral Strain by Visit after Study Vaccination as the 4th Dose in Part 2 – ANCOVA Model (PPSI – SARS-CoV-2 Negative)

	4th Dose	
Timepoint Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg	mRNA-1273 50 µg
Day 29		
N1	945	873
GLSM	3107.3	2964.9
99% CI	(2914.9, 3312.3)	(2775.1, 3167.6)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.048	–
99% CI	(0.958, 1.147)	–
Day 85 (Month 3)		
N1	747	671
GLSM	1804.9	1635.3
96% CI	(1722.3, 1891.5)	(1556.3, 1718.3)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.104	–
96% CI	(1.032, 1.180)	–
Day 179 (Month 6)[a]		
N1	350	325
GLSM	1183.2	1166.8
95% CI	(1079.0, 1297.6)	(1060.0, 1284.3)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.014	–

Timepoint Statistic	4th Dose	
	Bivalent Vaccine (Original and Omicron BA.1) 50 µg	mRNA-1273 50 µg
95% CI	(0.888, 1.158)	–
Day 179 (Month 6)[b]		
N1	181	162
GLSM	942.4	939.9
95% CI	(848.1, 1047.3)	(839.3, 1052.5)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.003	–
95% CI	(0.865, 1.162)	–
Day 359/EOS (Month 12)[a]		
N1	188	173
GLSM	772.8	937.7
95% CI	(696.8, 857.2)	(841.7, 1044.7)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	0.824	–
95% CI	(0.709, 0.957)	–
Day 359/EOS (Month 12)[b]		
N1	92	74
GLSM	684.2	661.1
95% CI	(583.2, 802.7)	(551.8, 791.9)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.035	–
95% CI	(0.817, 1.311)	–

Abbreviations: (–) = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; EOS = end of study; GLSM = geometric least squares mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least square; PPSI = Per-Protocol Set Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; ULOQ = upper limit of quantification.

Notes: Prototype was changed to Ancestral in table title.
N1=Number of participants with non-missing data at Baseline and the corresponding timepoint.
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 concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
B.1.1.529 is referred to as Omicron BA.1 in this table. The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

[a] Phase B Subgroup: Participants received an additional vaccination outside of the study.
[b] Phase B Subgroup: Participants did not receive an additional vaccination outside of the study.

Sources: Table 14.2.2.2.3.1.2 and Table 14.2.2.2.3.3.2

Table 30: Analysis of Neutralizing Antibody Concentrations against Ancestral Strain by Visit after Study Vaccination as the 4th Dose in Part 2 – ANCOVA Model (PPSI)

	4th Dose	
Timepoint Statistic	Bivalent Vaccine (Original and Omicron BA.1) 50 µg	mRNA-1273 50 µg
Day 29		
N1	1297	1263
GLSM	3937.4	3658.3
99% CI	(3654.8, 4241.8)	(3393.4, 3943.9)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.076	–
99% CI	(0.997, 1.162)	–
Day 85 (Month 3)		
N1	1286	1251
GLSM	2620.2	2545.0
96% CI	(2450.8, 2801.2)	(2378.8, 2722.9)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	1.030	–
96% CI	(0.961, 1.103)	–
Day 179 (Month 6)		
N1	1237	1205
GLSM	2214.3	2251.6
95% CI	(2032.4, 2412.4)	(2065.1, 2454.9)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	0.983	–
95% CI	(0.900, 1.075)	–
Day 359/EOS (Month 12)		
N1	1205	1147
GLSM	2159.5	2348.1
95% CI	(1995.2, 2337.3)	(2167.3, 2544.1)
GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273)	0.920	–
95% CI	(0.847, 0.999)	–

Abbreviations: (–) = not applicable; ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; EOS = end of study; GLSM = geometric least squares mean; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least square; PPSI = Per-Protocol Set Immunogenicity; ULOQ = upper limit of quantification.

Notes: Prototype was changed to Ancestral in table title.
N1=Number of participants with non-missing data at Baseline and the corresponding timepoint.
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 concentrations are analyzed using an ANCOVA model with the treatment variable as fixed effect, adjusting for age group (≥16 to < 65, ≥ 65 years), most recent COVID-19 vaccination type (mRNA, viral vector), and pre-booster antibody concentration. The LS means, difference of LS means, and 95% CI are back-transformed to the original scale for presentation.
B.1.1.529 is referred to as Omicron BA.1 in this table. The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

Source: Table 14.2.2.2.3.2.2

SARS-CoV-2 Specific Binding Antibodies

The GMC, GMFR, GMR, and SRR based on bAb responses were overall consistent with the nAb results.

Table 14.2.1.1.1.1.1 to Table 14.2.2.1.8.2.2 with bAb antibody response data for Part 1 are included in the CSR Section 14.2 (tables not presented in this AR).

Table 14.2.1.1.1.1.1 to Table 14.2.2.1.8.2.2 with bAb antibody response data for Part 2 are included in the CSR Section 14.2 (tables not presented in this AR).

MAH's Immunogenicity Conclusions

The pre-specified primary immunogenicity objectives were met in both Part 1 and Part 2. At Day 29 and Day 85, the Omicron BA.1 monovalent vaccine elicited a non-inferior nAb response against Omicron BA.1 compared with mRNA-1273, and the bivalent vaccine (original and Omicron BA.1) elicited a superior nAb response against Omicron BA.1 and a non-inferior nAb response against the ancestral strain compared with mRNA-1273.

In Part 1, the key secondary objective was met. The Omicron BA.1 monovalent vaccine elicited a superior nAb response against Omicron BA.1 compared with mRNA-1273 at Day 29 and Day 85. At both timepoints, as a secondary objective, the Omicron BA.1 monovalent vaccine also elicited a non-inferior nAb response against the ancestral strain compared with mRNA-1273.

As secondary objectives, the Omicron BA.1 monovalent vaccine elicited a higher SRR against Omicron BA.1 but a lower SRR against the ancestral strain compared with mRNA-1273. This was expected as the Omicron BA.1 monovalent vaccine does not contain the ancestral strain. On the other hand, bivalent vaccine (original and Omicron BA.1) elicited a higher SRR against Omicron BA.1 and a similar SRR against the ancestral strain compared with mRNA-1273.

Finally, both the Omicron BA.1 monovalent vaccine and the bivalent vaccine (original and Omicron BA.1) elicited high nAb responses against Omicron BA.1 and the ancestral strain through Month 12 post-study vaccination. The GMCs and GMFRs elicited by all study vaccines remained elevated above baseline through Month 12 in the PPSI-Neg population, suggesting a durable antibody response. Overall results support the development of variant-containing COVID-19 mRNA vaccines.

Assessor's comment:

Immune response against SARS-CoV-2 Omicron BA.1 strain

At Baseline in **part 1** (prior to study vaccination), the observed GMC was 70.1 (95% CI: 62.6, 78.3) in the Omicron BA.1 monovalent vaccine arm and 67.3 (95% CI: 60.0, 75.4) in the mRNA-1273 vaccine arm.
At Baseline in **part 2** (prior to study vaccination), the observed GMC was 50.5 (95% CI: 47.4, 53.8) in the bivalent vaccine (original and Omicron BA.1) arm and 52.3 (95% CI: 48.8, 56.0) in the mRNA-1273 vaccine arm.
Baseline GMCs are similar in part 1 and part 2.

In **part 1** at Day 29, the observed GMC was 537.7 (95% CI: 478.2, 604.6) for the Omicron BA.1 monovalent vaccine arm and 302.8 (95% CI: 274.8, 333.6) for the mRNA-1273 vaccine arm, which represent 7.7-fold and 4.5-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 7.7 [7.0, 8.4] and 4.5 [4.1, 4.9]), respectively.
In **part 2** at Day 29, the observed GMC was 465.7 (95% CI: 437.0, 496.3) and 311.0 (95% CI: 292.9, 330.1) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 9.2-fold and 5.9-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 9.2 [8.8, 9.7] and 5.9 [5.6, 6.3], respectively).

Day 29 GMCs are in the same range for part 1 and part 2.

The Day 29 GMRs were 1.73 (99% CI: 1.49, 2.01) in **part 1** and 1.54 (99% CI: 1.41, 1.67) in **part 2**, which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67).

In **part 1** at Day 85, the observed GMC was 284.7 (95% CI: 248.0, 326.7) for the Omicron BA.1 monovalent vaccine arm and 152.6 (95% CI: 135.1, 172.3) for the mRNA-1273 vaccine arm, which represent 4.0-fold and 2.3-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 4.0 [3.6, 4.4] and 2.3 [2.1, 2.5], respectively.
In **part 2** at Day 85, the observed GMC was 258.2 (95% CI: 239.3, 278.7) and 153.0 (95% CI: 142.2, 164.6) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 5.0-fold and 2.9-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 5.0 [4.7, 5.3] and 2.9 [2.7, 3.1], respectively).

The Day 85 GMRs were 1.763 (96% CI: 1.546, 2.001) in **part 1** and 1.71 (96% CI: 1.58, 1.85) in **part 2**, which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67).

Also, superiority of the immune responses at Day 29 and at Day 85 of Omicron BA.1 monovalent vaccine and the bivalent vaccine (original and Omicron BA.1) each compared with the mRNA-1273 vaccine against SARS-CoV-2 strain Omicron BA.1 was demonstrated based on the lower bound of the 99% CI >1.

GMC values are numerically lower as compared to titres determined against ancestral strain. Additionally, a drop in the GMC values to 46% and 55%, respectively, between Day 29 and Day 85 is observed, indicating a rapid waning of immunity.

Exemplarily, GMC values on Day 179 (6 months) and Day 359 (12 months) from part 2 against Omicron BA.1 strain (GMC values for participants that did not receive additional vaccination outside the study; bivalent vaccine vs. original) are shown:

Day 179: 141.1 (95% CI: 120.2, 165.5) vs. 87.5 (95% CI: 72.9, 105.1)
Day 359: 127.8 (95% CI: 96.9, 168.5) vs. 74.2 (95% CI: 54.2, 101.5)

Immune response against SARS-CoV-2 Ancestral strain

At Baseline in **part 1** (prior to study vaccination), the observed GMC was 731.7 (95% CI: 662.2, 808.5) in the Omicron BA.1 monovalent vaccine arm and 634.3 (95% CI: 575.6, 699.0) in the mRNA-1273 vaccine arm.
At Baseline in **part 2** (prior to study vaccination), the observed GMC was 502.7 (95% CI: 472.9, 534.4) in the bivalent vaccine (original and Omicron BA.1) arm and 521.2 (95% CI: 489.8, 554.7) in the mRNA-1273 vaccine arm.
Baseline GMCs are in a similar range in part 1 and part 2.

In **part 1** at Day 29, the observed GMC was 2699.7 (95% CI: 2431.3, 2997.7) for the Omicron BA.1 monovalent vaccine arm and 3020.6 (95% CI: 2776.5, 3286.2) for the mRNA-1273 vaccine arm, which represent 3.7-fold and 4.8-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 3.7 [3.4, 4.0] and 4.8 [4.4, 5.2]), respectively.
In **part 2** at Day 29, the observed GMC was 2998.8 (95% CI: 2825.4, 3182.8) for the bivalent vaccine (original and Omicron BA.1) arm and 2933.6 (95% CI: 2772.3, 3104.4) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 6.0-fold and 5.6-fold increases, respectively, over the baseline (observed GMFR [95% CI] values of 6.0 [5.6, 6.3] and 5.6 [5.3, 5.9], respectively).

Day 29 GMCs are in the same range for part 1 and part 2.

The Day 29 GMRs were 0.82 (95% CI: 0.74. 0.91) in **part 1** and 1.05 (99% CI: 0.96, 1.15) in **part 2**, which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67).

In **part 1** at Day 85, the observed GMC was 1401.2 (95% CI: 1236.9, 1587.4) for the Omicron BA 1 monovalent vaccine arm and 1559.4 (95% CI: 1401.2, 1735.5) for the mRNA-1273 vaccine arm, which represent 1.9-fold and 2.5-fold increases respectively, over the baseline (observed GMFR [95% CI] values of 1.9 [1.7, 2.1] and 2.5 [2.3, 2.7], respectively).
In **part 2** at Day 85, the observed GMC was 1753.1 (95% CI: 1650.0, 1862.6) for the bivalent vaccine (original and Omicron BA.1) arm and 1610.2 (95% CI: 1519.6, 1706.2) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 3.4-fold and 3.0-fold increases respectively, over the baseline (observed GMFR [95% CI] values of 3.4 [3.2, 3.6] and 3.0 [2.9, 3.2], respectively).

The Day 85 GMRs were 0.80 (95% CI: 0.71, 0.90) in **part 1** and 1.10 (96% CI: 1.03, 1.18) in **part 2**, which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67).

Against SARS-CoV-2 ancestral strain, superiority of the immune responses at Day 29 and at Day 85 of the bivalent vaccine (original and Omicron BA.1) compared with the mRNA-1273 vaccine against SARS-CoV-2 ancestral strain was demonstrated based on the lower bound of the 99% CI >1. Expectedly, superiority could not be demonstrated for the Omicron BA.1 monovalent vaccine, both, on Day 29 and Day 85, however, this was also no objective of study P305 part 1.

Additionally, a drop in the GMC values (GMC values remain 51% and 58% at Day 85 as compared to Day 29, respectively) between Day 29 and Day 85 is observed, indicating a rapid waning of immunity.

Exemplarily, GMC values on Day 179 (6 months) and Day 359 (12 months) from part 2 against SARS-CoV-2 ancestral strain (GMC values for participants that did not receive additional vaccination outside the study; bivalent vaccine vs. original) are shown:

Day 179: 918.8 (95% CI: 810.3,1041.9) vs. 911.9 (95% CI: 797.9, 1042.3)
Day 359: 673.8 (95% CI: 552.9, 821.2) vs. 585.6 (95% CI: 464.2, 738.7)

Efficacy results

Summary of Relative Efficacy Analysis

This study was not designed to measure vaccine efficacy. However, SARS-CoV-2 infection starting 14 days after randomization through the end of study in participants with no serologic or virologic evidence of prior SARS-CoV-2 infection pre-vaccination was an exploratory endpoint in Part 1 and a secondary endpoint in Part 2. This efficacy analysis was based on the PPSE analysis set, which consisted of all participants in the mITT who received the planned dose of study vaccination and had no major protocol deviations that had an impact on key or critical data. VE was defined as 1-ratio of the IR (Omicron BA.1 vaccine vs. mRNA-1273).

Part 1

SARS-CoV-2/COVID-19 Incidence Rates Following the Fourth Dose

Primary Case Definition of COVID-19

Starting 14 days after randomization, there were 145 events in the Omicron BA.1 monovalent vaccine arm and 152 events in the mRNA-1273 vaccine arm that met the primary case definition of COVID-19. During that time, following the fourth dose of Omicron BA.1 monovalent vaccine, 104 participants experienced COVID-19 over 167.8 person-years with an IR of 619.9 (95% CI: 506.49, 751.10) per 1000 person-years. Following the fourth dose of mRNA-1273, 107 participants experienced COVID-19 over 166.7 person-years with an IR of 641.9 (95% CI: 526.08, 775.71) per 1000 person-years. VE was <0.05 (95% CI: -0.28, 0.27).

Secondary Case Definition of COVID-19

Starting 14 days after randomization, there were 156 events in the Omicron BA.1 monovalent vaccine arm and 169 events in the mRNA-1273 vaccine arm that met the secondary case definition of COVID 19 (CDC 2022). For details refer to Table below.

Asymptomatic SARS-CoV-2 Infection

There were 74 asymptomatic SARS-CoV-2 events in the Omicron BA.1 monovalent vaccine arm and 65 asymptomatic SARS-CoV-2 events in the mRNA-1273 vaccine arm. For details refer to Table below.

Overall SARS-CoV-2 Infection

For details of overall SARS-CoV-2 infection starting 14 days after randomization through the end of the study, refer to Table below.

Table 31: Summary of Efficacy Analysis in Part 1 (PPSE)

	Omicron BA.1 Monovalent Vaccine 50 µg		mRNA-1273 50 µg	
	3rd Dose (N=1)	4th Dose (N=312)	3rd Dose (N=0)	4th Dose (N=312)
SARS-CoV-2 infection starting 14 days after randomization, n (%) [a]	0	147 (47.1)	-	162 (51.9)

	Omicron BA.1 Monovalent Vaccine 50 µg		mRNA-1273 50 µg	
	3rd Dose (N=1)	4th Dose (N=312)	3rd Dose (N=0)	4th Dose (N=312)
Number of events [b]	0	206	–	207
Person-years [c]	0.7	153.2	–	147.3
Incidence rate per 1,000 person-years (95% CI) [d]	0.0 (NE, 5411.10)	959.5 (810.66, 1127.75)	–	1099.9 (937.07, 1282.95)
VE based on incidence rate (95% CI) [e]	NE (NE, NE)	0.1 (-0.10, 0.31)	–	–
Asymptomatic SARS-CoV-2 infection starting 14 days after randomization, n (%) [f]	0	36 (11.5)	–	43 (13.8)
Number of events [b]	0	74	–	65
Person-years [c]	0.7	154.1	–	148.0
Incidence rate per 1,000 person-years (95% CI) [d]	0.0 (NE, 5411.10)	233.6 (163.64, 323.46)	–	290.6 (210.29, 391.39)
VE based on incidence rate (95% CI) [e]	NE (NE, NE)	0.2 (-0.28, 0.50)	–	–
Primary case definition of COVID-19 starting 14 days after randomization, n (%) [g]	0	104 (33.3)	–	107 (34.3)
Number of events [b]	0	145	–	152
Person-years [c]	0.7	167.8	–	166.7
Incidence rate per 1,000 person-years (95% CI) [d]	0.0 (NE, 5411.10)	619.9 (506.49, 751.10)	–	641.9 (526.08, 775.71)
VE based on incidence rate (95% CI) [e]	NE (NE, NE)	<0.05 (-0.28, 0.27)	–	–
Secondary case definition of COVID-19 starting 14 days after randomization, n (%) [h]	0	110 (35.3)	–	119 (38.1)
Number of events [b]	0	156	–	169
Person-years [c]	0.7	162.8	–	160.6
Incidence rate per 1,000 person-years (95% CI) [d]	0.0 (NE, 5411.10)	675.5 (555.16, 814.14)	–	740.9 (613.77, 886.59)
VE based on incidence rate (95% CI) [e]	NE (NE, NE)	0.1 (-0.19, 0.30)	–	–

Abbreviations: (–) = not applicable; bAb; binding antibody; CDC = US Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; NE = not evaluable; PPSE = per-protocol set for efficacy; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

Note: The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

a. SARS-CoV-2 infection was defined as either a positive post-baseline bAb level against SARS-CoV-2 nucleocapsid protein or a positive post-baseline RT-PCR test in participants with negative SARS-CoV-2 status pre-booster.
b. Could include more than one event per participant.
c. Person-years was defined as the total time from randomization date to the date of SARS-CoV-2 infection, last date of study participation, date of additional vaccination outside of the study, or efficacy data cut-off date, whichever was the earliest.
d. Incidence rate was defined as the number of participants with an event divided by the total person-years (total time at risk). The 95% CI was calculated using the exact method (Poisson distribution) and adjusted by person-years.
e. VE, defined as 1-ratio of incidence rate (Omicron BA.1 monovalent vaccine vs. mRNA-1273). Incidence rate was defined as the number of participants with an event divided by the total person-years (total time at risk). The 95% CI of the ratio was calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
f. Asymptomatic SARS-CoV-2 infection: infections were identified by absence of symptoms and infections as detected by RT-PCR or serology tests in participants with negative SARS-CoV-2 status pre-booster.
g. Protocol-defined COVID-19 case definition (primary case definition): cases were defined as meeting clinical criteria based on both symptoms of COVID-19 and positive RT-PCR test results.
h. CDC case definition of COVID-19 (secondary case definition): cases were defined as a positive post-baseline RT-PCR test result, together with eligible symptoms.

Sources: Table 14.2.10.1.1.1.1, Table 14.2.10.2.1.1.1, Table 14.2.10.2.2.1.1, Table 14.2.10.2.3.1.1, and Table 14.2.10.2.4.1.1.

Part 2

In Part 2 of the study, a secondary objective was to assess for symptomatic and asymptomatic SARS CoV-2 infection and COVID-19 starting 14 days after randomization through the end of the study in participants with a negative pre-vaccination SARS-CoV-2 status.

Primary Case Definition of COVID-19

Starting 14 days after randomization, there were 439 events in the bivalent vaccine (original and Omicron BA.1) arm and 385 events in the mRNA-1273 vaccine arm that met the primary case definition of COVID-19. During that time, following the fourth dose of bivalent vaccine (original and Omicron BA.1), 303 participants experienced COVID-19 over 540.0 person-years with an IR of 561.2 (95% CI: 499.74, 628.03) per 1000 person-years. Following the fourth dose of mRNA-1273, 271 participants experienced COVID-19 over 497.5 person-years with an IR of 544.8 (95% CI: 481.82, 613.62) per 1000 person-years. VE was >-0.05 (95% CI: -0.22, 0.13) (Table 31).

Secondary Case Definition of COVID-19

For details starting 14 days after randomization, there were 492 events in the bivalent vaccine (original and Omicron BA.1) arm and 419 events in the and mRNA-1273 vaccine arm that met the secondary case definition of COVID-19. For details refer to Table 31.

Asymptomatic SARS-CoV-2 Infection

For details starting 14 days after randomization, there were 245 asymptomatic SARS-CoV-2 events in the bivalent vaccine (original and Omicron BA.1) arm and 252 events in the mRNA-1273 vaccine arm. For details refer to Table 31.

Overall SARS-CoV-2 Infection

For details of overall SARS-CoV-2 infection, refer to Table below.

Table 32: Summary of Efficacy Analysis Results in Part 2 (PPSE)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg		mRNA-1273 50 µg	
	3rd Dose (N=2)	4th Dose (N=995)	3rd Dose (N=5)	4th Dose (N=932)
SARS-CoV-2 infection starting 14 days after randomization, n (%) [a]	1 (50.0)	505 (50.8)	3 (60.0)	453 (48.6)
Number of events [b]	1	656	3	609
Person-years [c]	0.7	472.7	3.0	434.7
Incidence rate per 1,000 person-years (95% CI) [d]	1443.7 (36.55, 8043.65)	1068.3 (977.15, 1165.68)	989.8 (204.13, 2892.72)	1042.0 (948.27, 1142.55)
VE based on incidence rate (95% CI) [e]	-0.5 (-17.16, 0.97)	>-0.05 (-0.17, 0.10)	–	–
Asymptomatic SARS-CoV-2 infection starting 14 days after randomization, n (%) [f]	0	168 (16.9)	2 (40.0)	165 (17.7)
Number of events [b]	0	245	2	252
Person-years [c]	0.7	475.8	3.0	435.5
Incidence rate per 1,000 person-years (95% CI) [d]	0.0 (NE, 5325.55)	353.1 (301.71, 410.70)	659.9 (79.92, 2383.76)	378.9 (323.29, 441.33)
VE based on incidence rate (95% CI) [e]	1.0 (-22.30, NE)	0.1 (-0.16, 0.25)	–	–
Primary case definition of COVID-19 starting 14 days after randomization, n (%) [g]	1 (50.0)	303 (30.5)	1 (20.0)	271 (29.1)
Number of events [b]	1	439	1	385
Person-years [c]	0.7	540.0	3.7	497.5
Incidence rate per 1,000 person-years (95% CI) [d]	1443.7 (36.55, 8043.65)	561.2 (499.74, 628.03)	270.0 (6.83, 1504.10)	544.8 (481.82, 613.62)
VE based on incidence rate (95% CI) [e]	-4.3 (-418.79, 0.93)	>-0.05 (-0.22, 0.13)	–	–
Secondary case definition of COVID-19 starting 14 days after randomization, n (%) [h]	1 (50.0)	333 (33.5)	1 (20.0)	288 (30.9)
Number of events [b]	1	492	1	419
Person-years [c]	0.7	522.7	3.7	489.9
Incidence rate per 1,000 person-years (95% CI) [d]	1443.7 (36.55, 8043.65)	637.1 (570.47, 709.30)	270.0 (6.83, 1504.10)	587.8 (521.90, 659.79)
VE based on incidence rate (95% CI) [e]	-4.3 (-418.79, 0.93)	-0.1 (-0.27, 0.08)	–	–

Abbreviations: (–) = not applicable; bAb = binding antibody; CDC = US Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; NE = not evaluable;

PPSE = per-protocol set for efficacy; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

Note: The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

a. SARS-CoV-2 infection: infections were defined as either a positive post-baseline bAb level against SARS-CoV-2 nucleocapsid protein or a positive post-baseline RT-PCR test in participants with negative SARS-CoV-2 status pre-booster.

b. Could include more than one event per participant.

c. Person-years was defined as the total time from randomization date to the date of SARS-CoV-2 infection, last date of study participation, date of additional vaccination outside of the study, or efficacy data cut-off date, whichever was the earliest.

d. Incidence rate was defined as the number of participants with an event divided by the total person-years (total time at risk). The 95% CI was calculated using the exact method (Poisson distribution) and adjusted by person-years.

e. VE, defined as 1 - ratio of incidence rate (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273). The 95% CI of the ratio was calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

f. Asymptomatic SARS-CoV-2 infection: infections were identified by absence of symptoms and infections as detected by RT-PCR or serology tests in participants with negative SARS-CoV-2 status pre-booster.

g. Protocol-defined COVID-19 case definition (primary case definition): cases were defined as meeting clinical criteria based on both symptoms of COVID-19 and positive RT-PCR test results.

h. CDC case definition of COVID-19 (secondary case definition): cases were defined as a positive post-baseline RT-PCR test result, together with eligible symptoms.

Sources: Table 14.2.10.1.1.1.2, Table 14.2.10.2.1.1.2, Table 14.2.10.2.2.1.2, Table 14.2.10.2.3.1.2, and Table 14.2.10.2.4.1.2.

Exploratory Analysis of Relative Efficacy of SARS-CoV-2 Infection and COVID-19 by Sublineages

The overall IRs of COVID-19 based on the primary case definition were initially numerically lower in the Omicron BA.1 monovalent vaccine study arm compared to the mRNA-1273 active control arm. However, this relative difference dissipated over time, and at the end of the study, similar IRs were observed in participants who received Omicron BA.1 monovalent vaccine compared with mRNA-1273 vaccination. For Kaplan Meyer representation refer to Figure 14.2.10.1.3.1 (not presented in this AR). Similarly, the overall IRs of COVID-19 based on the primary case definition were initially numerically lower in the bivalent vaccine (original and Omicron BA.1) study arm compared to the mRNA-1273 active control arm. However, this relative difference also dissipated over time, and at the end of the study, similar IRs were observed in participants who received bivalent vaccine (original and Omicron BA.1) compared with mRNA-1273 vaccination. For Kaplan Mayer representation refer to Figure 14.2.10.1.3.2 (not presented in this AR).

There was 1 case of COVID-19–related hospitalization in Part 1 of this study occurring in a participant who received the Omicron BA.1 monovalent vaccine. The SARS-CoV-2 infection was diagnosed using a rapid antigen/lateral flow test and not a PCR–based test. In Part 2, there were no cases of COVID-19 related hospitalization in Part 2 of this study.

Part 1

An exploratory analysis by BA.2, BA.4, BA.5, or BQ.1 sublineage sequences through the end of the study showed numerically lower IRs for the BA.2 sublineages in the Omicron BA.1 monovalent vaccine vs. mRNA-1273 vaccine arms. IRs were similar for the BA.4, BA.5, and BQ.1 sublineages between study arms (Table 32). Relative VE estimates (1-HR) were 39% (95% CI: 3%, 61%), -15% (95% CI: -217%, 58%), -28% (95% CI: -100%, 18%), and -213% (95% CI: -1480%, 38%) for Omicron BA.1 monovalent vaccine vs. mRNA-1273 for the BA.2, BA.4, BA.5, and BQ.1 sublineages, respectively.

Table 33: Exploratory Analysis of Relative VE of COVID-19 by Sublineages (Part 1, Per-Protocol Efficacy Set in the 4th Dose Group)

	Omicron BA.1 monovalent (N=312)	mRNA-1273 (N=312)
COVID-19 (protocol-defined)[a], participants: (%)	104 (33.3)	107 (34.3)
COVID-19 (protocol-defined)[a] with sequencing data, participants: (%)	88 (29.5%)	92 (29.5%)
COVID-19 cases with BA.2/BA.2 sublineages, participants (%)	30 (9.6%)	48 (15.4%)
Incidence rate per 1000 PY (95% CI)	178.8 (120.6, 255.2)	287.9 (212.3, 381.8)
Number of COVID-19 cases with competing event[b]	74 (23.7%)	59 (18.9%)
rVE based on hazard ratio	39%	
(95% CI)	(3%, 61%)	
Number (%) of COVID-19 cases with BA.4/BA.4 sublineages	8 (2.6%)	7 (2.2%)
Incidence rate per 1000 PY (95% CI)	42.0 (16.9, 86.5)	47.7 (20.6, 93.9)
Number of COVID-19 cases with competing event[b]	96 (30.8%)	100 (32.1%)
rVE based on hazard ratio	-15%	
(95% CI)	(-217%, 58%)	
Number (%) of COVID-19 cases with BA.5/BA.5 sublineages	44 (14.1%)	35 (11.2%)
Incidence rate per 1000 PY (95% CI)	262.2 (190.5, 353.0)	209.9 (146.2, 292.0)
Number of COVID-19 cases with competing event[b]	60 (19.2%)	72 (23.1%)
rVE based on hazard ratio	-28%	
(95% CI)	(-100%, 18%)	
Number (%) of COVID-19 cases with BQ.1/BQ.1 sublineages	6 (1.9%)	2 (0.6%)
Incidence rate per 1000 PY (95% CI)	35.7 (13.1, 77.9)	12.0 (1.4, 43.3)
Number of COVID-19 cases with competing event[b]	98 (31.4%)	105 (33.6%)
rVE based on hazard ratio	-213%	
(95% CI)	(-1480%, 38%)	

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; PY = person-years; rVE = relative vaccine efficacy.

Notes: Percentages are of number of participants in the Per-Protocol Set for Efficacy. Total person-years: 167.8 (Omicron BA.1 monovalent vaccine); 166.7 (mRNA-1273). Not displayed here was 1 case of BA.1 in the Omicron BA.1 monovalent vaccine arm.

a. Protocol-defined COVID-19 case definition (primary case definition): cases are defined as meeting clinical criteria based on at least 2 systemic symptoms or at least one of the following respiratory symptoms: cough, shortness of breath/difficulty breathing, or clinical or radiographical evidence of pneumonia, and at least one positive RT-PCR test result.

b. A competing risk method was used to analyze sublineage-specific events, where competing events were not censored. The Fine-Gray proportional hazards model for the subdistribution of a competing risk was used to estimate the hazard ratio and relative vaccine efficacy (1- hazard ratio) for specific sublineages.

Part 2

An exploratory analysis by BA.2, BA.4, BA.5, or BQ.1 sublineage sequences through the end of the study showed numerically lower IRs for the BA.2 and BA.4 sublineages in the bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 arms, whereas IRs were similar for the BA.5 and BQ.1 sublineages between study arms (Table 33). Relative VE (1-HR) estimates were 24% (95% CI: -18%, 51%), 49% (95% CI: 12%, 71%) and -8% (95% CI: -35%, 14%), and -18% (95% CI: -160%, 47%) for the bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 for the BA.2, BA.4, BA.5, and BQ.1 sublineages, respectively.

Table 34: Exploratory Analysis of Relative VE of COVID-19 by Sublineages (Part 2, Per-Protocol Efficacy Set in the 4th Dose Group)

	Bivalent (original and Omicron BA.1) (N=935)	mRNA-1273 (N=932)
COVID-19 (protocol-defined)[a], participants (%)	303 (30.5%)	271 (29.1%)
COVID-19 (protocol-defined)[a] with sequencing data, participants (%)	231 (24.8%)	232 (23.3%)
Number (%) of COVID-19 cases with BA.2/BA.2 sublineages	36 (3.5%)	44 (4.7%)
Incidence rate per 1000 PY (95% CI)	66.7 (46.7, 92.3)	88.3 (64.1, 118.5)
Number of COVID-19 cases with competing event[b]	267 (26.8%)	227 (24.4%)
rVE based on hazard ratio	24%	
(95% CI)	(-18%, 51%)	
Number (%) of COVID-19 cases with BA.4/BA.4 sublineages	19 (1.9%)	35 (3.8%)
Incidence rate per 1000 PY (95% CI)	35.2 (21.2, 54.9)	70.2 (48.9, 97.6)
Number of COVID-19 cases with competing event[b]	284 (28.5%)	236 (25.3%)
rVE based on hazard ratio	49%	
(95% CI)	(12%, 71%)	

	Bivalent (original and Omicron BA.1) (N=935)	mRNA-1273 (N=932)
Number (%) of COVID-19 cases with BA.5/BA.5 sublineages	163 (16.4%)	141 (15.1%)
Incidence rate per 1000 PY (95% CI)	301.9 (257.3, 351.9)	282.8 (238.1, 333.6)
Number of COVID-19 cases with competing event[b]	140 (14.1%)	130 (13.9%)
rVE based on hazard ratio	-8%	
(95% CI)	(-35%, 14%)	
Number (%) of COVID-19 cases with BQ.1/BQ.1 sublineages	14 (1.4%)	11 (1.2%)
Incidence rate per 1000 PY (95% CI)	25.9 (14.2, 43.5)	22.1 (11.0, 39.0)
Number of COVID-19 cases with competing event[b]	290 (29.1%)	261 (28.0%)
rVE based on hazard ratio	-18%	
(95% CI)	(-160%, 47%)	

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; PY = person-years; rVE = relative vaccine efficacy.

Notes: Percentages are of number of participants in the Per-Protocol Set for Efficacy. Total person years: 540.0 (bivalent [original and Omicron BA.1]); 498.5 (mRNA-1273).

[a] Protocol-defined COVID-19 case definition (primary case definition): cases are defined as meeting clinical criteria based on at least 2 systemic symptoms or at least one of the following respiratory symptoms: cough, shortness of breath/difficulty breathing, or clinical or radiographical evidence of pneumonia, and at least one positive RT-PCR test result.

[b] A competing risk method was used to analyze sublineage-specific events, where competing events were not censored. The Fine-Gray proportional hazards model for the subdistribution of a competing risk was used to estimate the hazard ratio and relative vaccine efficacy (1- hazard ratio) for specific sublineages.

MAH's SARS-CoV-2/COVID-19 Incidence Conclusions

The overall IRs of COVID-19 were initially numerically lower in the Omicron BA.1-containing vaccine (the Omicron BA.1 monovalent and the bivalent [original and Omicron BA.1]) vaccine arms compared to the mRNA-1273 vaccine arm. However, this relative difference dissipated over time, and at the end of the study, similar IRs were observed in participants who received Omicron BA.1-containing vaccines compared with mRNA-1273 vaccination. This may be explained by the evolution of Omicron sublineages during the conduct of the study. Numerically lower IRs of the Omicron BA.2 strain were observed among participants who received an Omicron BA.1 monovalent vaccine or bivalent vaccine (original and Omicron BA.1) compared to those who received mRNA-1273. However, the later emergence of the Omicron BA.5 strain, which is divergent from the Omicron BA.1 strain, may have contributed to the overall similar IRs of COVID-19 among all vaccine arms. Additionally, this study was not powered to detect a difference in relative efficacy between the study vaccines.

Assessor's comment:

While study P305 was not powered for effectiveness analysis results from SARS-CoV-2 BA.1 containing vaccines did not demonstrate effectiveness against SARS-CoV-2 infection as compared to vaccination with mRNA-1273 (original). During conduct of the study Omicron sub-lineages evolved that diverged from BA.1 strain.

Safety results

Safety Set

The safety and reactogenicity results are presented accordingly to Part 1 and Part 2.

Part 1: The safety set included 367/734 participants in the Omicron BA.1 monovalent vaccine arm and 357/724 participants in the mRNA-1273 vaccine arm. Across study vaccine arms, the median time on study was 357 days (range: 29 to 441 days).

Part 2: The Safety Set included 1422/2824 participants in the bivalent vaccine (original and Omicron BA.1) arm and 1402/2824 participants in the mRNA-1273 50 µg vaccine arm.
Across study vaccine arms, the median time on study was 359 days (range: 6 to 439 days).

The safety data for both Part 1 and Part 2 include the following:

- Solicited local and systemic ARs reported within 7 days after vaccination.
- Unsolicited AEs reported up to 28 days after vaccination.
- SAEs, MAAEs, AEs leading to discontinuation from study participation, AESIs, and pregnancies reported throughout the study (including events within 28 days after vaccination).

Assessor's comment:

The MAH has submitted the final results of this study in fulfilment of Article 46 of the paediatric regulation. Randomization in Part 1 and Part 2 were stratified by age groups were (16 to <65 years or ≥65 years) and results from subgroup analyses were presented. However, the vast majority of participants was represented by adults 18 years of age and older. The results are presented and assessed in the respective sessions of this report.

The safety of mRNA-1273 vaccine in pediatric population have been evaluated in previous Spikevax procedures such as EMEA/H/C/005791/II/0067. In that procedure data from the *Study P204*, from healthy children 6 months to less than 12 years of age have been submitted. The study population includes 3 age groups (≥6 years to <12 years, ≥2 years to <6 years, and ≥6 months to <2 years). The overall B/R of Spikevax for that age group was considered favourable.

Solicited Adverse Reactions

Part 1

The incidence of any solicited AR within 7 days was 91.3% participants for the Omicron BA.1 monovalent vaccine arm and 93.3% participants for the mRNA-1273.

In both vaccine arms, any solicited ARs were mostly Grade 1 with (52.6%) participants in the Omicron BA.1 monovalent vaccine arm, 47.9% participants in the mRNA-1273 arm followed by Grade 2 (32.7%) participants in the Omicron BA.1 monovalent vaccine arm, (35.9%) participants in the mRNA-1273 arm. Any solicited Grade 3 ARs were reported in (6.0%) participants in the Omicron BA.1 monovalent vaccine arm and in (9.5%) participants in the mRNA-1273 arm. There were no Grade 4 ARs reported.

By age subgroup, the incidence of local and systemic ARs was similar between study arms. In participants ≥65 years of age, incidence of solicited ARs was similar in the Omicron BA.1 monovalent vaccine arm (81.0%) compared to the mRNA-1273 arm (89.3%).

In participants between ≥16 and <65 years of age, incidence of solicited ARs was (96.7%) in the Omicron BA.1 monovalent vaccine arm and (95.3%) in the mRNA-1273 arm. No notable difference was observed in the incidences of local and systemic ARs by grade, onset day, and day of reporting between age subgroups.

Part 2

The incidence of any solicited AR within 7 days after vaccination was 90.5% participants for the bivalent vaccine (original and Omicron BA.1) arm and 94.3% participants in the mRNA-1273 arm.

In both vaccine arms, the solicited ARs were mostly Grade 1 (52.4%) participants in the bivalent vaccine (original and Omicron BA.1) arm, (47.9%) participants in the mRNA-1273 arm followed by Grade 2 (30.4%) participants in the bivalent vaccine (original and Omicron BA.1) arm, (35.6%) participants in the mRNA-1273 arm. Any solicited Grade 3 ARs were reported in (7.7%) participants in the bivalent vaccine (original and Omicron BA.1) arm and (10.8%) participants in the mRNA-1273 arm. There were no Grade 4 ARs reported.

By age subgroup, the incidence of local and systemic ARs was similar between study arms. Among participants aged ≥16 and <65 years, in both study arms, the incidence of solicited ARs was lower in the bivalent vaccine (original and Omicron BA.1) arm compared to the mRNA-1273 vaccine arm: (92.7%) participants in the bivalent vaccine (original and Omicron BA.1) arm, (97.0%) participants in the mRNA-1273 vaccine arm. This was due to the lower incidence of solicited local ARs in the bivalent vaccine (original and Omicron BA.1) arm compared to the mRNA-1273 vaccine arm: (86.7%) participants in the bivalent vaccine (original and Omicron BA.1) arm, (94.2%) participants in the mRNA-1273 vaccine arm. The incidence of solicited systemic ARs was similar for this age group between study arms. For participants ≥65 years of age, in both study arms, the incidence of local and systemic ARs was similar.

No notable difference was observed in the incidences of local and systemic ARs by grade, onset day, and day of reporting between age subgroups.

More details for the solicited local and systemic ARs within 7 Days after Injection by Grade in Part 1 and Part 2 are presented in the tables below:

Table 35: Summary of Participants With Solicited Local and Systemic ARs Within 7 Days After Injection by Grade in Part 1 (Solicited Safety Set)

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
Solicited Adverse Reaction Category Grade	3rd Dose (N=1) n (%)	4th Dose (N=366) n (%)	Total (N=367) n (%)	3rd Dose (N=0) n (%)	4th Dose (N=357) n (%)	Total (N=357) n (%)	Overall (N=724) n (%)
Solicited adverse reactions - N1	1	366	367	–	357	357	724
Any solicited adverse reactions	1 (100)	334 (91.3)	335 (91.3)	–	333 (93.3)	333 (93.3)	668 (92.3)
95% CI	2.5, 100.0	87.9, 93.9	87.9, 94.0	–	90.2, 95.6	90.2, 95.6	90.1, 94.1
Grade 1	1 (100)	192 (52.5)	193 (52.6)	–	171 (47.9)	171 (47.9)	364 (50.3)
Grade 2	0	120 (32.8)	120 (32.7)	–	128 (35.9)	128 (35.9)	248 (34.3)
Grade 3	0	22 (6.0)	22 (6.0)	–	34 (9.5)	34 (9.5)	56 (7.7)
Solicited local adverse reactions - N1	1	366	367	–	357	357	724
Any solicited local adverse reactions	1 (100)	309 (84.4)	310 (84.5)	–	318 (89.1)	318 (89.1)	628 (86.7)
95% CI	2.5, 100.0	80.3, 88.0	80.4, 88.0	–	85.4, 92.1	85.4, 92.1	84.1, 89.1
Grade 1	1 (100)	268 (73.2)	269 (73.3)	–	256 (71.7)	256 (71.7)	525 (72.5)
Grade 2	0	31 (8.5)	31 (8.4)	–	49 (13.7)	49 (13.7)	80 (11.0)
Grade 3	0	10 (2.7)	10 (2.7)	–	13 (3.6)	13 (3.6)	23 (3.2)
Pain - N1	1	366	367	–	357	357	724
Any	1 (100)	306 (83.6)	307 (83.7)	–	315 (88.2)	315 (88.2)	622 (85.9)
Grade 1	1 (100)	279 (76.2)	280 (76.3)	–	267 (74.8)	267 (74.8)	547 (75.6)
Grade 2	0	20 (5.5)	20 (5.4)	–	38 (10.6)	38 (10.6)	58 (8.0)
Grade 3	0	7 (1.9)	7 (1.9)	–	10 (2.8)	10 (2.8)	17 (2.3)
Erythema (redness) - N1	1	366	367	–	357	357	724
Any	0	15 (4.1)	15 (4.1)	–	13 (3.6)	13 (3.6)	28 (3.9)
Grade 1	0	6 (1.6)	6 (1.6)	–	8 (2.2)	8 (2.2)	14 (1.9)
Grade 2	0	7 (1.9)	7 (1.9)	–	5 (1.4)	5 (1.4)	12 (1.7)
Grade 3	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Swelling (hardness) - N1	1	366	367	–	357	357	724
Any	0	30 (8.2)	30 (8.2)	–	30 (8.4)	30 (8.4)	60 (8.3)
Grade 1	0	18 (4.9)	18 (4.9)	–	13 (3.6)	13 (3.6)	31 (4.3)
Grade 2	0	8 (2.2)	8 (2.2)	–	15 (4.2)	15 (4.2)	23 (3.2)
Grade 3	0	4 (1.1)	4 (1.1)	–	2 (0.6)	2 (0.6)	6 (0.8)
Axillary swelling or tenderness - N1	1	366	367	–	357	357	724
Any	1 (100)	62 (16.9)	63 (17.2)	–	60 (16.8)	60 (16.8)	123 (17.0)
Grade 1	1 (100)	54 (14.8)	55 (15.0)	–	52 (14.6)	52 (14.6)	107 (14.8)
Grade 2	0	8 (2.2)	8 (2.2)	–	5 (1.4)	5 (1.4)	13 (1.8)
Grade 3	0	0	0	–	3 (0.8)	3 (0.8)	3 (0.4)

Solicited systemic adverse reactions - N1	1	366	367	–	357	357	724
Any solicited systemic adverse reactions	1 (100)	255 (69.7)	256 (69.8)	–	265 (74.2)	265 (74.2)	521 (72.0)
95% CI	2.5, 100.0	64.7, 74.3	64.8, 74.4	–	69.4, 78.7	69.4, 78.7	68.5, 75.2
Grade 1	1 (100)	127 (34.7)	128 (34.9)	–	118 (33.1)	118 (33.1)	246 (34.0)
Grade 2	0	115 (31.4)	115 (31.3)	–	123 (34.5)	123 (34.5)	238 (32.9)
Grade 3	0	13 (3.6)	13 (3.5)	–	24 (6.7)	24 (6.7)	37 (5.1)
Fever - N1	1	366	367	–	357	357	724
Any	0	9 (2.5)	9 (2.5)	–	11 (3.1)	11 (3.1)	20 (2.8)
Grade 1	0	4 (1.1)	4 (1.1)	–	7 (2.0)	7 (2.0)	11 (1.5)
Grade 2	0	4 (1.1)	4 (1.1)	–	2 (0.6)	2 (0.6)	6 (0.8)
Grade 3	0	1 (0.3)	1 (0.3)	–	2 (0.6)	2 (0.6)	3 (0.4)
Headache - N1	1	366	367	–	357	357	724
Any	0	167 (45.6)	167 (45.5)	–	175 (49.0)	175 (49.0)	342 (47.2)
Grade 1	0	129 (35.2)	129 (35.1)	–	120 (33.6)	120 (33.6)	249 (34.4)
Grade 2	0	36 (9.8)	36 (9.8)	–	49 (13.7)	49 (13.7)	85 (11.7)
Grade 3	0	2 (0.5)	2 (0.5)	–	6 (1.7)	6 (1.7)	8 (1.1)
Fatigue - N1	1	366	367	–	357	357	724
Any	1 (100)	201 (54.9)	202 (55.0)	–	215 (60.2)	215 (60.2)	417 (57.6)
Grade 1	1 (100)	102 (27.9)	103 (28.1)	–	93 (26.1)	93 (26.1)	196 (27.1)
Grade 2	0	91 (24.9)	91 (24.8)	–	108 (30.3)	108 (30.3)	199 (27.5)
Grade 3	0	8 (2.2)	8 (2.2)	–	14 (3.9)	14 (3.9)	22 (3.0)
Myalgia - N1	1	366	367	–	357	357	724
Any	0	147 (40.2)	147 (40.1)	–	153 (42.9)	153 (42.9)	300 (41.4)
Grade 1	0	82 (22.4)	82 (22.3)	–	83 (23.2)	83 (23.2)	165 (22.8)
Grade 2	0	62 (16.9)	62 (16.9)	–	62 (17.4)	62 (17.4)	124 (17.1)
Grade 3	0	3 (0.8)	3 (0.8)	–	8 (2.2)	8 (2.2)	11 (1.5)
Arthralgia - N1	1	366	367	–	357	357	724
Any	1 (100)	104 (28.4)	105 (28.6)	–	114 (31.9)	114 (31.9)	219 (30.2)
Grade 1	1 (100)	60 (16.4)	61 (16.6)	–	73 (20.4)	73 (20.4)	134 (18.5)
Grade 2	0	42 (11.5)	42 (11.4)	–	37 (10.4)	37 (10.4)	79 (10.9)
Grade 3	0	2 (0.5)	2 (0.5)	–	4 (1.1)	4 (1.1)	6 (0.8)
Nausea/vomiting - N1	1	366	367	–	357	357	724
Any	1 (100)	39 (10.7)	40 (10.9)	–	42 (11.8)	42 (11.8)	82 (11.3)
Grade 1	1 (100)	35 (9.6)	36 (9.8)	–	34 (9.5)	34 (9.5)	70 (9.7)
Grade 2	0	4 (1.1)	4 (1.1)	–	8 (2.2)	8 (2.2)	12 (1.7)
Grade 3	0	0	0	–	0	0	0
Chills - N1	1	366	367	–	357	357	724
Any	0	102 (27.9)	102 (27.8)	–	87 (24.4)	87 (24.4)	189 (26.1)
Grade 1	0	59 (16.1)	59 (16.1)	–	46 (12.9)	46 (12.9)	105 (14.5)
Grade 2	0	43 (11.7)	43 (11.7)	–	41 (11.5)	41 (11.5)	84 (11.6)
Grade 3	0	0	0	–	0	0	0

Abbreviations: (–) = not applicable; AR = adverse reaction; CI = confidence intervals.
Notes: N1 = Number of exposed participants who submitted any data for the event within 7 days; Any = Grade 1 or higher.
Percentages were based on the number of exposed participants who submitted any data for the event (N1).
95% CI was calculated using the Clopper-Pearson method.
Toxicity grade for erythema (redness) was defined as: G1=25-50 mm; G2=51-100 mm; G3≥100 mm.
Toxicity grade for fever was defined as: G1=38°C-38.4°C; G2=38.5°C-38.9°C; G3=39°C-40°C; G4≥40°C.
No Grade 4 solicited ARs were reported.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.
Source: Table 14.3.1.1.1.1.

Table 36: Summary of Participants With Solicited Local and Systemic ARs Within 7 Days After Injection by Grade in Part 2 (Solicited Safety Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
Solicited Adverse Reaction Category Grade	3rd Dose (N=4) n (%)	4th Dose (N=1417) n (%)	Total (N=1421) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1392) n (%)	Total (N=1398) n (%)	Overall (N=2819) n (%)
Solicited adverse reactions - N1	4	1417	1421	6	1392	1398	2819
Any solicited adverse reactions	4 (100)	1282 (90.5)	1286 (90.5)	6 (100)	1312 (94.3)	1318 (94.3)	2604 (92.4)
95% CI	39.8, 100.0	88.8, 92.0	88.9, 92.0	54.1, 100.0	92.9, 95.4	92.9, 95.4	91.3, 93.3
Grade 1	1 (25.0)	743 (52.4)	744 (52.4)	3 (50.0)	666 (47.8)	669 (47.9)	1413 (50.1)
Grade 2	2 (50.0)	430 (30.3)	432 (30.4)	3 (50.0)	495 (35.6)	498 (35.6)	930 (33.0)
Grade 3	1 (25.0)	109 (7.7)	110 (7.7)	0	151 (10.8)	151 (10.8)	261 (9.3)
Solicited local adverse reactions - N1	4	1417	1421	6	1392	1398	2819
Any solicited local adverse reactions	4 (100)	1184 (83.6)	1188 (83.6)	6 (100)	1251 (89.9)	1257 (89.9)	2445 (86.7)
95% CI	39.8, 100.0	81.5, 85.5	81.6, 85.5	54.1, 100.0	88.2, 91.4	88.2, 91.4	85.4, 88.0
Grade 1	4 (100)	1031 (72.8)	1035 (72.8)	5 (83.3)	977 (70.2)	982 (70.2)	2017 (71.6)
Grade 2	0	110 (7.8)	110 (7.7)	1 (16.7)	206 (14.8)	207 (14.8)	317 (11.2)
Grade 3	0	43 (3.0)	43 (3.0)	0	68 (4.9)	68 (4.9)	111 (3.9)
Pain - N1	4	1417	1421	6	1392	1398	2819
Any	4 (100)	1163 (82.1)	1167 (82.1)	6 (100)	1242 (89.2)	1248 (89.3)	2415 (85.7)
Grade 1	4 (100)	1068 (75.4)	1072 (75.4)	5 (83.3)	1054 (75.7)	1059 (75.8)	2131 (75.6)
Grade 2	0	75 (5.3)	75 (5.3)	1 (16.7)	150 (10.8)	151 (10.8)	226 (8.0)
Grade 3	0	20 (1.4)	20 (1.4)	0	38 (2.7)	38 (2.7)	58 (2.1)
Erythema (redness)-N1	4	1417	1421	6	1392	1398	2819
Any	0	59 (4.2)	59 (4.2)	0	102 (7.3)	102 (7.3)	161 (5.7)
Grade 1	0	38 (2.7)	38 (2.7)	0	41 (2.9)	41 (2.9)	79 (2.8)
Grade 2	0	14 (1.0)	14 (1.0)	0	48 (3.4)	48 (3.4)	62 (2.2)
Grade 3	0	7 (0.5)	7 (0.5)	0	13 (0.9)	13 (0.9)	20 (0.7)
Swelling (hardness) - N1	4	1417	1421	6	1392	1398	2819
Any	0	109 (7.7)	109 (7.7)	1 (16.7)	168 (12.1)	169 (12.1)	278 (9.9)
Grade 1	0	63 (4.4)	63 (4.4)	1 (16.7)	92 (6.6)	93 (6.7)	156 (5.5)
Grade 2	0	30 (2.1)	30 (2.1)	0	50 (3.6)	50 (3.6)	80 (2.8)
Grade 3	0	16 (1.1)	16 (1.1)	0	26 (1.9)	26 (1.9)	42 (1.5)
Axillary swelling or tenderness - N1	4	1417	1421	6	1392	1398	2819
Any	0	248 (17.5)	248 (17.5)	1 (16.7)	252 (18.1)	253 (18.1)	501 (17.8)
Grade 1	0	219 (15.5)	219 (15.4)	1 (16.7)	212 (15.2)	213 (15.2)	432 (15.3)
Grade 2	0	25 (1.8)	25 (1.8)	0	36 (2.6)	36 (2.6)	61 (2.2)

Grade 3	0	4 (0.3)	4 (0.3)	0	4 (0.3)	4 (0.3)	8 (0.3)
Solicited systemic adverse reactions - N1	4	1417	1421	6	1392	1398	2819
Any solicited systemic adverse reactions	4 (100)	993 (70.1)	997 (70.2)	5 (83.3)	1048 (75.3)	1053 (75.3)	2050 (72.7)
95% CI	39.8, 100.0	67.6, 72.5	67.7, 72.5	35.9, 99.6	72.9, 77.5	73.0, 77.6	71.0, 74.4
Grade 1	1 (25.0)	509 (35.9)	510 (35.9)	2 (33.3)	477 (34.3)	479 (34.3)	989 (35.1)
Grade 2	2 (50.0)	409 (28.9)	411 (28.9)	3 (50.0)	463 (33.3)	466 (33.3)	877 (31.1)
Grade 3	1 (25.0)	75 (5.3)	76 (5.3)	0	108 (7.8)	108 (7.7)	184 (6.5)
Fever - N1	4	1413	1417	6	1386	1392	2809
Any	0	35 (2.5)	35 (2.5)	0	63 (4.5)	63 (4.5)	98 (3.5)
Grade 1	0	20 (1.4)	20 (1.4)	0	45 (3.2)	45 (3.2)	65 (2.3)
Grade 2	0	12 (0.8)	12 (0.8)	0	11 (0.8)	11 (0.8)	23 (0.8)
Grade 3	0	3 (0.2)	3 (0.2)	0	7 (0.5)	7 (0.5)	10 (0.4)
Headache - N1	4	1417	1421	6	1392	1398	2819
Any	3 (75.0)	646 (45.6)	649 (45.7)	3 (50.0)	698 (50.1)	701 (50.1)	1350 (47.9)
Grade 1	2 (50.0)	494 (34.9)	496 (34.9)	1 (16.7)	505 (36.3)	506 (36.2)	1002 (35.5)
Grade 2	0	131 (9.2)	131 (9.2)	2 (33.3)	167 (12.0)	169 (12.1)	300 (10.6)
Grade 3	1 (25.0)	21 (1.5)	22 (1.5)	0	26 (1.9)	26 (1.9)	48 (1.7)
Fatigue - N1	4	1417	1421	6	1392	1398	2819
Any	4 (100)	806 (56.9)	810 (57.0)	4 (66.7)	859 (61.7)	863 (61.7)	1673 (59.3)
Grade 1	1 (25.0)	415 (29.3)	416 (29.3)	1 (16.7)	384 (27.6)	385 (27.5)	801 (28.4)
Grade 2	3 (75.0)	343 (24.2)	346 (24.3)	3 (50.0)	392 (28.2)	395 (28.3)	741 (26.3)
Grade 3	0	48 (3.4)	48 (3.4)	0	83 (6.0)	83 (5.9)	131 (4.6)
Myalgia - N1	4	1417	1421	6	1392	1398	2819
Any	3 (75.0)	535 (37.8)	538 (37.9)	3 (50.0)	593 (42.6)	596 (42.6)	1134 (40.2)
Grade 1	0	309 (21.8)	309 (21.7)	2 (33.3)	299 (21.5)	301 (21.5)	610 (21.6)
Grade 2	3 (75.0)	200 (14.1)	203 (14.3)	1 (16.7)	252 (18.1)	253 (18.1)	456 (16.2)
Grade 3	0	26 (1.8)	26 (1.8)	0	42 (3.0)	42 (3.0)	68 (2.4)
Arthralgia - N1	4	1417	1421	6	1392	1398	2819
Any	3 (75.0)	393 (27.7)	396 (27.9)	2 (33.3)	452 (32.5)	454 (32.5)	850 (30.2)
Grade 1	1 (25.0)	233 (16.4)	234 (16.5)	1 (16.7)	259 (18.6)	260 (18.6)	494 (17.5)
Grade 2	2 (50.0)	141 (10.0)	143 (10.1)	1 (16.7)	165 (11.9)	166 (11.9)	309 (11.0)
Grade 3	0	19 (1.3)	19 (1.3)	0	28 (2.0)	28 (2.0)	47 (1.7)
Nausea/vomiting - N1	4	1417	1421	6	1392	1398	2819
Any	1 (25.0)	151 (10.7)	152 (10.7)	2 (33.3)	176 (12.6)	178 (12.7)	330 (11.7)
Grade 1	1 (25.0)	128 (9.0)	129 (9.1)	2 (33.3)	139 (10.0)	141 (10.1)	270 (9.6)
Grade 2	0	23 (1.6)	23 (1.6)	0	37 (2.7)	37 (2.6)	60 (2.1)
Grade 3	0	0	0	0	0	0	0
Chills - N1	4	1417	1421	6	1392	1398	2819
Any	0	337 (23.8)	337 (23.7)	3 (50.0)	384 (27.6)	387 (27.7)	724 (25.7)
Grade 1	0	235 (16.6)	235 (16.5)	3 (50.0)	203 (14.6)	206 (14.7)	441 (15.6)
Grade 2	0	98 (6.9)	98 (6.9)	0	171 (12.3)	171 (12.2)	269 (9.5)
Grade 3	0	4 (0.3)	4 (0.3)	0	10 (0.7)	10 (0.7)	14 (0.5)

Abbreviations: AR = adverse reaction; CI=confidence intervals.
Notes: N1 = Number of exposed participants who submitted any data for the event within 7 days; Any = Grade 1 or higher.
Percentages were based on the number of exposed participants who submitted any data for the event (N1). 95% CI was calculated using the Clopper-Pearson method.
Toxicity grade for erythema (redness) was defined as: G1=25-50 mm; G2=51-100 mm; G3≥100 mm.
Toxicity grade for fever was defined as: G1=38°C-38.4°C; G2=38.5°C-38.9°C; G3=39°C-40°C; G4≥40°C.
No Grade 4 solicited ARs were reported.
Note: The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.
Source: Table 14.3.1.1.1.2.

Part 1

Solicited Local ARs

The incidence of solicited local ARs was (84.5%) participants in the Omicron BA.1 monovalent vaccine arm and 89.1% participants in the mRNA-1273 arm.

In both vaccine arms, the most commonly reported solicited local AR was injection site pain (respectively 83.7% and 88.2% participants), followed by axillary swelling or tenderness (17.2% and 16.8 % participants) and swelling (hardness) (8.2% and 8.4% participants).

In both vaccine arms, the majority of solicited local ARs were Grade 1 (73.3% and 71.7% participants, respectively), followed by Grade 2 (8.4% and 13.7% participants, respectively). Grade 3 solicited local ARs were reported by (2.7% and 3.6% participants, respectively). No Grade 4 solicited local ARs were reported.

Solicited Systemic ARs

The incidence of solicited systemic ARs was (69.8% participants) in the Omicron BA.1 monovalent vaccine arm and (74.2% participants) in the mRNA-1273 arm. In both vaccine arms, the most commonly reported solicited systemic AR was fatigue (55.0% and 60.2% participants, respectively), followed by headache (45.5% and 49.0% participants, respectively), myalgia (40.1% and 42.9% participants, respectively), and arthralgia (28.6% and 31.9% participants, respectively).

In both vaccine arms, the majority of solicited systemic ARs were Grade 1 (34.9% and 33.1% participants, respectively) and Grade 2 (31.3% and 34.5% participants, respectively). Grade 3 solicited systemic ARs were reported by (3.5% and 6.7% participants, respectively). No Grade 4 solicited systemic ARs were reported.

Part 2

Solicited Local ARs

The incidence of solicited local ARs was 83.6%] participants in the bivalent vaccine (original and Omicron BA.1) arm and 89.9% participants in the mRNA-1273 arm**.**

In both vaccine arms, the most commonly reported solicited local AR was injection site pain (82.1% and 89.3% participants, respectively), followed by axillary swelling or tenderness (17.5% and 18.1% participants, respectively), and swelling (hardness) (7.7% and 12.1% participants, respectively).

In both vaccine arms, the majority of solicited local ARs were Grade 1 (72.8% and 70.2% participants, respectively), followed by Grade 2 (7.7% and 14.8% participants, respectively). Grade 3 solicited local ARs were reported by (3.0% and 4.9% participants, respectively). No Grade 4 solicited local ARs were reported.

Solicited Systemic ARs

The incidence of solicited systemic ARs was 70.2% participants in the bivalent vaccine (original and Omicron BA.1) arm and 75.3%] participants in the mRNA-1273 arm.

In both vaccine arms, the most commonly reported solicited systemic AR was fatigue (57.0% and 61.7% participants, respectively), followed by headache (45.7% and 50.1% participants, respectively), myalgia (37.9% and 42.6% participants, respectively), and arthralgia (27.9% and 32.5% participants, respectively).

In both vaccine arms, the majority of solicited systemic ARs were Grade 1 (35.9% and 34.3% participants, respectively) and Grade 2 (28.9% and 33.3%participants, respectively). Grade 3 solicited

systemic ARs were reported by (5.3% and 7.7% of participants, respectively). No Grade 4 solicited systemic ARs were reported.

Unsolicited Adverse Events

Part 1

Unsolicited AEs Reported Up To 28 Days After Vaccination

Up to 28 days after vaccination, the incidence of all unsolicited AEs was 38.7% participants in the Omicron BA.1 monovalent vaccine arm and 34.7% in the mRNA-1273 arm. The incidence of severe unsolicited of AEs was 1.6% participants in the Omicron BA.1 monovalent vaccine arm, and 1.7% in the mRNA-1273 arm. There were no Grade 4 AEs reported.

The incidences of SAEs and AESIs were similar between the vaccine arms, and there were no deaths reported up to 28 days after vaccination. SAEs were reported 1.4% participants in the Omicron BA.1 monovalent vaccine arm and 0.3% participants in the mRNA-1273 arm. AESIs were reported for 1.9% participants in the Omicron BA.1 monovalent vaccine arm and 1.1% participants in the mRNA-1273 arm. Two SAEs were reported, which were assessed by the Investigator as related to study vaccine, 1 event of pulmonary embolism and 1 event of ventricular tachycardia, both of which were reported in the Omicron BA.1 monovalent vaccine arm.

Overall, medically attended AEs were reported in 18.2% participants, with similar incidences reported across the vaccine arms. A total of 6.4% participants had unsolicited TEAEs assessed by the Investigator as related to study vaccine and with similar incidences across the vaccine arms. Of these, only 1 participant had a treatment-related non-serious MAAE (seronegative arthritis).

Details are presented in the table below.

Table 37: **Participant Incidence of Unsolicited TEAEs up to 28 Days After Injection in Part 1 (Safety Set)**

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=1) n (%)	4th Dose (N=366) n (%)	Total (N=367) n (%)	3rd Dose (N=0) n (%)	4th Dose (N=357) n (%)	Total (N=357) n (%)	Overall (N=724) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination							
All	0	142 (38.8)	142 (38.7)	–	124 (34.7)	124 (34.7)	266 (36.7)
Serious	0	5 (1.4)	5 (1.4)	–	1 (0.3)	1 (0.3)	6 (0.8)
Fatal	0	0	0	–	0	0	0
Medically Attended	0	70 (19.1)	70 (19.1)	–	62 (17.4)	62 (17.4)	132 (18.2)
Leading to study discontinuation	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Grade 3/severe	0	6 (1.6)	6 (1.6)	–	6 (1.7)	6 (1.7)	12 (1.7)
AE of special interest	0	7 (1.9)	7 (1.9)	–	4 (1.1)	4 (1.1)	11 (1.5)
Unsolicited TEAEs related to study vaccination							
All	0	22 (6.0)	22 (6.0)	–	24 (6.7)	24 (6.7)	46 (6.4)
Serious	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Fatal	0	0	0	–	0	0	0
Medically Attended	0	5 (1.4)	5 (1.4)	–	2 (0.6)	2 (0.6)	7 (1.0)
Leading to study discontinuation	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Grade 3/severe	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)

AE of special interest	0	3 (0.8)	3 (0.8)	–	1 (0.3)	1 (0.3)	4 (0.6)

Abbreviations: (–) = not applicable; AE = adverse event; TEAE = treatment-emergent adverse event.
Notes: A treatment-emergent adverse event (TEAE) was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
Solicited adverse reactions with toxicity Grade=0 that started after Day 7 were not included in the summary.
Numbers were based on actual vaccine arm and percentages were based on the number of participants in Safety Set.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

Unsolicited AEs Reported Throughout the Study

Throughout the study (including within 28 days after vaccination), 79.1% participants reported unsolicited AEs with similar incidences between the Omicron BA.1 monovalent vaccine and mRNA-1273 arms. Grade 3/severe unsolicited AEs were reported for 5.7% in the Omicron BA.1 monovalent vaccine arm and 5.9% participants in the mRNA-1273 arm. There were no Grade 4 AEs reported.

Overall, MAAEs were reported in 68.9% and AESIs in 9.7%, most of the MAAEs and AESIs were assessed by the Investigator as not related to study vaccine. SAEs were reported for 5.4% in the Omicron BA.1 monovalent vaccine arm. Of these, 2 participants had SAEs that was assessed by the Investigator as related to study vaccine (1 event of pulmonary embolism and 1 event of ventricular tachycardia as mentioned above). SAEs were reported for 3.6% participants in the mRNA-1273 arm, none of which were assessed by the Investigator as related to study vaccine.

A total of 5 participants across the vaccine arms reported unsolicited AEs that led to discontinuation from study participation and included 1 event that was reported within 28 days after vaccination.

The events (in the remaining 4 participants) that led to discontinuation beyond 28 days after vaccination and were assessed by the Investigator as unrelated to study vaccine included: malignant glioma, prostate cancer, brain neoplasm malignant, and 1 participant with 2 events: infective exacerbation of chronic obstructive airways disease and fatal small cell lung cancer.

Unsolicited non-serious AEs were reported for 78.5% participants with similar incidences across the vaccine arms. Most of the non-serious AEs were MAAEs, 67.7% of participants overall. The incidence of MAAEs was similar or lower in the Omicron BA.1 monovalent vaccine arm (64.0%) than in the mRNA-1273 arm (71.4%). Of these, 1.1% participants in the Omicron BA.1 monovalent vaccine and 0.6% participants in the mRNA-1273 arm had MAAEs assessed by the Investigator as related to study vaccine.

Details are presented in the table below.

Table 38: Participant Incidence of Unsolicited TEAEs Throughout the Study in Part 1 (Safety Set)

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=1) n (%)	4th Dose (N=366) n (%)	Total (N=367) n (%)	3rd Dose (N=0) n (%)	4th Dose (N=357) n (%)	Total (N=357) n (%)	Overall (N=724) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination							
All	0	284 (77.6)	284 (77.4)	–	289 (81.0)	289 (81.0)	573 (79.1)
Serious	0	20 (5.5)	20 (5.4)	–	13 (3.6)	13 (3.6)	33 (4.6)
Fatal	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Medically Attended	0	242 (66.1)	242 (65.9)	–	257 (72.0)	257 (72.0)	499 (68.9)
Leading to study discontinuation	0	2 (0.5)	2 (0.5)	–	3 (0.8)	3 (0.8)	5 (0.7)
Grade 3/severe	0	21 (5.7)	21 (5.7)	–	21 (5.9)	21 (5.9)	42 (5.8)
AE of special interest	0	42 (11.5)	42 (11.4)	–	28 (7.8)	28 (7.8)	70 (9.7)
Unsolicited TEAEs related to study vaccination							
All	0	22 (6.0)	22 (6.0)	–	24 (6.7)	24 (6.7)	46 (6.4)
Serious	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Fatal	0	0	0	–	0	0	0
Medically Attended	0	5 (1.4)	5 (1.4)	–	2 (0.6)	2 (0.6)	7 (1.0)
Leading to study discontinuation	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Grade 3/severe	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
AE of special interest	0	3 (0.8)	3 (0.8)	–	1 (0.3)	1 (0.3)	4 (0.6)

Abbreviations: (–) = not applicable; AE = adverse event; TEAE = treatment-emergent adverse event.
Notes: A treatment-emergent adverse event (TEAE) was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
Solicited adverse reactions with toxicity Grade=0 that started after Day 7 were not included in the summary.

Numbers were based on actual vaccine arm and percentages were based on the number of participants in Safety Set.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

Part 2

Unsolicited AEs Reported Up To 28 Days After Vaccination

Up to 28 days after vaccination, the incidence of all unsolicited AEs was 31.1% participants in the bivalent vaccine (original and Omicron BA.1) arm and 30.6% participants in the mRNA-1273 arm. The incidence of severe unsolicited AEs was 0.6% participants in the bivalent vaccine arm 0.6% participants in the mRNA-1273 arm.

The incidences of SAEs and AESIs were similar between the vaccine arms. SAEs were reported in 0.4% participants in the bivalent vaccine arm and 0.4% participants in the mRNA-1273 arm.
AESIs were reported in 0.3% participants in the bivalent vaccine arm and 0.6% participants in the mRNA-1273 arm. There were no SAEs assessed by the Investigator as related to study vaccine in the bivalent vaccine arm. One SAE assessed by the Investigator as related to study vaccine was a case of pulmonary embolism reported in the mRNA-1273 arm. One death due to event of arrhythmia (assessed by the Investigator as unrelated to study vaccine) was reported within 28 days after vaccination in the mRNA-1273 arm.

MAAEs were reported in 12.0% participants, with similar incidences across the vaccine arms, of those a total MAAEs of 3.5% participants had AEs assessed by the Investigator as related to study vaccine, with similar incidences across the vaccine arms. Of these, 1 participant had a treatment-related non-serious MAAE (syncope) that was also reported as severe.

Unsolicited AEs Reported Throughout the Study

Throughout the study (including within 28 days after vaccination), 80.6% participants reported unsolicited AEs with similar incidences between the vaccine arms. Grade 3/severe unsolicited AEs were reported by 3.7% in the bivalent vaccine (original and Omicron BA.1) arm and 4.6% participants in the mRNA-1273 arm.

Overall, MAAEs were reported for 68.0% and AESIs were reported for 4.2% of participants; most of the MAAEs and AESIs were assessed by the Investigator as not related to study vaccine.

SAEs were reported for 4.2% in the bivalent vaccine arm with all events assessed by the Investigator as not related to study vaccine. SAEs were reported for 5.1% participants in the mRNA-1273 arm including the 1 participant with an SAE (pulmonary embolism up to 28 days after vaccination) assessed by the Investigator as related to study vaccine.

Unsolicited AEs that led to study discontinuation were reported for 3 participants in the bivalent vaccine arm and included high-grade B-cell lymphoma, completed suicide, and road traffic accident, all of which occurred more than 28 days after vaccination. Unsolicited AEs that led to discontinuation from study participation were reported for 1 participant (arrhythmia) within 28 days after vaccination and 6 participants in the mRNA-1273 arm and included GI carcinoma (2 participants), sudden unexplained death in epilepsy, motor neurone disease, and avulsion fracture, all of which were reported beyond 28 days after vaccination.

Details are presented in the table below.

Table 39: Participant Incidence of Unsolicited TEAEs Throughout the Study in Part 2 (Safety Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4) n (%)	4th Dose (N=1418) n (%)	Total (N=1422) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1396) n (%)	Total (N=1402) n (%)	Overall (N=2824) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination							
All	1 (25.0)	1136 (80.1)	1137 (80.0)	5 (83.3)	1134 (81.2)	1139 (81.2)	2276 (80.6)
Serious	0	60 (4.2)	60 (4.2)	0	72 (5.2)	72 (5.1)	132 (4.7)
Fatal	0	2 (0.1)	2 (0.1)	0	4 (0.3)	4 (0.3)	6 (0.2)
Medically Attended	1 (25.0)	955 (67.3)	956 (67.2)	4 (66.7)	960 (68.8)	964 (68.8)	1920 (68.0)
Leading to study discontinuation	0	3 (0.2)	3 (0.2)	0	6 (0.4)	6 (0.4)	9 (0.3)
Grade 3/severe	0	52 (3.7)	52 (3.7)	0	65 (4.7)	65 (4.6)	117 (4.1)
AE of special interest	0	60 (4.2)	60 (4.2)	1 (16.7)	59 (4.2)	60 (4.3)	120 (4.2)
Unsolicited TEAEs related to study vaccination							
All	0	43 (3.0)	43 (3.0)	1 (16.7)	55 (3.9)	56 (4.0)	99 (3.5)
Serious	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Fatal	0	0	0	0	0	0	0
Medically Attended	0	3 (0.2)	3 (0.2)	0	7 (0.5)	7 (0.5)	10 (0.4)
Leading to study discontinuation	0	0	0	0	0	0	0
Grade 3/severe	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
AE of special interest	0	1 (0.1)	1 (0.1)	0	3 (0.2)	3 (0.2)	4 (0.1)

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.
Notes: A treatment-emergent adverse event (TEAE) was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
Solicited adverse reactions with toxicity Grade=0 that started after Day 7 were not included in the summary.
Numbers were based on actual vaccine arm and percentages were based on the number of participants in Safety Set.
The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

Commonly Reported Unsolicited Adverse Events

Part 1

Commonly Reported Unsolicited AEs Up To 28 Days After Vaccination

Overall, 266/724 (36.7%) participants reported a total of 410 unsolicited AEs up to 28 days after vaccination, with similar incidences across the vaccine arms (38.7% participants in the

Omicron BA.1 monovalent vaccine arm and 34.7% participants in the mRNA-1273 arm). The most commonly reported AE of COVID-19 followed by upper respiratory tract infection and headache were reported with no imbalances in the incidences of events between the vaccine arms.

Commonly Reported Unsolicited AEs Throughout the Study

Overall, 573/724 (79.1%) participants reported a total of 1412 unsolicited AEs throughout the study (including events within 28 days after vaccination), with similar incidences across the vaccine arms (77.4% participants in the Omicron BA.1 monovalent vaccine arm and 81.0% participants in the mRNA-1273 arm). The most commonly reported AE of COVID-19 followed by SARS-CoV-2 test negative and upper respiratory tract infection were reported with similar incidences of events between the vaccine arms.

Part 2

Commonly Reported Unsolicited AEs Up To 28 Days After Vaccination

Overall, 871/2824 (30.8%) participants reported a total of 1291 unsolicited AEs up to 28 days after vaccination, with similar incidences in the bivalent vaccine arm (31.1%) and mRNA-1273 arm (30.6%). The most commonly reported AE of COVID-19 followed by headache, nasopharyngitis, and oropharyngeal pain were reported with similar incidences of events between the vaccine arms. The most commonly reported unsolicited AE by PT was COVID-19 (3.9% participants overall), followed by headache (2.4%), and nasopharyngitis and oropharyngeal pain (1.6% and 1.6% participants overall), with similar incidences of events across vaccine arms.

Commonly Reported Unsolicited AEs Throughout the Study

Overall, 2276/2824 (80.6%) participants reported a total of 5736 unsolicited AEs throughout the study (including events within 28 days after vaccination), with similar incidences in the bivalent vaccine arm (80.0%) and mRNA-1273 arm (81.2%). The most commonly reported AE of COVID-19, followed by SARS-CoV-2 test negative and asymptomatic COVID-19 were reported with generally similar incidences of events between the vaccine arms.

Unsolicited Adverse Events Reported as Severe

Part 1

Severe Unsolicited AEs Reported Up to 28 Days After Vaccination

A total of 14 unsolicited severe AEs were reported for 12 participants up to 28 days after vaccination with 1.6% participants in the Omicron BA.1 monovalent vaccine and 1.7% participants in the mRNA-1273 arms.

In the Omicron BA.1 monovalent vaccine arm, severe events that were assessed by the Investigator as related to the study vaccine included pulmonary embolism (reported verbatim: multiple bilateral pulmonary emboli), and seronegative arthritis.

- Seronegative arthritis was reported in a 60-70 year-old participant with a known medical history of seronegative inflammatory arthritis and osteoarthritis, had a non-serious medically attended AE of seronegative arthritis (reported verbatim: worsening of inflammatory arthritis left hip + shoulder) on Day 2. Concurrently, the participant experienced worsening of asthma. Treatment included paracetamol. The event resolved on Day 122.

Severe Unsolicited AEs Reported Throughout the Study

A total of 56 unsolicited severe AEs were reported for 42 participants throughout the study with incidences of 5.7% and 5.9% participants in the Omicron BA.1 monovalent vaccine and mRNA-1273 arms, respectively.

In the Omicron BA.1 monovalent vaccine arm, 1 event of malignant glioma that started on Day 298 and remained ongoing led to discontinuation of study participation; this event was assessed by the Investigator as not related to study vaccine. Severe AEs that were reported for 0.5% participants included myocardial infarction (MI), which were assessed by the Investigator as not related to study vaccine.

In the mRNA-1273 arm, severe AEs that were reported for 2/357 (0.6%) participants included: pneumonia, blood pressure increased, and hypertension, all of which were assessed by the Investigator as not related to study vaccine.

Part 2

Unsolicited Severe AEs Reported Up to 28 Days After Vaccination

A total of 19 unsolicited severe AEs were reported for 18 participants up to 28 days after vaccination with similar incidences of (0.6% participants) in the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 arms, respectively. In the bivalent vaccine (original and Omicron BA.1) arm, all severe events reported were assessed by the Investigator as not related to study vaccine. Severe events that were reported as SAEs and assessed by the Investigator as not related to study vaccine included pneumonia, lung neoplasm malignant, open fracture, pyrexia, and abdominal pain. Severe events that were non-serious AEs included productive cough, muscle spasm, musculoskeletal chest pain, cholecystitis acute, varicose vein.

In the mRNA-1273 arm, a severe event of syncope was assessed by the Investigator as related to study vaccine, reported in a 60-70-year-old, with a positive test result for SARS-CoV-2 at Baseline, had a non-serious medically attended AE of syncope (reported verbatim: syncope [cardiovascular cause]) on Day 1; no concomitant medication was reported. The event resolved on Day 2.

Unsolicited Severe AEs Reported Throughout the Study

A total of 140 unsolicited severe AEs were reported for 117 participants throughout the study with similar incidences of 3.7% and 4.6% participants in the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 arms, respectively. Most of the severe AEs were reported for no more than 1 participant. All of the severe AEs occurring more than 28 days after study vaccine were assessed by the Investigator as not related to study vaccine.

In the bivalent vaccine (original and Omicron BA.1) arm, severe events that led to discontinuation from study participation included SAEs of high-grade B-cell lymphoma, completed suicide, and road traffic accident (with fatal outcome).

In the mRNA-1273 arm, severe AEs that led to discontinuation from study participation included GI carcinoma (1 of 2 participants with fatal outcome) and motor neurone disease (with fatal outcome).

Unsolicited AEs related to Study Vaccine

Part 1

Up to 28 days after vaccination, a total of 57 unsolicited AEs assessed by the Investigator as related to study vaccine were reported for 46 participants, with similar incidences (22/367 [6.0%] and 24/357 [6.7%] participants) in the Omicron BA.1 monovalent vaccine and mRNA-1273 arms, respectively. Most AEs assessed by the Investigator as related to study vaccine were reported for 1 participant in each vaccine arm.

In the Omicron BA.1 monovalent vaccine arm, the most frequently reported AE by PT that was assessed by the Investigator as related to study vaccine was lymphadenopathy (0.8%), followed by palpitations and nasal congestion (0.5%). One participant had pulmonary embolism on Day 14 that led to discontinuation from study participation.

The highest incidence of AEs by SOC that was assessed by the Investigator as related to Omicron BA.1 monovalent vaccine was skin and subcutaneous tissue disorders (1.4%] participants), followed by respiratory, thoracic, and mediastinal disorders (1.1%).

In the mRNA-1273 arm, the most frequently reported AE by PT that was assessed by the Investigator as related to study vaccine was diarrhea (1.1%), followed by gingivitis (0.6%). The highest incidence of AEs by SOC related to mRNA-1273 was general disorders and administration site conditions (1.7%), followed by GI disorders (1.1%).

More details are presented in the below table:

Table 40: Participant Incidence of Unsolicited TEAEs Related to Study Vaccine up to 28 Days After Vaccination in Part 1 (Safety Set)

System Organ Class Preferred Term	3rd Dose (N=1) n (%)	4th Dose (N=366) n (%)	Total (N=367) n (%)	3rd Dose (N=0) n (%)	4th Dose (N=357) n (%)	Total (N=357) n (%)	Overall (N=724) n (%)
Number of participants reporting unsolicited adverse events	0	22 (6.0)	22 (6.0)	–	24 (6.7)	24 (6.7)	46 (6.4)
Number of unsolicited adverse events	0	28	28	–	29	29	57
Infections and infestations	0	1 (0.3)	1 (0.3)	–	3 (0.8)	3 (0.8)	4 (0.6)
Gingivitis	0	0	0	–	2 (0.6)	2 (0.6)	2 (0.3)
Nasopharyngitis	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Oral herpes	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Blood and lymphatic system disorders	0	3 (0.8)	3 (0.8)	–	1 (0.3)	1 (0.3)	4 (0.6)
Lymphadenopathy	0	3 (0.8)	3 (0.8)	–	1 (0.3)	1 (0.3)	4 (0.6)
Psychiatric disorders	0	1 (0.3)	1 (0.3)	–	2 (0.6)	2 (0.6)	3 (0.4)
Depression	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Insomnia	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Nightmare	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Nervous system disorders	0	1 (0.3)	1 (0.3)	–	2 (0.6)	2 (0.6)	3 (0.4)
Dizziness	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Paraesthesia	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Restless legs syndrome	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Eye disorders	0	1 (0.3)	1 (0.3)	–	2 (0.6)	2 (0.6)	3 (0.4)
Visual impairment	0	1 (0.3)	1 (0.3)	–	1 (0.3)	1 (0.3)	2 (0.3)
Blepharospasm	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Ear and labyrinth disorders	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Ear pain	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Cardiac disorders	0	3 (0.8)	3 (0.8)	–	1 (0.3)	1 (0.3)	4 (0.6)
Palpitations	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Tachycardia	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Ventricular tachycardia	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	4 (1.1)	4 (1.1)	–	1 (0.3)	1 (0.3)	5 (0.7)
Nasal congestion	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Asthma	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Dyspnoea	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Pulmonary embolism	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Rhinorrhoea	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Gastrointestinal disorders	0	3 (0.8)	3 (0.8)	–	4 (1.1)	4 (1.1)	7 (1.0)
Diarrhoea	0	1 (0.3)	1 (0.3)	–	4 (1.1)	4 (1.1)	5 (0.7)
Lip swelling	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Oral pain	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Skin and subcutaneous tissue disorders	0	5 (1.4)	5 (1.4)	–	2 (0.6)	2 (0.6)	7 (1.0)
Alopecia	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Angioedema	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Erythema	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)

Granuloma annulare	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Hyperhidrosis	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Lichen planus	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Skin discolouration	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Musculoskeletal and connective tissue disorders	0	2 (0.5)	2 (0.5)	–	3 (0.8)	3 (0.8)	5 (0.7)
Arthralgia	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Joint range of motion decreased	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Muscle twitching	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Musculoskeletal pain	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Pain in extremity	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Seronegative arthritis	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Reproductive system and breast disorders	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Menorrhagia	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
General disorders and administration site conditions	0	1 (0.3)	1 (0.3)	–	6 (1.7)	6 (1.7)	7 (1.0)
Injection site pain	0	1 (0.3)	1 (0.3)	–	1 (0.3)	1 (0.3)	2 (0.3)
Axillary pain	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Cyst	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Injection site discomfort	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Injection site pruritus	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Non-cardiac chest pain	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)

Abbreviations: (–) = not applicable; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Notes: A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.
Table is sorted by SOC in internationally agreed order and PT in descending frequency based on "Overall" group, then alphabetically.
Numbers are based on actual vaccine arm and percentages are based on the number of participants in Safety Set.
Adverse events were coded using MedDRA 23.0.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.
Source: Table 14.3.2.3.1.1.

Part 2

Up to 28 days after vaccination, a total of 116 unsolicited AEs assessed by the Investigator as related to study vaccine were reported for 98 participants, with similar incidences (42/1422 [3.0%] and 56/1402 [4.0%] participants) in the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 arms, respectively. Most AEs assessed by the Investigator as related to study vaccine were reported for 1 participant in each vaccine arm. None of the AEs assessed by the Investigator as related to study vaccine led to discontinuation from study participation.

In the bivalent vaccine (original and Omicron BA.1) arm, the most frequently reported AE by PT that was assessed by the Investigator as related to study vaccine was lymphadenopathy (0.4%), followed by palpitations and rhinorrhoea (0.2%).

The highest incidence of AEs by SOC that was assessed by the Investigator as related to bivalent vaccine (original and Omicron BA.1) was musculoskeletal and connective tissue disorders (0.6%), followed by respiratory, thoracic and mediastinal disorders (0.5%) and blood and lymphatic system disorder (0.4%).

In the mRNA-1273 arm, the most frequently reported AE assessed by the Investigator as related to study vaccine was diarrhoea (0.4%), followed by dizziness, paresthesia and fatigue (0.2%).

The highest incidence of AEs by SOC that was assessed by the Investigator as related to mRNA-1273 was nervous system disorders (0.9%), followed by musculoskeletal and connective tissue disorders and general disorders and administration site conditions (0.6%), and GI disorders (0.5%).

More details are presented in the below table:

Table 41: Participant Incidence of Unsolicited TEAEs Related to Study Vaccine up to 28 Days After Vaccination in Part 2 (Safety Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
System Organ Class Preferred Term	3rd Dose (N=4) n (%)	4th Dose (N=1418) n (%)	Total (N=1422) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1396) n (%)	Total (N=1402) n (%)	Overall (N=2824) n (%)
Number of participants reporting unsolicited adverse events	0	42 (3.0)	42 (3.0)	1 (16.7)	55 (3.9)	56 (4.0)	98 (3.5)
Number of unsolicited adverse events	0	47	47	1	68	69	116
Infections and infestations	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Herpes simplex	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Oral herpes	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Blood and lymphatic system disorders	0	6 (0.4)	6 (0.4)	0	0	0	6 (0.2)
Lymphadenopathy	0	6 (0.4)	6 (0.4)	0	0	0	6 (0.2)
Psychiatric disorders	0	1 (0.1)	1 (0.1)	1 (16.7)	2 (0.1)	3 (0.2)	4 (0.1)
Abnormal dreams	0	0	0	1 (16.7)	0	1 (0.1)	1 (<0.1)
Depressed mood	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Insomnia	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Panic attack	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Nervous system disorders	0	4 (0.3)	4 (0.3)	0	12 (0.9)	12 (0.9)	16 (0.6)
Dizziness	0	1 (0.1)	1 (0.1)	0	3 (0.2)	3 (0.2)	4 (0.1)
Paraesthesia	0	0	0	0	3 (0.2)	3 (0.2)	3 (0.1)
Headache	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Syncope	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Balance disorder	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Dizziness exertional	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Dysgeusia	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Facial paralysis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Hemianopia	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Migraine	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Ear and labyrinth disorders	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Ear discomfort	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Vertigo positional	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Cardiac disorders	0	4 (0.3)	4 (0.3)	0	1 (0.1)	1 (0.1)	5 (0.2)
Palpitations	0	3 (0.2)	3 (0.2)	0	0	0	3 (0.1)
Bradycardia	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Tachycardia	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Vascular disorders	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Hypertension	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Respiratory, thoracic and mediastinal disorders	0	7 (0.5)	7 (0.5)	0	6 (0.4)	6 (0.4)	13 (0.5)
Rhinorrhoea	0	3 (0.2)	3 (0.2)	0	1 (0.1)	1 (0.1)	4 (0.1)
Cough	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Dyspnoea	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Oropharyngeal pain	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Asthma	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)

System Organ Class Preferred Term	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
	3rd Dose (N=4) n (%)	4th Dose (N=1418) n (%)	Total (N=1422) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1396) n (%)	Total (N=1402) n (%)	Overall (N=2824) n (%)
Catarrh	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Nasal congestion	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Pulmonary embolism	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Wheezing	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Gastrointestinal disorders	0	2 (0.1)	2 (0.1)	0	7 (0.5)	7 (0.5)	9 (0.3)
Diarrhoea	0	0	0	0	6 (0.4)	6 (0.4)	6 (0.2)
Abdominal pain	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Aphthous ulcer	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Enlarged uvula	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Skin and subcutaneous tissue disorders	0	4 (0.3)	4 (0.3)	0	6 (0.4)	6 (0.4)	10 (0.4)
Rash	0	1 (0.1)	1 (0.1)	0	2 (0.1)	2 (0.1)	3 (0.1)
Hyperhidrosis	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Angioedema	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Erythema	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Pruritus	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Rash macular	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Urticaria	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Musculoskeletal and connective tissue disorders	0	8 (0.6)	8 (0.6)	0	8 (0.6)	8 (0.6)	16 (0.6)
Myalgia	0	1 (0.1)	1 (0.1)	0	2 (0.1)	2 (0.1)	3 (0.1)
Pain in extremity	0	2 (0.1)	2 (0.1)	0	1 (0.1)	1 (0.1)	3 (0.1)
Arthralgia	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Muscular weakness	0	2 (0.1)	2 (0.1)	0	0	0	2 (0.1)
Back pain	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Costochondritis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Joint stiffness	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Limb discomfort	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Muscle spasms	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Musculoskeletal chest pain	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Musculoskeletal discomfort	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Tenosynovitis	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Reproductive system and breast disorders	0	3 (0.2)	3 (0.2)	0	4 (0.3)	4 (0.3)	7 (0.2)
Menorrhagia	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Menstruation delayed	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Menstrual disorder	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Menstruation irregular	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Postmenopausal haemorrhage	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
General disorders and administration site conditions	0	5 (0.4)	5 (0.4)	0	8 (0.6)	8 (0.6)	13 (0.5)
Fatigue	0	0	0	0	3 (0.2)	3 (0.2)	3 (0.1)
Non-cardiac chest pain	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Pain	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Chest pain	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Injection site bruising	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Injection site hypersensitivity	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Injection site lymphadenopathy	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Injection site pain	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Injection site paraesthesia	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Vaccination site bruising	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Injury, poisoning and procedural complications	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Procedural hypertension	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Scar	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC=system organ class; TEAE = treatment-emergent adverse event.

Notes: A TEAE was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
Table is sorted by SOC in internationally agreed order and PT in descending frequency based on "Overall" group, then alphabetically.
Numbers were based on actual vaccine arm and percentages were based on the number of participants in Safety Set.
Adverse events were coded using MedDRA 23.0.
The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

Source: Table 14.3.2.3.1.2.

Unsolicited AEs by Age Groups

The incidence of unsolicited AEs was similar for both study arms and consistent across both age groups.

Part 1

The incidence of unsolicited AEs up to 28 days after vaccination by age group was as follows:

- Adults ≥16 and <65 years of age: (39.8%) participants in the Omicron BA.1 monovalent vaccine arm and (34.5%) participants in the mRNA-1273 vaccine arm.
- Older Adults ≥65 years of age: (36.5%) and (35.2%) participants, respectively.

The incidence of unsolicited AEs by age group assessed as related to study vaccine by the Investigator and the incidence of SAEs was also similar between vaccine arms and no safety concerns were identified.

Part 2

Up to 28 days after study vaccination, the incidence of unsolicited AEs was similar for both study arms and consistent across age groups, as follows:

- Adults ≥16 and <65 years of age: (33.2%) and (30.3%) participants, respectively.
- Older Adults ≥65 years of age: (26.8%) and (31.3%) participants, respectively.

The incidence of unsolicited AEs by age group assessed as related to study vaccine by the Investigator and the incidence of SAEs was also similar between vaccine arms and no safety concerns were identified.

One adolescent participant was included in Part 2 of the study and no safety concerns were identified. The adolescent participant was a 17-year-old (mRNA-1273 vaccine arm) who had 2 non-serious AEs: COVID-19 (on Day 213, reported verbatim: symptomatic COVID-19 infection) and anosmia (on Day 216, reported verbatim: anosmia – due to COVID).

Both events were assessed by the Investigator as not related to study vaccine. The participant also reported solicited ARs of Grade 2 fatigue and nausea/vomiting and Grade 1 pain, chills, and headache within 7 days of study vaccination.

Deaths, Other Serious Adverse Events, and Other Significant Unsolicited Adverse Events

Overall, no safety concerns were identified based on SAEs, MAAEs, or AESIs reported throughout the study (including events within 28 days after vaccination). No deaths assessed by the Investigator as related to study vaccine were reported.

Deaths

<u>Part 1</u>

One death was reported in the mRNA-1273 vaccine arm, which was assessed by the Investigator as not related to study vaccine:

- *Small cell lung cancer (mRNA-1273)*: A 60-70-year-old participant with a relevant medical history of chronic obstructive pulmonary disease (severe emphysema) and who was an ex-tobacco user (40 pack years) died due to small cell lung cancer (reported verbatim: small cell lung cancer) on Study Day 346. No autopsy was performed.

No death was reported in the Omicron BA.1 monovalent vaccine arm.

Part 2

Six deaths were reported in Part 2 of the study, which were all assessed by the Investigator as not related to study vaccine.

In the bivalent vaccine (original and Omicron BA.1) arm, 2 deaths were reported, and both were assessed by the Investigator as not related to the study vaccine:

- *Road traffic accident (bivalent vaccine [original and Omicron BA.1])***:** A 60-70-year-old participant died due to a road traffic accident on Study Day 196. It is unknown if an autopsy was performed.
- *Completed suicide (bivalent vaccine [original and Omicron BA.1]):* A 70-80-year-old died due to suicide on Study Day 198. It is unknown if an autopsy was performed.

In the mRNA-1273 vaccine arm, 4 deaths were reported, which were assessed by the Investigator as not related to study vaccine:

- *Sudden unexplained death in epilepsy (mRNA-1273):* A 40-50 year-old with relevant medical history of epilepsy, depression, and hypothyroidism died due to sudden unexplained death in epilepsy (reported verbatim: sudden unexplained death in epilepsy) on Study Day 112. Relevant concomitant medications included fluoxetine, lamotrigine, levothyroxine, and topiramate. The participant was found unresponsive at home and was deceased upon arrival to the hospital. Autopsy findings found no anatomical or toxicological causes for death and concluded it was consistent with the sudden unexpected death in epilepsy.
- *Gastrointestinal carcinoma (mRNA-1273)***:** A 60-70 year-old with a medical history of benign prostatic hyperplasia died due to gastrointestinal carcinoma (reported verbatim: bowel cancer) on Study Day 235. Relevant concomitant medications included atorvastatin, tamsulosin, amlodipine, and omeprazole.
- *Motor neurone disease (mRNA-1273):* A 60-70-year-old with a medical history of Hodgkin's disease, pulmonary fibrosis, and type 2 diabetes mellitus died due to motor neurone disease (reported verbatim: motor neurone disease) on Study Day 300. Radiologic examinations and consultations with neurologist were conducted, the participant died due to respiratory failure secondary to motor neurone disease, on Study Day 300.
- *Arrhythmia (mRNA-1273):* A 50-60-year-old with a medical history of menopause and anxiety died due to arrhythmia (reported verbatim: sudden cardiac death due to arrhythmia) on Study Day 16. On Study Day 15, the participant appeared to start choking and coughing up foamy liquid. The participant then collapsed and was unresponsive reportedly due to cardiac arrhythmia. Bystander cardiopulmonary resuscitation was started immediately, and paramedics were called. The participant was transferred to a hospital where there was a transient return of spontaneous circulation. Despite the efforts made to resuscitate, no reversible factors were identified, and after discussion with the participant's family regarding very poor prognosis, resuscitation attempts were ceased. The participant was extubated and subsequently died on Study Day 16.

Assessor's comment:

The narratives of the deaths have been provided. The deaths have different causes related to road traffic accidents (SD 196), suicide (SD198), sudden unexplained death in epilepsy (SD 112), Gastrointestinal carcinoma (SD 235), Motor neurone disease (SD 300).

The death event of Arrhythmia (reported verbatim: sudden cardiac death due to arrhythmia) in the *mRNA-1273 vaccine arm*- received the fourth dose of mRNA-1273 50 µg, in the left arm on Study Day 1 and consented to Part 2. The previous medical history included anxiety and no concomitant treatment. On SD 15 the participant start choking and coughing up foamy liquid. Bystander cardiopulmonary resuscitation was started immediately and despite the efforts made to resuscitate, no reversible factors were identified. Participant died on SD 16, per the reporter, the cause of death was likely sudden arrhythmogenic cardiac death (exact cause was unknown). Genetic testing for sudden cardiac death mutation screen was performed on a piece of psoas muscle, which was negative. Autopsy findings were inconclusive. The Investigator assessed the event of arrhythmia to be not related to the study vaccine.

Other Serious Adverse Events

Up to 28 days after vaccination, 6 SAEs were reported, 5 of which were reported for participants in the Omicron BA.1 monovalent vaccine arm. Of these, 2 SAEs were assessed by the Investigator as related to study:

- *Ventricular tachycardia (Omicron BA.1 monovalent vaccine)*: reported in a 60-70-year-old with a relevant medical history (MI, ventricular tachycardia, cardiac pacemaker, congestive cardiac failure, cardiac stents (3 stents placed), psoriasis, and coronary bypass graft had ventricular tachycardia (reported verbatim: multiple episodes of ventricular tachycardia), which was not medically attended. Concomitant medications included simvastatin, pantoprazole, aspirin, bisoprolol, and ramipril. The participant had 2 runs of ventricular tachycardia (VT) on Study Day 18 and Study Day 22, since having the ICD implanted, these were the only episodes of VT. No treatment was given, and the event resolved on Study Day 22.
- *Pulmonary embolism (Omicron BA.1 monovalent vaccine)*: A 60-70 year-old with a medical history of asthma and hypertension had a medically attended pulmonary embolism (reported verbatim: multiple bilateral pulmonary emboli) on Study Day 14. Concurrently, the participant had palpitations (subsequently diagnosed as atrial fibrillation). Concomitant medications included fluticasone and formoterol, amlodipine, and salbutamol. On Study Day 6, the participant noted shortness of breath and chest tightness on exertion. The participant had 7 to 8 episodes of palpitations, the majority of which presented as fast irregular pulses lasting for about 1 hour.

  A CTPA showed results consistent with bilateral extensive acute pulmonary embolism. There was no evidence of acute pulmonary infarct, cardiomegaly, or right heart strain on the CT. ECG was reported as normal. On Study Day 24, the participant was given subcutaneous enoxaparin and discharged. On Study Day 204, an echocardiogram had indicated a dilated aortic root with mild regurgitation.

All other SAEs reported within 28 days after study vaccination (systemic viral infection, pelvi-ureteric obstruction, and wrist fracture) were assessed by the Investigator as not related to study vaccine. Of the SAEs beyond 28 day of vaccination, all were assessed by the Investigator as not related to study vaccine.

Table 42: Participant Incidence of Serious TEAEs by System Organ Class and Preferred Term Throughout the Study in Part 1 (Safety Set)

	Omicron BA.1 Monovalent Vaccine 50 µg			mRNA-1273 50 µg			
System Organ Class Preferred Term	3rd Dose (N=1) n (%)	4th Dose (N=366) n (%)	Total (N=367) n (%)	3rd Dose (N=0) n (%)	4th Dose (N=357) n (%)	Total (N=357) n (%)	Overall (N=724) n (%)
Number of participants reporting unsolicited serious adverse events	0	20 (5.5)	20 (5.4)	–	13 (3.6)	13 (3.6)	33 (4.6)
Number of unsolicited serious adverse events	0	27	27	–	19	19	46
Infections and infestations	0	4 (1.1)	4 (1.1)	–	4 (1.1)	4 (1.1)	8 (1.1)
Pneumonia	0	0	0	–	2 (0.6)	2 (0.6)	2 (0.3)
COVID-19	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Diverticulitis	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Herpes zoster	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Infective exacerbation of chronic obstructive airways disease	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Pilonidal cyst	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Systemic viral infection	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (0.5)	2 (0.5)	–	5 (1.4)	5 (1.4)	7 (1.0)
Brain neoplasm malignant	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Breast cancer	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Lung neoplasm malignant	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Malignant glioma	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Malignant pleural effusion	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Prostate cancer	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Small cell lung cancer	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Thyroid adenoma	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Immune system disorders	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Food allergy	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Metabolism and nutrition disorders	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Dehydration	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Nervous system disorders	0	1 (0.3)	1 (0.3)	–	2 (0.6)	2 (0.6)	3 (0.4)
Cerebrovascular accident	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)

Ischaemic stroke	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Transient ischaemic attack	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Eye disorders	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Cataract	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Retinal tear	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Cardiac disorders	0	3 (0.8)	3 (0.8)	–	2 (0.6)	2 (0.6)	5 (0.7)
Myocardial infarction	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Ventricular tachycardia	0	1 (0.3)	1 (0.3)	–	1 (0.3)	1 (0.3)	2 (0.3)
Angina pectoris	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Sinus tachycardia	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Vascular disorders	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Aortic aneurysm	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Pulmonary embolism	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Gastrointestinal disorders	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Colitis	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Pancreatitis chronic	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Hepatobiliary disorders	0	2 (0.5)	2 (0.5)	–	0	0	2 (0.3)
Liver injury	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Portal vein thrombosis	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Skin and subcutaneous tissue disorders	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Idiopathic angioedema	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Musculoskeletal and connective tissue disorders	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Rotator cuff syndrome	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Renal and urinary disorders	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Pelvi-ureteric obstruction	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Reproductive system and breast disorders	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Benign prostatic hyperplasia	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Injury, poisoning and procedural complications	0	2 (0.5)	2 (0.5)	–	2 (0.6)	2 (0.6)	4 (0.6)
Hip fracture	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Rib fracture	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Sternal fracture	0	0	0	–	1 (0.3)	1 (0.3)	1 (0.1)
Subdural haematoma	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)
Wrist fracture	0	1 (0.3)	1 (0.3)	–	0	0	1 (0.1)

Abbreviations: (–) = not applicable; COVID-19 = coronavirus disease 2019; incl = including; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC=system organ class; TEAE = treatment-emergent adverse event.

Notes: A TEAE was defined as any event, which was not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
The table is sorted by SOC in internationally agreed order and by PT in descending frequency based on "Overall" group, then alphabetically.
Numbers were based on actual vaccine arm, and percentages were based on the number of participants in the Safety Set.
Adverse events were coded using MedDRA 23.0.
The Omicron BA.1 monovalent vaccine refers to the mRNA-1273.529 study vaccine.

Part 2

Up to 28 days after vaccination, a total of 12 SAEs were reported for 12 participants, respectively similar incidences between the 2 vaccine arms with (0.4%) participants.

One SAE up to 28 days after vaccination was assessed by the Investigator as related to study vaccine:

- *Pulmonary embolism (mRNA-1273):* A 50-60-year-old with a recent (within the prior 6 months) medical history of deep vein thrombosis had serious, medically attended pulmonary

embolism (reported verbatim: multiple pulmonary emboli) on Study Day 2. No concomitant medications were reported. On Study Day 2, the participant had experienced shortness of breath since 24 hours post vaccination but did not inform the site or a physician until Study Day 15. On Study Day 18, an electrocardiogram showed T-wave inversion, and the participant was hospitalized overnight. Laboratory assessments showed (reference ranges not reported): D-dimer >3000 and Wells Score 1.5. On Study Day 22, a CTPA showed bilateral extensive pulmonary embolism. Treatment included apixaban. The event resolved on Study Day 30 and was assessed by the Investigator as related to study vaccine.

All other SAEs reported within 28 days after study vaccination were assessed by the Investigator as not related to study vaccine.

Throughout the study (including within 28 days after vaccination), a total of 163 SAEs were reported for 132 participants, respectively with (4.2%) in the bivalent vaccine and (5.1%) participants in the mRNA-1273 vaccine arm.

In the bivalent vaccine (original and Omicron BA.1) arm, SAEs reported for 3/1422 (0.2%) participants included pyelonephritis, prostate cancer, and atrial fibrillation, all of which were assessed by the Investigator as not related to study vaccine. The highest incidence of SAEs by SOC in the bivalent vaccine (original and Omicron BA.1) arm was infections and infestations (0.8%), followed by neoplasms benign, malignant and unspecified (including cysts and polyps); cardiac disorders; and injury, poisoning and procedural complications (each with 0.6% participants).

In the mRNA-1273 arm, SAEs reported for (0.3%) participants included pulmonary embolism, of which 1 was assessed by the Investigator as related to the study vaccine. Six SAEs that led to discontinuation of study participation and were assessed by the Investigator as not related to the mRNA-1273 vaccine. The highest incidence of SAEs in the mRNA-1273 arm by SOC was neoplasms benign, malignant and unspecified (including cysts and polyps) (1.1%), followed by infections and infestations (0.7%).

Table 43: Participant Incidence of Serious TEAEs by System Organ Class and preferred Term Throughout the Study in Part 2 (Safety Set)

	Bivalent Vaccine (Original and Omicron BA.1) 50 µg			mRNA-1273 50 µg			
System Organ Class Preferred Term	3rd Dose (N=4) n (%)	4th Dose (N=1418) n (%)	Total (N=1422) n (%)	3rd Dose (N=6) n (%)	4th Dose (N=1396) n (%)	Total (N=1402) n (%)	Overall (N=2824) n (%)
Number of participants reporting unsolicited adverse events	0	60 (4.2)	60 (4.2)	0	72 (5.2)	72 (5.1)	132 (4.7)
Number of unsolicited adverse events	0	76	76	0	87	87	163
Infections and infestations	0	11 (0.8)	11 (0.8)	0	10 (0.7)	10 (0.7)	21 (0.7)
Cellulitis	0	1 (0.1)	1 (0.1)	0	2 (0.1)	2 (0.1)	3 (0.1)
Pneumonia	0	2 (0.1)	2 (0.1)	0	1 (0.1)	1 (0.1)	3 (0.1)
Pyelonephritis	0	3 (0.2)	3 (0.2)	0	0	0	3 (0.1)
Anal abscess	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Sepsis	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Appendicitis	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
COVID-19	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Diverticulitis	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)

Gastroenteritis viral	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Lower respiratory tract infection	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Mastoiditis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Nail infection	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Otitis externa	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Periorbital cellulitis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Urinary tract infection	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Wound infection staphylococcal	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	9 (0.6)	9 (0.6)	0	15 (1.1)	15 (1.1)	24 (0.8)
Prostate cancer	0	3 (0.2)	3 (0.2)	0	1 (0.1)	1 (0.1)	4 (0.1)
Breast cancer	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Gastrointestinal carcinoma	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Lung neoplasm malignant	0	2 (0.1)	2 (0.1)	0	0	0	2 (0.1)
Benign lung neoplasm	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Benign ovarian tumour	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Bladder transitional cell carcinoma	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Colon cancer	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Colorectal cancer metastatic	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Glioblastoma	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
High-grade B-cell lymphoma	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Invasive ductal breast carcinoma	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Malignant melanoma	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Meningioma	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Metastases to liver	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Oesophageal carcinoma	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Plasma cell myeloma	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Squamous cell carcinoma	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Squamous cell carcinoma of skin	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Metabolism and nutrition disorders	0	1 (0.1)	1 (0.1)	0	2 (0.1)	2 (0.1)	3 (0.1)
Obesity	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Gout	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Psychiatric disorders	0	3 (0.2)	3 (0.2)	0	2 (0.1)	2 (0.1)	5 (0.2)
Alcohol withdrawal syndrome	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Anxiety	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Completed suicide	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Depression	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Mixed anxiety and depressive disorder	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Suicide attempt	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Nervous system disorders	0	4 (0.3)	4 (0.3)	0	9 (0.6)	9 (0.6)	13 (0.5)
Seizure	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Ageusia	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Anosmia	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Cauda equina syndrome	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Cerebral haemorrhage	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Cerebral infarction	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Epilepsy	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Haemorrhagic stroke	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Intracranial hypotension	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Motor neurone disease	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Myasthenia gravis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Oromandibular dystonia	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Parkinson's disease	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Syncope	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Transient ischaemic attack	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Eye disorders	0	2 (0.1)	2 (0.1)	0	2 (0.1)	2 (0.1)	4 (0.1)
Cataract	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Retinal detachment	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Retinal tear	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Uveitis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Ear and labyrinth disorders	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Deafness unilateral	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Vertigo	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Cardiac disorders	0	9 (0.6)	9 (0.6)	0	3 (0.2)	3 (0.2)	12 (0.4)
Atrial fibrillation	0	3 (0.2)	3 (0.2)	0	1 (0.1)	1 (0.1)	4 (0.1)
Acute coronary syndrome	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Aortic valve stenosis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Arrhythmia	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)

Atrial flutter	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Coronary artery stenosis	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Extrasystoles	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Myocardial infarction	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Tachycardia	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Vascular disorders	0	1 (0.1)	1 (0.1)	0	3 (0.2)	3 (0.2)	4 (0.1)
Aortic stenosis	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Deep vein thrombosis	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Poor peripheral circulation	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Thrombophlebitis superficial	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	0	4 (0.3)	4 (0.3)	0	4 (0.3)	4 (0.3)	8 (0.3)
Pulmonary embolism	0	2 (0.1)	2 (0.1)	0	4 (0.3)	4 (0.3)	6 (0.2)
Asthma	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Epistaxis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Gastrointestinal disorders	0	4 (0.3)	4 (0.3)	0	7 (0.5)	7 (0.5)	11 (0.4)
Inguinal hernia	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Abdominal pain	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Abdominal wall haematoma	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Anal fistula	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Colitis ischaemic	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Hiatus hernia	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Intestinal obstruction	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Mesenteric panniculitis	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Richter's hernia	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Umbilical hernia	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Hepatobiliary disorders	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Jaundice	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Musculoskeletal and connective tissue disorders	0	2 (0.1)	2 (0.1)	0	5 (0.4)	5 (0.4)	7 (0.2)
Osteoarthritis	0	1 (0.1)	1 (0.1)	0	2 (0.1)	2 (0.1)	3 (0.1)
Rotator cuff syndrome	0	0	0	0	2 (0.1)	2 (0.1)	2 (0.1)
Arthritis	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Musculoskeletal chest pain	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Renal and urinary disorders	0	2 (0.1)	2 (0.1)	0	2 (0.1)	2 (0.1)	4 (0.1)
Ureterolithiasis	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.1)
Acute kidney injury	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)
Urinary retention	0	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)
Tibia fracture	0	1 (0.1)	1 (0.1)	0	0	0	1 (<0.1)

Abbreviations: COVID-19 = coronavirus disease 2019; incl = including; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Notes: A TEAE was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure.
The table is sorted by SOC in internationally agreed order and by PT in descending frequency based on "Overall" group, then alphabetically.
Numbers were based on actual vaccine arm and percentages were based on the number of participants in the Safety Set.
Adverse events were coded using MedDRA 23.0.
The bivalent vaccine (original and Omicron BA.1) refers to the mRNA-1273.214 study vaccine.

AEs Leading to Discontinuations from Study Participation

Within 28 days after vaccination, 1 participant reported pulmonary embolism that led to discontinuation from study participation and was assessed by the Investigator as related to the Omicron BA.1 monovalent study vaccine.

Throughout the study, a total of (0.7%) participants reported a total of 6 unsolicited AEs that led to discontinuation from study participation, 5 of which were reported beyond 28 days after vaccination. *In the Omicron BA.1 monovalent vaccine arm*, 1 participant reported malignant glioma beyond 28 days after vaccination, which was assessed by the Investigator as not related to the study vaccine. *In the mRNA-1273 arm*, 3 participants reported AEs leading to discontinuation from study participation, all were assessed by the Investigator as not related to study vaccine.

Part 2

Throughout the study, a total of (0.3%) participants reported unsolicited AEs that led to discontinuation from study participation, including 1 event of arrhythmia reported within 28 days after vaccination and 8 events reported beyond 28 days after vaccination.

In the bivalent vaccine (original and Omicron BA.1) arm, 3 participants had AEs that led to discontinuation from study participation. Of these 3 events, all were reported as SAEs and were assessed by the Investigator as not related to study vaccine.

In the mRNA-1273 arm, 6 participants had AEs that led to discontinuation from study participation. Of these 6 events, 4 were fatal, 5 were reported as SAEs, and all 6 were assessed by the Investigator as not related to study vaccine.

MAAEs

Part 1

Up to 28 days after vaccination, a total of 156 MAAEs were reported (18.2%) participants. The incidences of MAAEs were similar between the Omicron BA.1 monovalent vaccine arm (19.1%) and mRNA-1273 arm (17.4%). The most commonly reported MAAE was COVID-19 (7.4%) participants in the Omicron BA.1 monovalent vaccine arm and (8.1%) participants in the mRNA-1273 arm, followed by asymptomatic COVID-19 (0.5%) participants in the Omicron BA.1 monovalent vaccine arm and (1.1%) participants in the mRNA-1273 arm.

In the Omicron BA.1 monovalent vaccine arm, other MAAEs reported for 2 or more participants included anxiety, headache, ageusia, and hypertension. In the mRNA-1273 arm, other MAAEs reported for 2 or more participants included tooth infection, lower respiratory tract infection, and arthralgia.

Throughout the study, a total of 955 MAAEs were reported for (68.9%) participants. There were no significant differences observed between the total incidences in the Omicron BA.1 monovalent vaccine arm (65.9%) and mRNA-1273 arm (72.0%).

In the Omicron BA.1 monovalent vaccine arm, the most commonly reported MAAE was COVID-19 (45.8%), followed by asymptomatic COVID-19 (3.0%), and anosmia and ageusia (2.2% participants for each event). In the mRNA-1273 arm, the most commonly reported MAAE was COVID-19 (51.5% participants), followed by hypertension (4.2%), and asymptomatic COVID-19 (2.8% participants).

All other MAAEs that were reported for at least 1% of participants in any vaccine arm included lower respiratory tract infection, urinary tract infection, upper respiratory tract infection, anxiety, asthma, rotator cuff syndrome, blood cholesterol increased (active comparator arm only), fall, tooth infection, migraine, and osteoarthritis.

Part 2

Up to 28 days after vaccination, a total of 418 MAAEs were reported for (12.0%) participants, respectively for 12.6% participants in the *bivalent vaccine (original and Omicron BA.1)* and for 11.5% participants in the *mRNA-1273 arm*. The most commonly reported MAAE was COVID-19 (respectively 3.9% and 3.1% participants. MAAEs of diarrhea were reported for 0.4% participants in the bivalent vaccine (original and Omicron BA.1) arm only. Most MAAEs that occurred in each vaccine arm were reported for 1 or 2 participants.

Throughout the study, a total of 3760 MAAEs were reported for 68.0% participants, respectively 67.2% participants in the bivalent vaccine (original and Omicron BA.1) arm and 68.8% in the mRNA-1273 arm.

In the bivalent vaccine (original and Omicron BA.1) arm, the most commonly reported MAAE

was COVID-19 (41.8%), followed by asymptomatic COVID-19 (3.0%), and hypertension (2.6%).

In the mRNA-1273 arm, the most commonly reported MAAE was COVID-19 (40.1%), followed by asymptomatic COVID-19 (2.8%), and hypertension (2.2%). No other MAAEs reached an incidence of 2.6% in the bivalent vaccine (original and Omicron BA.1) arm or 2.2% in the mRNA-1273 arm.

Adverse Events of Special Interest (Investigator-Assessed)

Part 1

Up to 28 days after study vaccination, the incidence of participants with Investigator-assessed AESIs was (1.9%) participants in the Omicron BA.1 monovalent vaccine arm and (1.1%) participants in the mRNA-1273 vaccine arm. Of these events, 3 in the Omicron BA.1 monovalent vaccine arm and 1 in the mRNA-1273 were assessed by the Investigator as related to study vaccine:

- *Ventricular tachycardia (Omicron BA.1 monovalent vaccine)*: A 60-70-year-old had serious ventricular tachycardia (reported verbatim: multiple episodes of ventricular tachycardia) on D18.
- *Pulmonary embolism (Omicron BA.1 monovalent vaccine):* A 60-70-year-old had serious pulmonary embolism (reported verbatim: multiple bilateral pulmonary emboli) on D14.
- *Restless legs syndrome (Omicron BA.1 monovalent vaccine):* A 60-70-year-old with a history of restless leg syndrome (1 to 2 nights per month for the past 3 years) and osteoarthritis (bilateral knees and neck) had non-serious medically attended restless leg syndrome (reported verbatim: exacerbation of restless leg syndrome) on D3. The participant had 3 consecutive nights of restless leg syndrome. No underlying cause was identified. Treatment included paracetamol, and the event resolved on D66.
- *Tachycardia (mRNA-1273):* A 70-80-year-old, with no reported history of cardiac dysrhythmia, had non-serious tachycardia (reported verbatim: palpitations/tachycardia), which was not medically attended, 6 hours after vaccination on D1 and resolved on D2. No other cardiac symptoms were exhibited.

Throughout the study, the incidence of participants with Investigator-assessed AESIs was 11.4% participants in the Omicron BA.1 monovalent vaccine arm and 7.8% participants in the mRNA-1273 vaccine arm. All of the events reported beyond 28 days were assessed by the Investigator as not related to study vaccine.

Part 2

Up to 28 days after study vaccination, the incidence of participants with Investigator-assessed AESIs was 0.3% participants in the bivalent vaccine (original and Omicron BA.1) arm and (0.6%) participants in the mRNA-1273 vaccine arm. Of these,1 AESI in the bivalent vaccine (original and Omicron BA.1) arm and 3 AESIs in the mRNA-1273 were assessed by the Investigator as related to study vaccine:

- *Facial paralysis (Bivalent vaccine [original and Omicron BA.1]):* A 30-40-year-old of unknown race with a concurrent methicillin-resistant *Staphylococcus aureus* infection, had non-serious facial paralysis (reported verbatim: facial palsy), which was not medically attended on Study Day 1, 8 hours after study vaccination and fully resolved on D3.
- *Pulmonary embolism (mRNA-1273)***:** A 50-60-year-old had serious pulmonary embolism (reported verbatim: multiple pulmonary emboli) on D2 and assessed as related to study vaccine by the investigator.

- *Tachycardia (mRNA-1273)***:** A 60-70-year-old had non-serious tachycardia, which was not medically attended on D2 and resolved without treatment within the same day.
- *Urticaria (mRNA-1273)*: A 30-40-year-old with a history of allergies to codeine and contrast media, had non-serious medically attended urticaria (reported verbatim: generalized urticaria) on D3. No rashes, red marks, or lumps were observed. Concurrently, the participant experienced diarrhoea, anorectal discomfort, and skin irritation. Treatment included loratadine. At the end of study, the event had not resolved.

Throughout the study, the incidence of participants with Investigator-assessed AESIs was similar between vaccine arms, respectively 4.2% participants in the bivalent vaccine arm and 4.3% in the mRNA-1273 vaccine arm. All of the events reported beyond 28 days were assessed by the Investigator as not related to study vaccine.

In Part 2, there was 1 event of reported clinically suspected pericarditis in the bivalent vaccine (original and Omicron BA.1) arm and 1 event of reported myocarditis in the mRNA-1273 vaccine arm. Both were assessed by the Investigator as not related to study vaccine:

- *Pericarditis (Bivalent vaccine [original and Omicron BA.1]):* in a 60-70-year-old, with a history of sleep apnea syndrome, hypertension, and cardiomegaly, had non-serious medically attended pericarditis (reported verbatim: clinically suspected pericarditis) on D286. The participant also had a non-study Moderna COVID-19 booster on D155 and had an AE of COVID-19 from D255 to D266. Concomitant medications included vitamin D NOS and vitamin C. On D286, the participant experienced chest pain and the diagnosis was likely a viral pericarditis. Treatment included paracetamol and the event was considered resolved on D324. The Investigator assessed the event as not related to study vaccine. The CEAC adjudicated the case as "not a Charter-defined event.
- *Myocarditis (mRNA-1273):* A 30-40-year-old, with history of migraine and mitral valve prolapse, had non-serious medically attended myocarditis on D39. The participant had a concurrent symptomatic COVID-19 from D21 to D49, and an unsolicited AE of tachycardia was reported. Treatment included fludrocortisone and midodrine. The participant received a non-study COVID-19 booster on D181, and experienced another AE of COVID-19 from D302 to D315, during which the participant had symptoms of malaise, cough, and sore throat. In addition, the participant again had chest discomfort and mild shortness of breath. A cardiac MRI on Study Day 317 showed scarring in keeping with myocarditis, likely in the last 3 years, and myocarditis was diagnosed. Forty-eight-hour Holter monitoring on an unknown date showed a sinus rhythm with a high heart rate profile in the absence of exercise, including one episode of nonsustained ventricular tachycardia that explained the chest pains and intermittent palpitations following the first episode of COVID-19 infection.

  A typical pattern for post-viral myocarditis was noted. The cardiologist felt myocarditis was related to the participant's episode of COVID-19 on Study Day 21 as this was when the cardiac symptoms had started; the Investigator updated the event of tachycardia on D39 to myocarditis. Treatment with ivabradine led to significant improvement in symptoms. At the time of study end, the event of myocarditis was resolving. The Investigator assessed myocarditis as not related to study vaccine. The CEAC adjudicated the case as "not a Charter-defined event."

Programmed SMQ Events of Interest

Anaphylactic Reaction: No events of anaphylaxis or anaphylactic reaction were reported throughout the study.

Hypersensitivity

Part 1

Narrow Scope: Up to 28 days after study vaccination, reported by 1.9% participants the incidence in the Omicron BA.1 monovalent vaccine arm and 0.6% participants in the mRNA-1273 vaccine arm.

2 events were assessed by the Investigator as related to study vaccine:

- *Lip swelling (Omicron BA.1 monovalent vaccine):*50-60-year-old with an ongoing history of granuloma annulare, had non-serious lip swelling (reported verbatim: swollen lips [intermittent]), which was not medically attended, from study Day 4 – Day 88. Concurrently the participant experienced insomnia and osteoarthritis. Treatment included acyclovir.
- *Angioedema (mRNA-1273):* 40-50-year-old with a history of asthma and eczema had non-serious angioedema (reported verbatim: delayed angioedema tongue), which was not medically attended, on Study Day 2- Day 3. Treatment included cetirizine.

Narrow/Broad Scope

Hypersensitivity SMQ was reported for 3.5% participants in the Omicron BA.1 monovalent vaccine arm and 2.2% participants in the mRNA-1273 vaccine arm.

2 events (asthma on Study Day 2 and erythema on Study Day 1) in the Omicron BA.1 monovalent vaccine arm were assessed by the Investigator as related to study vaccine.

Part 2

Narrow Scope

Hypersensitivity SMQ was reported for 1.0% and 1.4% participants, respectively. Of these, 4 events in the bivalent vaccine arm and 3 events in the mRNA-1273 arm were assessed by the Investigator as related to study vaccine.

In the Bivalent vaccine [original and Omicron BA.1] arm*:*

- *Angioedema (reported verbatim: angioedema on left lip [swollen left lip])* in a 70-80 yo on D4 and resolved on D8. Treatment included prednisolone.
- *Rash macular (reported verbatim: macular rash on back, chest, and abdomen [non-urticarial])* in a 30-40 yo on D3 and resolved on D4. The event was not medically attended.
- *Injection site hypersensitivity* in a 50-60 yo on D13 and resolved on D16. The event was not medically attended, and concurrently, the participant experienced migraine.
- *Rash (reported verbatim: non-urticarial bilateral self-limiting pedal rash),* in a 70-80 yo female on D5 and resolved on D7. Participant had a history of ocular shingles had rash.

In the mRNA-1273 arm:

- *Rash (reported verbatim: both arms rash after exercise [non-urticarial, maculopapular]):* in a 30-40 yo on D3 and resolved within the same day. The event was not medically attended and the treatment included loratadine.
- *Urticaria (reported verbatim: generalized urticaria)***:** in a 30-40 yo on D3 and reported as not resolved to the end of study.
- *Rash (reported verbatim: rash on chest):* in a 50-60 yo on D3 and resolved on D4.

Angioedema

Part 1**:** Up to 28 days after study vaccination, angioedema SMQ was reported in 0.8% participants in the Omicron BA.1 monovalent vaccine arm and none in the mRNA-1273 vaccine arm. Of these, 2 participants with events of lip swelling and angioedema in the Omicron BA.1 monovalent vaccine arm were assessed by the Investigator as related to study vaccine.

Throughout the study, angioedema SMQ was reported for 1.1% and 0.3 % participants, respectively. No additional related events in the broad scope SMQ beyond 28 days were assessed by the Investigator as related to study vaccine.

Part 2

Up to 28 days after study vaccination, angioedema SMQ was reported for 0.2% and 0.1% participants, respectively. Of these, 2 participants with events of angioedema and wheezing in the bivalent vaccine (original and Omicron BA.1) arm and 1 event of urticaria in the mRNA-1273 vaccine arm were assessed by the Investigator as related to study vaccine.

Throughout the study, angioedema SMQ was reported with similar incidences of (0.4%) participants in both arms. None of the events beyond 28 days were assessed by the Investigator as related to study vaccine.

Narrow/Broad Scope

Up to 28 days after study vaccination, the incidence of events in the narrow and broad scope angioedema SMQ was reported for 0.5% and 0.3% participants, respectively in the bivalent vaccine and in the mRNA-1273 vaccine arm. Throughout the study, by (1.0%) and (0.6%) participants, respectively. All of the events that occurred beyond 28 days after study vaccination were assessed by the Investigator as not related to study vaccine.

Assessor's comment:

In the section 4.8 of the SmPC, urticaria is included in the SOC of Skin and subcutaneous tissue disorders with frequency uncommon, while mechanical and chronic urticaria are included with frequency not known. Rash is also a labelled event with the frequency common. The events of angioedema (swollen lip) are included under the adverse reactions of Anaphylaxis and hypersensitivity with the frequency Not Known under Immune system disorders SOC.

Cardiac Events Including Ischaemic Heart Disease, Cardiac Arrhythmia, Cardiac Failure, and Cardiomyopathy

Part 1

Narrow/Broad Scope:

All of the events in the ischaemic heart disease SMQ were in the narrow scope. Throughout the study (including within 28 days after vaccination), the incidence of events of cardiac arrhythmia SMQ was (1.9%) participants in the Omicron BA.1 monovalent vaccine arm and (4.5%) participants in the mRNA-1273 vaccine arm. The incidence of events of cardiac failure SMQ was 0 participants in the Omicron BA.1 monovalent vaccine arm and (0.3%) participants in the mRNA-1273 vaccine arm. The incidence of cardiomyopathy SMQ was (1.4%) and (3.6%) participants, respectively. All of the events that occurred beyond 28 days after study vaccination were assessed by the Investigator as not related to study vaccine.

Part 2:

Narrow/Broad Scope:

There were no participants with reported events in the narrow scope ischaemic heart disease SMQ in either vaccine arm. Of the incidences of events in the narrow and broad scope cardiac arrhythmia SMQ and cardiomyopathy SMQ, 10 participants had events that were assessed by the Investigator as related to study vaccine; Six of these events, bradycardia, chest pain, dyspnoea, and 3 events of palpitations, occurred in the bivalent vaccine (original and Omicron BA.1) arm, with event onset ranging from Study Days 1 to 3. Of these, one participant in the in the bivalent vaccine (original and Omicron BA.1) arm, had events of chest pain and dyspnea. The remaining 4 events, tachycardia, dyspnoea, and 2 events of syncope, occurred in the mRNA-1273 vaccine arm, with event onset ranging from Study Days 1 to 4.

Throughout the study, the incidence of events in the scope of ischaemic heart disease SMQ was (0.4%) participants in the bivalent vaccine (original and Omicron BA.1) arm and 3/1402 (0.2%) participants in the mRNA-1273 vaccine arm. The incidence of events of cardiac arrhythmia SMQ was (2.4%) and (2.0%) participants, respectively. The incidence of events of cardiac failure SMQ was (0.2%) and (0.1%) participants, respectively. The incidence of events of cardiomyopathy SMQ was (1.9%) and (2.1%) participants, respectively. All of the events that occurred beyond 28 days after study vaccination were assessed by the Investigator as not related to study vaccine.

Embolic and Thrombotic Events

All of the events in the embolic and thrombotic events SMQ were in the narrow scope for both parts 1 and 2. Part 1: Throughout the study, the incidence of events was (1.4%) and (0.8%) participants, respectively. Part 2: Throughout the study, the incidence of events in the narrow scope embolic and thrombotic events SMQ was reported for (0.5%) and (0.9%) participants, respectively.

Central Nervous System Vascular Disorders

Part 1

Narrow Scope: Up to 28 days after study vaccination, there were no events reported and throughout the study, the incidence of events in the was similar between the vaccine arms, with (0.5%) participants in the Omicron BA.1 monovalent vaccine arm and (0.6%) participants in the mRNA-1273 vaccine arm. All of the events were assessed by the Investigator as not related to study vaccine.

Part 2:

Narrow/Broad Scope: Throughout the study (including within 28 days after vaccination), the incidence of events in the narrow and broad scope central nervous system vascular disorders SMQ was (0.2%) participants in the bivalent vaccine (original and Omicron BA.1) arm and (0.4%) participants in the mRNA-1273 vaccine arm.

Arthritis

Part 1

Up to 28 days after study vaccination, was reported one event of seronegative arthritis on Study Day 2 in the Omicron BA.1 monovalent vaccine arm and assessed by the Investigator as related to study vaccine.

Narrow/Broad Scope: Up to 28 days after study vaccination, the incidence of events in the narrow and broad scope arthritis SMQ was (1.9%) participants in the Omicron BA.1 monovalent vaccine arm and (2.8%) participants in the mRNA-1273 vaccine arm (Table 14.3.2.15.2.1). Of these, 2 events in the

mRNA-1273 vaccine arm, joint range of motion decreased on Study Day 1 and arthralgia on Study Day 9, were assessed by the Investigator as related to study vaccine.

Part 2

Narrow/Broad Scope: Up to 28 days after study vaccination, the incidence of events in the narrow and broad scope arthritis SMQ was (1.7%) and (1.7%) participants, respectively. Of these events, 2 events in 1 participant (arthralgia and joint stiffness both on Study Day 13) in the bivalent vaccine (original and Omicron BA.1) arm and 1 event of arthralgia on D8 in the mRNA-1273 vaccine arm were assessed by the Investigator as related to study vaccine.

Hearing and Vestibular Disorders

Part 1

Narrow/Broad Scope: Up to 28 days after study vaccination, the incidence of events was (1.1%) participants in the Omicron BA.1 monovalent vaccine arm and (1.1%) participants in the mRNA-1273 vaccine arm. Of these events, one non-serious event of dizziness on Study D2 to D4 in the mRNA-1273 vaccine arm was assessed by the Investigator as related to study vaccine.

Throughout the study, the incidence of events was (1.6%) and (2.2%) participants, respectively.

All of the events more than 28 days after study vaccination were assessed by the Investigator as not related to study vaccine.

Part 2

Narrow/Broad Scope:

Up to 28 days after study vaccination, 3 events (facial paralysis on Study Day 1, dizziness on Study Day 2, and balance disorder on Study Day 2) in the bivalent vaccine (original and Omicron BA.1) arm and 4 events of dizziness (all occurring on Study Days 1 and 2) in the mRNA-1273 vaccine arm were assessed by the Investigator as related to study vaccine.

Throughout the study, the incidence of events was (2.5%) and (2.3%) participants, respectively.

Convulsions

Part 1

Narrow/Broad Scope: Throughout the study, there were no events reported in the narrow and broad scope convulsions SMQ.

Part 2

Narrow Scope: All of the events reported in the convulsions SMQ were in the narrow scope.

The incidence of events was similar between the vaccine arms, with (0.1%) participants, respectively.

Demyelinating Disease of Central Nervous System

Part 1

Throughout the study (including within 28 days after vaccination), there were no events reported in the narrow and broad scope demyelinating disease of central nervous system SMQ.

Part 2

Narrow/Broad Scope: Throughout the study (including within 28 days after vaccination), the incidence of events was similar between the vaccine arms, with (0.1%) participants, respectively. The events were assessed by the Investigator as not related to study vaccine.

Haematopoietic Cytopenias

Part 1

Narrow/Broad Scope: Throughout the study (including within 28 days after vaccination), the incidence of events in the haematopoietic cytopenias SMQ was (0.5%) participants in the Omicron BA.1 monovalent vaccine arm and (0.6%) participants in the mRNA-1273 vaccine arm.

Part 2

Narrow/Broad Scope: Throughout the study (including within 28 days after vaccination), the incidence of events in the narrow and broad scope haematopoietic cytopenias SMQ was (0.2%) and (0.6%) participants, respectively. All of the events were assessed by the Investigator as not related to study vaccine.

Peripheral Neuropathy

Part 1

Narrow/Broad Scope: Up to 28 days after study vaccination, 1 event of paraesthesia on Study Day 12 in the Omicron BA.1 monovalent vaccine arm was assessed by the Investigator as not related to study vaccine and 1 event of paraesthesia on Study Day 9 in the mRNA-1273 vaccine arm were assessed by the Investigator as related to study vaccine.

Throughout the study, the incidence of events in the narrow and broad scope peripheral neuropathy SMQ was (0.8%) participants in the Omicron BA.1 monovalent vaccine arm and (0.6%) participants in the mRNA-1273 vaccine arm.

Part 2

Narrow/Broad Scope: Throughout the study (including within 28 days after vaccination), the incidence of events was (1.1%) and (0.7%) participants in the respective vaccine arms.

Vasculitis

Part 1

Narrow Scope: Up to 28 days after study vaccination, one event of eosinophilic granulomatosis with polyangiitis in the Omicron BA.1 monovalent vaccine arm on Study Day 22, assessed as not related to study vaccine.

All of the events in the vasculitis SMQ were in the narrow scope. Throughout the study, the incidence of events was (0.5%) participants in the Omicron BA.1 monovalent vaccine arm and (0.3%) participants in the mRNA-1273 vaccine arm. These events were assessed by the Investigator as not related to study vaccine.

Part 2

All of the events in the vasculitis SMQ were in the narrow scope. Throughout the study (including within 28 days after vaccination), the incidence of events was similar between the vaccine arms, with (0.1%) participants, respectively.

CMQ Assessments for Myocarditis and Pericarditis

Part 1

In the mRNA-1273 vaccine arm, a total of 7 CMQ events were reported in 7 participants within 14 days after vaccination. Upon Sponsor medical review of these events (per the CDC case definitions for acute myocarditis or acute pericarditis), no additional events of a potential case of myocarditis or pericarditis were identified.

In the Omicron BA.1 monovalent vaccine arm, 3 CMQ events were reported in 3 participants within 14 days after vaccination. Upon Sponsor medical review of these events (per the CDC case definitions for acute myocarditis or acute pericarditis), no additional events of a potential case of myocarditis or pericarditis were identified.

Part 2

In the bivalent vaccine (original and Omicron BA.1) arm, a total of 14 CMQ events were reported in 13 participants (1 participant had 2 CMQ events) within 14 days after vaccination. Upon Sponsor medical review of these cases, there were no potential cases of myocarditis or pericarditis identified (per the CDC case definitions for acute myocarditis or acute pericarditis).

One participant had 2 events in the CMQ within 14 days of study vaccination. Both events were assessed by the Investigator as related to study vaccination:

- *Dyspnoea and Chest pain (Bivalent vaccine [original and Omicron BA.1]):* a 50-60-year-old with history of irritable bowel syndrome, had mild non-serious dyspnoea and moderate non-serious chest pain (reported verbatim: mild chest pain unknown etiology) from Study Day 3 to Day 4. The events were not medically attended and were assessed by the Investigator as related to study vaccine.

In the mRNA-1273 arm, a total of 13 CMQ events were reported in 12 participants (1 participant had 2 events) within 14 days of study vaccination. One participant had 2 events in the CMQ within 14 days of study vaccination, one of which was assessed by the Investigator as related to study vaccination:

- *Dyspnoea and musculoskeletal chest pain (mRNA-1273):* A 40-50-year-old with no medical history had mild non-serious dyspnoea (reported verbatim: shortness of breath) on Study Day 4 and severe serious musculoskeletal chest pain on Study Day 5. Concurrently the participant had cough. The cardiac work-up in the hospital was negative. The events resolved respectively on Study Day 4, and Study Day 9. The event of dyspnoea was assessed by the Investigator as related to study vaccine.

Assessor's comment:

The events of Myocarditis and Pericarditis are included in the section 4.8 of the SmPC in the Cardiac disorders SOC with the frequency very rare. In the medical review conducted by the MAH (per the CDC case definitions for acute myocarditis or acute pericarditis), no additional events of a potential events of a potential case of myocarditis or pericarditis were identified, apart the events identified during the CMQ assessment for myocarditis and pericarditis.

Evaluation of Clinical Laboratory Tests

No scheduled laboratory assessments for safety were planned. No clinically significant abnormal laboratory findings were reported in the Phase 1 and Phase 2 studies ofmRNA-1273 in adults.

Vital Signs

No clinically relevant change or trends were noted in vital sign parameters (diastolic and systolic blood pressure, pulse rate, respiratory rate) in any vaccine arm for either Part 1 or Part 2.

Pregnancies

Part 1

All pregnancy test results were negative at Screening and/or Day 1 (prior to vaccination). During the study, positive test results for pregnancy were reported in 3 participants and all occurred in the mRNA-1273 vaccine arm.

- 20-30-year-old had a positive pregnancy test On Day 212, the participant lost to follow up and the outcome of the pregnancy was unknown.
- The participant had a positive pregnancy test on Day 188. The participant noted that the spouse was also taking part in the study (Part 1, mRNA-1273 50 µg). No problems were noted during pregnancy. On Day 433, the participant had a vaginal delivery with no complications; and there were no noticeable abnormalities at birth and at 1 month post-partum.
- 30-40-year-old (pregnancy history unknown) had a positive pregnancy test received on Day 296, the participant had a positive pregnancy test. On Day 528, gestational diabetes was diagnosed. On Day 540, the participant had a full-term birth (39 weeks, 4 days) with complications (C-section delivery). There were no noticeable abnormalities at birth or at the end of pregnancy.

Part 2

All pregnancy test results were negative at Screening and/or Day 1 (prior to vaccination). During the study, positive test results for pregnancy were reported in 4 participants.

- *Bivalent vaccine (original and Omicron BA.1) arm*: 20-30-year-old had a positive pregnancy test on Day 307, the participant had a positive pregnancy test. On an unspecified date, the participant had a term birth without complications and were no reported anomalies.
- *Bivalent vaccine (original and Omicron BA.1)*: 30-40-year-old had a positive pregnancy test on Day 174. On Day 425, the participant had a term birth with complications. There were fetal/infant abnormalities/congenital anomalies at the end of pregnancy: right aortic arch with left subclavian adherent artery and tongue tie. Infant abnormalities/congenital anomalies at 1 month included right-sided aortic arch.
- *Bivalent vaccine (original and Omicron BA.1)*: 30-40-year-old had a positive pregnancy test on Day 294. On Day 483 (at 39 + 2 weeks), the participant had a full-term birth with no abnormalities.
- *mRNA-1273 vaccine arm*: 40-50-year-old had a positive pregnancy test on Day 246. On Day 481, the participant underwent elective cesarean section with no complications and no clinical concerns regarding the participant or baby were observed on discharge.

2.3.3 Discussion on clinical aspects

The MAH submitted final results of study mRNA-1273- P305 – A Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine for Spikevax, in fulfilment of Article 46 of the paediatric regulation.

Article 46 (paediatric population)

Study P305 was conducted in 2 parts. Part 1 compared vaccination with monovalent Omicron BA.1 variant vaccine against vaccination with mRNA-1273 (original), and part 2 compared vaccination with bivalent Original/Omicron BA.1 variant vaccine against vaccination with mRNA-1273 (original).

In part 1, the age range was 19 years of age – 87 years of age. Therefore, no pediatric population results were generated in part 1.

In part 2, the age range was 17 years of age – 89 years of age. As broken down in the demographics table 11 there were 17 years old participants included only in the group who received mRNA-1273 (original) as a third dose. This group consisted of six (6) participants in total. Out of these, up to four (4) participants in this group were in the range of 16 years of age – 65 years of age. Besides the low number of up to four (4) participants at 17 years of age in this study P305, no results were generated from vaccination with bivalent Original/Omicron BA.1 variant vaccine in participants younger than 18 years of age.

Results from the up to four (4) participants at 17 years of age are not provided separately in the final CSR. However, as these up to four (4) participants belong all to the group of 3rd vaccination with mRNA-1273 (original) no relevant new information can be expected from any sub-group analysis, which is in turn not requested from the MAH.

Study P305

Endpoints used in this study (immunogenicity, safety, and efficacy) are standard and relevant to the objectives. The objectives and endpoints are well reflected in the study design.

The study aimed to enroll healthy participants at the age of 16 years and older. Immunocompromised participants were excluded which is acceptable for the purpose of the study to investigate the effect of variant adapted vaccines against the original vaccine mRNA-1273.

The study consisted of 2 parts each with 2 phases. Both Part 1 and Part 2 had a randomized blinded phase (Phase A) and an exploratory open-label observational phase (Phase B). In Part 1, participants were randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose (booster vaccination) of either 50 µg of the Omicron BA.1 monovalent vaccine or 50 µg of mRNA-1273 (active control). In Part 2, participants were randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose (booster vaccination) of either 50 µg of the bivalent vaccine (original and Omicron BA.1) or 50 µg of mRNA-1273 (active control).

The primary immunogenicity objective was considered met if non-inferiority against the Omicron BA.1 strain and the ancestral strain were both demonstrated, i.e., the lower bound of the 99% CI of the GMR at Day 29 of bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 against Omicron BA.1 was >0.667 (1/1.5), and the lower bound of the 99% CI of the GMR of bivalent vaccine (original and Omicron BA.1) vs. mRNA-1273 against the ancestral strain was >0.667.

Once the non-inferiority of bivalent vaccine (original and Omicron BA.1) as compared to mRNA-1273 against the Omicron BA.1 strain and against the ancestral strain was demonstrated, the 99% CI of GMR (bivalent vaccine [original and Omicron BA.1] vs. mRNA-1273) was used to assess superiority of bivalent vaccine (original and Omicron BA.1) as compared to mRNA-1273. If the lower bound of the GMR ruled out >1 at Day 29, superiority of bivalent vaccine (original and Omicron BA.1) compared to mRNA-1273 against Omicron BA.1 strain was considered demonstrated.

The hypotheses reflect the endpoints and the sequential hypothesis testing strategy is deemed reasonable and adequate.

The analyses of immunogenicity were based on the PPSI-Neg analysis population which is reasonable to exclude effects from prior SARS-CoV-2 infections for which the infecting strain and timepoint is unknown.

Participant demographics are overall well balanced in part 1 and part 2 with regards to age, sex and ethnicity. Also rates of prior SARS-CoV-2 infections and duration since last booster vaccination are well balanced.

Immune response against SARS-CoV-2 Omicron BA.1 strain

Baseline GMCs are similar in part 1 and part 2.

In part 1 at Day 29, the observed GMC was 537.7 (95% CI: 478.2, 604.6) for the Omicron BA.1 monovalent vaccine arm and 302.8 (95% CI: 274.8, 333.6) for the mRNA-1273 vaccine arm, which represent 7.7-fold and 4.5-fold increases, respectively.

In part 2 at Day 29, the observed GMC was 465.7 (95% CI: 437.0, 496.3) and 311.0 (95% CI: 292.9, 330.1) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 9.2-fold and 5.9-fold increases, respectively.

Day 29 GMCs are in the same range for part 1 and part 2.

The Day 29 GMRs were 1.73 (99% CI: 1.49, 2.01) in part 1 and 1.54 (99% CI: 1.41, 1.67) in part 2, which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67).

In part 1 at Day 85, the observed GMC was 284.7 (95% CI: 248.0, 326.7) for the Omicron BA.1 monovalent vaccine arm and 152.6 (95% CI: 135.1, 172.3) for the mRNA-1273 vaccine arm, which represent 4.0-fold and 2.3-fold increases, respectively.

In part 2 at Day 85, the observed GMC was 258.2 (95% CI: 239.3, 278.7) and 153.0 (95% CI: 142.2, 164.6) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 5.0-fold and 2.9-fold increases, respectively.

The Day 85 GMRs were 1.763 (96% CI: 1.546, 2.001) in part 1 and 1.71 (96% CI: 1.58, 1.85) in part 2, which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67).

Also, superiority of the immune responses at Day 29 and at Day 85 of Omicron BA.1 monovalent vaccine and the bivalent vaccine (original and Omicron BA.1) each compared with the mRNA-1273 vaccine against SARS-CoV-2 strain Omicron BA.1 was demonstrated based on the lower bound of the 99% CI >1.

GMC values are numerically lower as compared to titres determined against ancestral strain. Additionally, a drop in the GMC values to 46% and 55%, respectively, between Day 29 and Day 85 is observed, indicating a rapid waning of immunity.

Immune response against SARS-CoV-2 Ancestral strain

Baseline GMCs are in a similar range in part 1 and part 2.

In part 1 at Day 29, the observed GMC was 2699.7 (95% CI: 2431.3, 2997.7) for the Omicron BA.1 monovalent vaccine arm and 3020.6 (95% CI: 2776.5, 3286.2) for the mRNA-1273 vaccine arm, which represent 3.7-fold and 4.8-fold increases, respectively.

In part 2 at Day 29, the observed GMC was 2998.8 (95% CI: 2825.4, 3182.8) for the bivalent vaccine (original and Omicron BA.1) arm and 2933.6 (95% CI: 2772.3, 3104.4) after the bivalent vaccine

(original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 6.0-fold and 5.6-fold increases, respectively.

Day 29 GMCs are in the same range for part 1 and part 2.

The Day 29 GMRs were 0.82 (95% CI: 0.74. 0.91) in part 1 and 1.05 (99% CI: 0.96, 1.15) in part 2, which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67).

In part 1 at Day 85, the observed GMC was 1401.2 (95% CI: 1236.9, 1587.4) for the Omicron BA 1 monovalent vaccine arm and 1559.4 (95% CI: 1401.2, 1735.5) for the mRNA-1273 vaccine arm, which represent 1.9-fold and 2.5-fold increases respectively.

In part 2 at Day 85, the observed GMC was 1753.1 (95% CI: 1650.0, 1862.6) for the bivalent vaccine (original and Omicron BA.1) arm and 1610.2 (95% CI: 1519.6, 1706.2) after the bivalent vaccine (original and Omicron BA.1) and the mRNA-1273 vaccine, which represent 3.4-fold and 3.0-fold increases respectively.

The Day 85 GMRs were 0.80 (95% CI: 0.71, 0.90) in part 1 and 1.10 (96% CI: 1.03, 1.18) in part 2, which met the pre-specified primary immunogenicity criterion of non-inferiority (the lower bound of 99% CI ≥0.67).

Against SARS-CoV-2 ancestral strain, superiority of the immune responses at Day 29 and at Day 85 of the bivalent vaccine (original and Omicron BA.1) compared with the mRNA-1273 vaccine against SARS-CoV-2 ancestral strain was demonstrated based on the lower bound of the 99% CI >1. Expectedly, superiority could not be demonstrated for the Omicron BA.1 monovalent vaccine, both, on Day 29 and Day 85, however, this was also no objective of study P305 part 1.

Additionally, a drop in the GMC values (GMC values remain 51% and 58% at Day 85 as compared to Day 29, respectively) between Day 29 and Day 85 is observed, indicating a rapid waning of immunity.

Effectiveness

While study P305 was not powered for effectiveness analysis results from SARS-CoV-2 BA.1 containing vaccines did not demonstrate additional effectiveness against SARS-CoV-2 infection as compared to vaccination with mRNA-1273 (original). However, it is well known that during conduct of the study Omicron sub-lineages evolved that diverged from BA.1 strain.

In summary, final results from study P305 support the decision to develop variant adapted vaccines against newly evolving SARS-CoV-2 variant strains.

Safety

The safety conclusions as presented by the MAH, respectively for both parts are as following:

Part 1

Within 7 days after vaccination, the incidence of any solicited AR was similar in the Omicron BA.1 monovalent vaccine arm (91.3%) participants and mRNA-1273 arm (93.3%) participants, with most of the solicited ARs reported as Grade 1 in both study arms. Most solicited local and systemic ARs had onset on Day 1, after 15 or 30 minutes of vaccination, and on Day 2; the median duration was 3 days and was similar across the vaccine arms.

In both vaccine arms, the most commonly reported solicited local AR was injection site pain, and the most commonly reported solicited systemic AR was fatigue, followed by myalgia, headache, and arthralgia. Up to 28 days after vaccination, (36.7%) participants reported a total of 410 unsolicited AEs, with similar incidences across the vaccine arms (38.7%) participants in the Omicron BA.1

monovalent vaccine arm and (34.7%) participants in the mRNA-1273 arm. The most commonly reported unsolicited AE by PT up to 28 days after vaccination was COVID-19 (8.0%) participants overall).

Throughout the study (including within 28 days after vaccination), (79.1%) participants overall reported a total of 1412 unsolicited AEs, with similar incidences across the study vaccine arms. Commonly reported unsolicited AEs included COVID-19 (56.9%) participants overall, SARS-CoV-2 test negative (7.3%) participants overall, and upper respiratory tract infection (5.8%) overall, with no notable differences in the incidences of events between the Omicron BA.1 monovalent vaccine arm and mRNA-1273 vaccine arm.

Up to 28 days after vaccination, 14 unsolicited severe AEs were reported for 12 participants with similar incidences (1.6%) and (1.7%) participants in the Omicron BA.1 monovalent vaccine and mRNA-1273 arms, respectively.

Throughout the study (including within 28 days after vaccination), a total of 56 unsolicited severe AEs were reported for 42 participants with similar incidences (5.7%) and (5.9%) participants in the Omicron BA.1 monovalent vaccine and mRNA-1273 arms, respectively. In the Omicron BA.1 monovalent vaccine arm, a severe event of non-serious seronegative arthritis was assessed by the Investigator as related to study vaccine.

Up to 28 days after vaccination, a total of 57 unsolicited AEs assessed by the Investigator as related to study vaccine were reported for (6.4%) participants overall, with similar incidences across vaccine arms. The incidences of SAEs and AESIs were similar between the vaccine arms, and there were no deaths reported up to 28 days after vaccination.

Overall, no new safety concerns were identified based on SAEs, MAAEs, or AESIs reported throughout the study (including within 28 days after vaccination). No deaths assessed by the Investigator as related to study vaccine were reported.

Throughout the study (including within 28 days after vaccination), a total of 46 SAEs were reported for 33 participants, with similar incidences between the 2 vaccine arms (5.4%) participants in the Omicron BA.1 monovalent vaccine arm and (3.6%) participants in the mRNA-1273 vaccine arm. Except for 2 serious AEs, all other SAEs reported up to EOS were assessed by the Investigator as not related to study vaccine.

The 2 SAEs, ventricular tachycardia and pulmonary embolism, were assessed by the Investigator as related to the Omicron BA.1 monovalent vaccine, and both were reported within 28 days after vaccination. Overall, (0.7%) participants experienced a total of 6 unsolicited AEs that led to discontinuation from study participation, none of which were assessed by the Investigator as related to study vaccine. With the exception of pulmonary embolism, all other AEs were reported beyond 28 days after vaccination. All 6 events that led to discontinuation were reported as SAEs, 1 of which had a fatal outcome (small cell lung cancer).

Throughout the study (including within 28 days after vaccination), medically attended AEs were reported for (68.9%) participants with no significant differences between the total incidences in the vaccine arms.

Up to 28 days after vaccination, the incidences of unsolicited AEs by age groups were similar. For adults aged ≥16 and <65 years, the incidence was (39.8%) participants in the Omicron BA.1 monovalent vaccine arm and (34.5%) participants in the mRNA-1273 vaccine arm. For adults aged

≥65 years, the incidence was (36.5) participants in the Omicron BA.1 monovalent vaccine arm and (35.2%) participants in the mRNA-1273 vaccine arm.

Overall, the Omicron BA.1 monovalent vaccine and the mRNA-1273 booster doses were well tolerated with comparable safety and reactogenicity profiles.

Part 2

Within 7 days after vaccination, the incidence of any solicited AR was similar in the bivalent vaccine (original and Omicron BA.1) arm (90.5% participants and mRNA-1273 arm (94.3%) participants, with most of the solicited ARs reported as Grade 1 in both study arms. Most solicited local and systemic ARs had onset on Day 1, after 15 or 30 minutes of vaccination, and on Day 2; median duration was 3 days and was similar across the vaccine arms.

In both vaccine arms, the most commonly reported solicited local AR was injection site pain, and the most commonly reported solicited systemic AR was fatigue, followed by headache, myalgia, and arthralgia.

Up to 28 days after vaccination, (30.8%) participants reported a total of 1291 unsolicited AEs, with similar incidences in the bivalent vaccine (original and Omicron BA.1) arm (31.1%) and mRNA-1273 arm (30.6%).

The most commonly reported unsolicited AE by PT was COVID-19 (3.9%) participants overall.

Throughout the study (including within 28 days after vaccination), (80.6%) participants overall reported a total of 5736 unsolicited AEs, with similar incidences across study vaccine arms. Commonly reported unsolicited AE included COVID-19 (48.9%) participants overall and SARS-CoV-2 test negative (12.3%) participants overall.

Up to 28 days after vaccination, 19 unsolicited severe AEs were reported for 18 participants with similar incidences (0.6%) and (0.6%) participants in the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 arms, respectively. All severe events in the bivalent vaccine (original and Omicron BA.1) arm were assessed by the Investigator as not related to study vaccine. In the mRNA-1273 arm, severe AEs that were assessed by the Investigator as related to study vaccine included a serious event of pulmonary embolism and non-serious event of syncope.

Throughout the study (including within 28 days after vaccination), a total of 140 unsolicited severe AEs were reported for 117 participants with similar incidences (3.7%) and (4.6%) participants in the bivalent vaccine (original and Omicron BA.1) and mRNA-1273 arms, respectively. All severe AEs occurring beyond 28 days after study vaccination were assessed by the Investigator as not related to study vaccine.

Up to 28 days after vaccination, a total of 116 unsolicited AEs assessed by the Investigator as related to study vaccine were reported for (3.5%) participants overall with similar incidences across vaccine arms. None of the AEs assessed by the Investigator as related to study vaccine led to discontinuation from study participation.

The most frequently reported AE that was assessed by the Investigator as related to the bivalent vaccine (original and Omicron BA.1) was lymphadenopathy (0.4%) participants, followed by palpitations and rhinorrhea (0.2%) participants. The most frequently reported AE assessed by the Investigator as related to mRNA-1273 was diarrhoea (0.4%) participants.

The incidences of SAEs and AESIs were similar between vaccine arms. One event with fatal outcome (arrythmia) and assessed by the Investigator as not related to study vaccine was reported within 28 days after vaccination.

Overall, no new safety concerns were identified based on SAEs, MAAEs, or AESIs reported throughout the study (including within 28 days after vaccination). No deaths assessed by the Investigator as

related to study vaccine were reported. There were no SAEs assessed by the Investigator as related to the bivalent vaccine (original and Omicron BA.1).

Throughout the study (including within 28 days after vaccination), a total of 163 SAEs were reported for 132 participants, with similar incidences between the 2 vaccine arms: (4.2%] in the bivalent vaccine (original and Omicron BA.1) arm and (5.1%) participants in the mRNA-1273 vaccine arm. All but 1 serious AE reported up to end of study were assessed by the Investigator as not related to study vaccine. The SAE of pulmonary embolism was assessed by the Investigator as related to mRNA-1273 vaccine and was reported within 28 days after vaccination.

Overall, 9/2824 (0.3%) participants reported unsolicited AEs that led to discontinuation from study participation, none of which were assessed by the Investigator as related to study vaccine. With the exception of arrhythmia, all other AEs were reported beyond 28 days after vaccination. Of the 9 AEs that led to discontinuation, 8 events were reported as SAEs and 6 events had fatal outcomes. Throughout the study (including within 28 days after vaccination), medically attended AEs were reported for (68.0%) participants, with similar incidences in the bivalent vaccine (original and Omicron BA.1) arm (67.2%) participants and mRNA-1273 arm (68.8%) participants. COVID-19 was the most commonly reported MAAE in each arm: (41.8%) participants in the bivalent vaccine (original and Omicron BA.1) arm and (40.1%) participants in the mRNA-1273 arm.

Analysis of AEs of interest did not identify any safety concerns. No events of anaphylaxis were reported. Up to 28 days after vaccination, the incidences of unsolicited AEs by age groups were similar. For adults aged ≥16 and <65 years, the incidence was (33.2%) participants in the bivalent vaccine (original and Omicron BA.1) arm and (30.3%) participants in the mRNA-1273 vaccine arm. For older adults aged ≥65 years, the incidence was (26.8%) participants in the bivalent vaccine (original and Omicron BA.1) arm and (31.3%) participants in the mRNA-1273 vaccine arm.

Overall, the bivalent vaccine and the mRNA-1273 booster doses were well tolerated with comparable safety and reactogenicity profiles.

3. CHMP overall conclusion and recommendation

Final immunogenicity results from study P305 support the decision to develop variant adapted vaccines against newly evolving SARS-CoV-2 variant strains. The bivalent vaccine and the mRNA-1273 booster doses were well tolerated with comparable safety and reactogenicity profiles. There were no new safety aspects identified which might affect the overall benefit/risk assessment and no changes are proposed to be done in the Summary of Product Characteristics (SmPC). The paediatric data consist of up to 4 participants of 17 years of age all to the group of 3rd vaccination with mRNA-1273 (original). No relevant new information can be expected from any sub-group analysis

☒ Fulfilled:

No regulatory action required.