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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AI/ID	autoimmune or inflammatory disorder
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BEST	Biologics Effectiveness and Safety
BUN	blood urea nitrogen
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMQ	custom MedDRA query
CNS	central nervous system
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
DHPC	Direct Healthcare Professional Communication
DME	designated medical event
DSMB	data and safety monitoring board
EB05	lower bound of the 90% confidence interval for the empiric Bayes geometric mean
eDiary	electronic diary
EEA	European Economic Area
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HA	health authority
HCP	healthcare practitioner

Abbreviation	Definition
HIV	human immunodeficiency virus
HLT	high level term
IBD	International Birth Date
IM	intramuscular(ly)
IP	investigational product
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MSSR	Monthly Summary Safety Report
NCT	National Clinical Trial (number)
NOCMC	new-onset chronic medical condition
PDV	participant decision visit
PFRR	proportional fractional reporting ratio
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
PSSF	Product Signaling Strategy Form
PT	preferred term
RMP	risk management plan
RP	reporting period
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCS	Summary of Clinical Safety
SD	standard deviation
SMQ	standardized MedDRA query
SOC	system organ class
Study 101	Study 20-0003: Phase 1 dose-ranging study
Study 201	Study mRNA-1273-P201: Phase 2a safety and immunogenicity study
Study 301	Study mRNA-1273-P301: Phase 3 clinical efficacy and safety study
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TTO	time to onset
VAERD	vaccine-associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
WBC	white blood cell

2.7.4.1 EXPOSURE TO THE VACCINE

2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

ModernaTX, Inc. (Sponsor) is developing mRNA-1273 as a vaccine to prevent COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first identified in 2019.

The clinical safety data presented in this Summary of Clinical Safety (SCS) represent results from 3 studies conducted in the US, as follows:

- mRNA-1273-P301 (hereafter Study 301): Study 301 (NCT04470427) is a Phase 3 efficacy, safety, and immunogenicity study with a safety database of over 30,000 participants (Section 2.7.4.1.1.2.1) that provides the primary clinical evidence characterizing vaccine safety (100 µg mRNA-1273 compared with placebo) for this application. The randomization ratio was 1:1 and 15,184 participants received at least one dose of vaccine. The study design is described fully in Section 2.7.3.1.1.1 and efficacy results are described in Section 2.7.3.2.1.

- mRNA-1273-P201 (hereafter Study 201): Study 201 (NCT04405076) is a Phase 2a safety, reactogenicity, and immunogenicity study (Section 2.7.4.1.1.2.2). The dose levels assessed were 50 and 100 µg mRNA-1273 and 400 participants received at least one dose of vaccine (200 participants received placebo). The 100 µg dose level was selected for Study 301 based on safety and immunogenicity data. The design of Study 201 is described in Section 2.7.3.1.1.2 and immunogenicity results are described in Section 2.7.3.2.2.

- 20-0003 (hereafter Study 101): Study 101 (NCT04283461) is a Phase 1 dose-ranging study of safety and immunogenicity that provided support for mRNA-1273 dose selection. The dose levels assessed were 25, 50, 100, and 250 µg mRNA 1273, and 120 participants received at least one dose of mRNA-1273 (Section 2.7.4.1.1.2.3). Due to the severity of reactions at the 250 µg dose level considered in combination with immunogenicity findings at the other dose levels, the 50 and 100 µg dose levels were selected for further evaluation in a larger study population (Study 201). The study design is described in Section 2.7.3.1.1.3 and the immunogenicity results are described in Section 2.7.3.2.3.

An overview of the development program is presented in Module 2.2 of this application; greater detail is provided in Module 2.5. The Summary of Clinical Efficacy is in Module 2.7.3. A

comprehensive program of nonclinical studies has provided support for the clinical development of mRNA-1273 (Module 2.4, Nonclinical Overview). mRNA-1273 has been well-tolerated, is immunogenic, and has provided protection from viral challenge.

2.7.4.1.1.1 Methods Used to Evaluate Safety and Reactogenicity

The SCS summarizes safety data separately for each clinical study. Data pooling has not been performed due to heterogeneity in demographic characteristics, medical history, or comorbidities across the studies. The population in Study 301 includes 30,346 participants (Table 7), among whom 41.5% were considered at risk for severe COVID-19 and 37.2% are considered to be part of communities of color (Section 2.7.4.1.3.1.1). The populations evaluated in Study 201 and Study 101 were smaller, less representative of communities of color, and generally healthier with fewer comorbidities. Additionally, over 95% of participant exposure occurred in the Phase 3 study; thus, pooled summaries would differ only minimally from the Phase 3 study results. The presentation of pooled data would therefore be of only marginal value and provide no meaningful additional power to detect clinically important events (data pooling was also not performed in applications for emergency and conditional authorizations for use in persons 18 years of age and older). Presentation of data by study allows consideration of any potential findings from the smaller studies that would be obscured in pooled data. In addition to clinical study data, post-authorization data are summarized based on over 182.7 million doses administered in the post-authorization setting (in the US, the adult Emergency Use Authorization [EUA] was issued on 18 Dec 2020; Section 2.7.4.6).

Clinical safety data are presented in this application for the Phase 3, 2a, and 1 studies in descending order by number of participants. A tabular listing of all studies is provided in Table 1, the numbers of participants in each study are summarized in Table 5, methods for collection of safety data are described in Section 2.7.4.1.1.1, and brief descriptions of the study designs are provided in Section 2.7.4.1.1.2.

Data collection for protocol-specified assessments is ongoing in all studies as of the date of this submission. Details about the data locks for study data presented in the SCS, including duration of follow-up for each study relative to study milestones and reporting activities, are provided in Table 2.

Detailed descriptions of statistical methods used for the safety evaluation for each study are provided in the respective statistical analysis plans (Appendix 16.1.9 of the Study 301 Part A CSR [applies for Part B as well], Study 201 Primary Analysis CSR [applies for Day 209/Part A as well], and Study 101 Day 119 CSR [applies for Day 209 as well]).

Table 1 Clinical Studies Included in the Summary of Clinical Safety

Study Number (Country)	Study Population	Study Design	Vaccine Dose and Schedule	Safety Endpoints	Study Status[a]
Study 301 (US)	Men and nonpregnant women at least 18 years of age, at appreciable risk of SARS-CoV-2 infection, with no known history of SARS-CoV-2 infection Approximately 30,000 participants randomized in a 1:1 ratio; ≥ 25% to ≤ 50% of participants either ≥ 65 years of age or < 65 years of age and at increased risk due to medical conditions.	**Part A:** Phase 3, case-driven, randomized, stratified, observer-blind, placebo-controlled; randomization stratified by a combination of age and health risk for COVID-19: • < 65 years old, not at risk for severe COVID-19 • < 65 years old, at risk for severe COVID-19 • ≥ 65 years old **Part B:** Open-label observational phase: participants had the option to be unblinded and, if received placebo in Part A, had the option to receive mRNA-1273	100 µg mRNA-1273 or placebo (2 IM doses, 28 days apart) 100 µg mRNA-1273 (2 IM doses, 28 days apart)	Safety and reactogenicity of mRNA-1273 vaccine: • Solicited local and systemic ARs through 7 days after each injection until resolution (Part A: Blinded Phase only) • Unsolicited AEs through 28 days after each injection (Part A: Blinded Phase only) • MAAEs or AEs leading to withdrawal through the entire study period • SAEs throughout the entire study period • Pregnancies and perinatal outcomes	Ongoing[a] 95% of those eligible have entered Part B
Study 201 (US)[b]	Men and nonpregnant women, at least 18 years of age, in good health ≥ 18 to < 55 (n=300) ≥ 55 (n=300) Participants were randomized in a 1:1:1 ratio to receive placebo or 50 or 100 µg mRNA-1273.	**Part A:** Phase 2a, randomized, observer-blind, placebo-controlled Age cohorts: ≥ 18 to < 55 years; ≥ 55 years Primary analysis through Day 57; safety addendum through Day 209 **Parts B and C:** Open-label interventional phase (not presented in this SCS).	50 or 100 µg mRNA-1273 or placebo (2 IM doses, 28 days apart)	Safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine: • Solicited local and systemic ARs through 7 days after each injection until resolution • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs throughout the entire study period	Ongoing[a]

Study Number (Country)	Study Population	Study Design	Vaccine Dose and Schedule	Safety Endpoints	Study Status[a]
				• Safety laboratory test abnormalities at Day 29 and Day 57 (Cohort 2 only; ≥ 55 years of age) • Vital sign measurements and physical examination findings	
Study 101 (US)	Males and nonpregnant females, at least 18 years of age and above, in good health 18 to 55 (n=60) 56 to 70 (n=30) ≥ 71 (n=30)	Phase 1 open-label, dose-ranging study. Age cohorts: • 18 to 55 years old • 56 to 70 years old • ≥ 71 years old Analysis of immunogenicity through Day 119; safety addendum through Day 209.	25, 50, 100, or 250 µg mRNA-1273 2 IM doses, 28 days apart Note: A 10 µg cohort was planned but not enrolled.	Safety and reactogenicity of 4 dose levels of mRNA-1273 vaccine: • Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period after each injection • Frequency and grade of any unsolicited AEs during the 28-day follow-up period after each injection • Frequency of SAEs, NOCMCs, and MAAEs from Day 1 to Day 394	Ongoing[a]

Abbreviations: AE = adverse event; AR = adverse reaction; COVID-19 = coronavirus disease 2019; IM = intramuscular; MAAE = medically attended adverse event; NOCMC = new-onset chronic medical condition; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCS = Summary of Clinical Safety.

[a] The extent of data presented in this SCS from completed and ongoing study parts is described in Table 2.

[b] Study 201 included 2 open-label interventional phases. In Part B, participants who received placebo in Part A could request to receive 2 doses of active vaccine (100 µg); participants who received 1 or 2 injections of 50 or 100 µg mRNA-1273 were able to receive a single booster dose of 50 µg mRNA-1273. In Part C, participants from Study 301 who had received 2 doses of mRNA-1273 at least 6 months previously could receive 1 IM dose of mRNA-1273.351 or mRNA-1273/mRNA-1273.351 mixture. No data from these parts of the study are presented in this SCS.

Table 2 Status of Study Data Included in the Summary of Clinical Safety

Study and Period	Clinical Study Reports and Summary of Clinical Safety			
	Data Included	**Data Cutoff/Data Freeze**	**Database Lock**	**Clinical Study Report Final**
301 Part A	Safety data for participants across each age cohort through the PDV if completed, or through the data cutoff (blinded and placebo-controlled portion of the study)	26 Mar 2021 Note: Safety data presented in the EUA used a cutoff date of 25 Nov 2020, which corresponded to the analysis of efficacy performed based on 196 cases of COVID-19.	04 May 2021	05 Aug 2021 (Study 301 Part A CSR)
301 Part B	Safety data for participants in the open-label observational phase from the PDV to the data cutoff	26 Mar 2021	04 May 2021	05 Aug 2021 (Study 301 CSR Addendum 1 [Part B])
201 Day 57	Data collected through Day 57 (28 days after most recent injection)	05 Nov 2020	06 Nov 2020 (data extraction)	23 Feb 2021 (Study 201 Primary Analysis CSR)
201 Part A	Data collected through Day 209 (180 days [6 months] after most recent injection)	Date of PDV for each participant	10 Jun 2021	13 Aug 2021 (Study 201 CSR Addendum 1 [End of Part A])
101 Day 119	Data collected through Day 119 (3 months after second injection) for Cohorts 1-5, 7, and 8 and through Day 57 for Cohorts 10-12	07 Oct 2020	07 Oct 2020	31 Mar 2021 (Study 101 Day 119 CSR)
101 Day 209	Data collected through Day 209 for Cohorts 1-5, 7, 8, and 10-12	17 Mar 2021	17 Mar 2021	14 Jul 2021 (Study 101 CSR Addendum 1 [Day 209])

Abbreviations: COVID-19 = coronavirus disease 2019; CSR = clinical study report; EUA = Emergency Use Authorization; PDV = participant decision visit.

The safety and reactogenicity of mRNA-1273 are being evaluated in the same manner used for other preventive vaccines for infectious diseases. Safety assessments used in Studies 301 and 201 are as follows:

- Solicited local and systemic adverse reactions (ARs) occurring within 7 days after each vaccination and until resolution
- Unsolicited adverse events (AEs) occurring within 28 days after each vaccination
- Medically attended AEs (MAAEs) and serious AEs (SAEs) throughout study follow-up
- AEs leading to discontinuation from dosing and/or study participation
- Vital signs and physical examinations
- Pregnancies and pregnancy outcomes at any time during the study

Study 101 included assessments of new-onset chronic medical conditions (NOCMCs). Studies 201 and 101 included clinical safety laboratory tests. Study 301 included monitoring for vaccine harm including enhanced disease (Section 2.7.4.1.1.1.6).

Enrollment or randomization was stratified by age cohort in all studies. In the Phase 3 study, participants < 65 years old were further stratified by risk level for complications from COVID-19 (based on presence of chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, human immunodeficiency virus [HIV] infection; all as defined in the Study 301 protocol [Study 301 Part A CSR, Appendix 16.1.1, Section 6.2.1.1]), and site selection and enrollment were adjusted to enable enrollment of a representative sample of participants from racial and ethnic minorities. All of these measures were designed to ensure the availability of an adequate safety database for assessment in particular subgroups. Demographics and baseline characteristics, medical history, and concomitant medication use are presented for each study in Section 2.7.4.1.3.

2.7.4.1.1.1.1 Analysis Populations

A Solicited Safety Set was defined for Studies 301 and 201 as all randomized participants who received any study injection and contributed any solicited AR data (collection of AR data is described in Section 2.7.4.1.1.1.3). Separate solicited safety sets were defined for the first and second injections. The First Injection Solicited Safety Set included all participants in the Solicited Safety Set who received the first study injection and contributed any solicited AR data

from the time of first study injection through the following 6 days. The Second Injection Solicited Safety Set was defined similarly. The Solicited Safety Sets were used for analyses of solicited ARs. A Safety Set was defined for all other analyses of safety and included all participants who received any study injection. Participants were categorized for analysis purposes according to the treatment actually received (even if different from randomization, if applicable).

In Study 101, the Safety Analysis Population was used for analyses of solicited ARs and for all other analyses of safety and included all participants who received any study injection.

2.7.4.1.1.1.2 Analysis Methods

Adverse event data were coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 23.0). All safety analyses were descriptive in nature. Presentations of solicited AR data included 2-sided 95% exact confidence intervals (CI) using the Clopper-Pearson method. In Study 301, AE preferred terms (PTs) reported for at least 7 participants in any treatment group (and different from zero in the other) were reported with a rate ratio (percentages of participants treated with mRNA-1273 divided by percentage of participants treated with placebo) and 95% CIs. The CIs were for review purposes and were not a formal assessment of statistical significance.

2.7.4.1.1.1.3 Solicited Adverse Reactions

An AR was defined as any AE for which there was a reasonable possibility that the investigational product (IP) caused the AE; thus, all solicited ARs were considered to be causally related to dosing. Solicited local and systemic ARs (ie, reactogenicity) were a prespecified list of AE PTs that were assessed during the 7 days following each injection (ie, the day of injection and 6 subsequent days).

In Studies 301 and 201, solicited ARs were recorded daily using electronic diaries (eDiaries), and if solicited ARs were entered into the eDiary on Day 7 after injection, the collection of ARs in the eDiary was automatically extended by 1 day until no ARs were reported. Solicited ARs and grading used in Study 301 is presented in Table 3; terms and grading were similar in Studies 201 and 101.

In Study 101, a memory aid was used to record solicited ARs using the same terms as for Studies 301 and 201, except that axillary swelling or tenderness was not included in Study 101.

Table 3 Solicited Adverse Reactions and Grades Used in Studies 301 and 201

Reaction	Grade 1	Grade 2	Grade 3	Grade 4
Local Adverse Reactions				
Injection site pain	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Systemic Adverse Reactions				
Headache	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization

Reaction	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	38.0 – 38.4°C 100.4 – 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 – 104.0°F	> 40.0°C > 104.0°F

Source: Study 301 Part A CSR Appendix 16.1.1, Protocol Table 5.

2.7.4.1.1.1.4 Unsolicited Adverse Events

An AE was defined as any untoward medical occurrence associated with the use of a vaccine in humans, whether or not considered vaccine-related. A treatment-emergent AE (TEAE) was defined as any event not present before exposure to IP or any event already present that worsened in intensity or frequency after exposure. Unsolicited AEs were defined as any AE reported by the participant that was not specified as a solicited AR in the protocol or, if specified as a solicited AR in the protocol, started outside of the protocol-defined period for reporting solicited ARs (ie, beyond the 7 days after vaccination). Otherwise, unsolicited AEs were those observed or reported with onset during the 28 days following each injection (ie, the day of injection and 27 subsequent days).

2.7.4.1.1.1.5 Other Adverse Event Assessments

Deaths, SAEs, and MAAEs were to be collected from Day 1 through at least Day 394 (one year after the second injection) or participant withdrawal from the study. In Study 101, NOCMCs were also to be collected from Day 1 through at least Day 394. Standard regulatory definitions were used for SAEs. Definitions for MAAEs and NOCMCs were as follows:

- MAAE: An AE that led to an unscheduled visit to a healthcare practitioner (HCP); included visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up, SARS-CoV-2 infection) and visits to HCPs external to the study site (eg, urgent care, primary care physician).

- NOCMC: Any new International Statistical Classification of Diseases diagnosis (per current International Statistical Classification of Diseases and Related Health Problems) that was applied to the participant during the course of the study, after receipt of the study agent, that was expected to continue for at least 3 months and that required continued health care intervention (used in only Study 101).

Supplemental analyses of AEs of interest have been performed using standardized MedDRA queries (SMQs) or custom MedDRA queries (CMQs). These queries were developed and used to facilitate assessment of potential risks of mRNA-1273 use based in part on important observed events (in studies and in post-authorization clinical use), risks observed with other vaccines, and in response to regulatory requests. The SMQs used for Study 301 were for terms associated with anaphylactic reaction, angioedema, arthritis, cardiomyopathy, central nervous system (CNS) vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy,

thrombophlebitis, vasculitis, autoimmune disorder (CMQ), and dermal filler reaction post-vaccination (CMQ) (complete lists of queries and terms are provided in Study 301 Part A CSR, Appendix 16.1.13). The SMQs used for Study 201 were for terms associated with angioedema, arthritis, convulsions, demyelination, hypersensitivity, peripheral neuropathy, and vasculitis (complete lists of queries and terms are provided in Study 201 Primary Analysis CSR, Appendix 16.1.13). No SMQ or CMQ analyses were performed in Study 101.

2.7.4.1.1.1.6 Vaccine-Associated Enhanced Respiratory Disease

Development of the vaccine has occurred with consideration of the theoretical risk that active vaccination could cause a paradoxical increase in the risk for and/or severity of the target disease. In nonclinical studies in several species, viral load, viral replication, and histopathology of lung tissue after viral challenge was not consistent with a disease enhancement phenotype at protective or subprotective dose levels (Section 2.4.2.1 [Nonclinical Overview]). No evidence of enhanced disease after vaccination was observed in Studies 101 or 201 (which did not include formal monitoring).

Harm monitoring and monitoring for any signal of vaccine-associated enhanced respiratory disease (VAERD) in the Phase 3 study was performed by the independent data and safety monitoring board (DSMB) that was established to safeguard the interests of study participants and advise the Sponsor on study conduct. The DSMB reviewed unblinded cases of COVID-19 to assess for lack of efficacy and for numerical imbalance between the mRNA-1273 and placebo groups in cases of both COVID-19 and severe COVID-19 (symptomatic disease). Cases of COVID-19 were defined as for the primary efficacy endpoint (Study 301 Part A CSR, Appendix 16.1.1 Protocol Section 8.4.2) but were based on the Safety Set rather than the Per Protocol Set to ensure inclusion of all potential cases of COVID-19, regardless of when they occurred. If the prespecified stopping boundary were to have been reached for either COVID-19 or severe COVID-19, then the unblinded statisticians were to have informed the DSMB.

Monitoring was based on COVID-19 (all cases of any severity) and severe COVID-19 cases separately. The monitoring for each was implemented with exact 1-sided binomial tests of H_0: $p = 0.5$ versus H_1: $p > 0.5$, where p is the probability that a case participant would be in the vaccine group given the total number of cases. The bounds for harm monitoring were based on the assumption that vaccine efficacy = 0%, which corresponds to $p = 0.5$. Details about VAERD and harm monitoring are provided in the DSMB analysis plan (Study 301 Part A CSR, Appendix 16.1.13).

Formal harm monitoring by the DSMB was planned to continue up to the blinded primary analysis and was concluded after the monthly DSMB meeting in January (29 Jan 2021). No evidence of VAERD was observed in the study (Section 2.7.4.2.1.4.5). The observed high efficacy of the vaccine to prevent COVID-19 together with the fact that the few breakthrough cases in vaccinated individuals showed a reduced viral load and were on average milder supports the absence of VAERD. The DSMB recommended discontinuation of the harm monitoring reports to the DSMB.

2.7.4.1.1.1.7 Pregnancy and Lactation

In Studies 301, 201, and 101, female participants of childbearing potential were required to have a negative pregnancy test before each study vaccination, use adequate contraception for at least 28 days before the first vaccination and through 3 months after the second vaccination, and were not to be currently breastfeeding a child.

Details of all pregnancies in female participants were to be collected after the start of study treatment and until up to Day 759 (Study 301); Part A Day 394 (Study 201), and Day 394 (Study 101). Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) were considered SAEs. If the participant agreed to submit this information, the pregnancy was to be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up was to occur even if the intended duration of the safety follow-up for the study had ended.

Post-authorization experience with pregnancy and lactation is described in Section 2.7.4.6.4.5.1.

2.7.4.1.1.1.8 Other Safety Assessments

2.7.4.1.1.1.8.1 Vital Sign Measurements

Vital sign measurements were collected at prespecified time points including before and at least 30 minutes after injection of vaccine or placebo. Measurements included systolic and diastolic blood pressure, heart rate, and body temperature (preferred route was oral). Respiratory rate was included as part of the vital sign measurements in Studies 301 and 201 but not Study 101. Any vital sign measurement that met toxicity grading criteria for clinical abnormalities of grade 3 or higher was reported as an AE.

2.7.4.1.1.1.8.2 Physical Examinations

A full physical examination was performed at screening in all studies. Thereafter, unless a full examination was scheduled per the study protocol, symptom-directed physical examinations were performed at the discretion of the investigator. Any clinically significant finding identified during a study visit was reported as a MAAE (or NOCMC if applicable [Study 101 only]). In Studies 301 and 201, immediately before injection, the arm receiving the injection was examined and the associated lymph nodes evaluated; this examination was repeated 7 days after each injection in Study 201.

2.7.4.1.1.1.8.3 Safety Laboratory Assessments

Study 301 did not include scheduled safety laboratory test assessments. In Study 201, safety laboratory assessments were performed at screening for all participants; follow-up assessments were scheduled only for Cohort 2 (participants ≥ 55 years of age) on Days 29 and 57 and included complete blood count (CBC) with differential, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin, alkaline phosphatase (ALP), creatinine, blood urea nitrogen (BUN)/creatinine ratio, and prothrombin time/partial thromboplastin time. In Study 101, clinical safety laboratory evaluations included white blood cell (WBC) count, hemoglobin, platelet count, ALT, AST, ALP, total bilirubin, creatinine, lipase, and prothrombin time/partial thromboplastin time. Samples collected immediately prior to the first vaccination served as the baseline (Day 1), and post-baseline samples were collected on Days 8, 29, and 36.

2.7.4.1.1.2 Brief Descriptions of Clinical Studies

2.7.4.1.1.2.1 Study 301

This is an ongoing 2-part Phase 3 study. Part A was a randomized, parallel, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who had no known history of SARS-CoV-2 infection but whose locations or occupations (such as health care workers or emergency responders) put them at appreciable risk of acquiring COVID-19 and/or asymptomatic SARS-CoV-2 infection. Exposure risk due to location or circumstance was assessed primarily based on the SARS-COV-2 epidemiology in the participants' geographic locations and occupational risk of exposure. To obtain a more representative population with respect to racial and ethnic minorities, site selection and participant enrollment were adjusted in accordance with the Food and Drug Administration

(FDA) Draft Guidance "Enhancing the Diversity of Clinical Trial Populations - Eligibility Criteria, Enrollment Practices, and Trial Designs" (DHHS 2019).

Approximately 30,000 participants were randomly assigned to receive either mRNA-1273 or placebo using a 1:1 randomization ratio with stratification by age group and health risk (< 65 years old and not at risk for severe COVID-19, < 65 years old and at risk for severe COVID-19, ≥ 65 years old). Risk for severe COVID-19 was based on the presence of comorbid chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV infection (Study 301 Part A CSR, Section 4.2.1.3). This was a case-driven study and the planned sample size was driven by the total number of cases to demonstrate vaccine efficacy (mRNA-1273 vs. placebo) to prevent COVID-19.

The safety and reactogenicity endpoints included solicited local and systemic ARs that began within the 7 days after each dose and for as long as they persisted, unsolicited AEs through 28 days after each dose, AEs leading to withdrawal, MAAEs, and SAEs. The endpoints and data collection for efficacy, immunogenicity, and exploratory endpoints are described in Section 2.7.3.1.1.1.

Participants received an intramuscular (IM) injection (0.5 mL) of either mRNA-1273 (100 µg) or saline placebo on Day 1 and Day 29. Participants were given an eDiary to report solicited ARs for 7 days after each dose of IP until resolution and to prompt an unscheduled clinic visit for clinical evaluation and nasopharyngeal swab sample if a participant experienced any symptoms of COVID-19. Participants used the eDiary to report solicited ARs for 7 days and beyond if present on Day 7 after each dose of IP and weekly eDiary prompts (every 7 days) were sent to participants to elicit an unscheduled Illness Visit if the participant experienced COVID-19 symptoms. All participants received safety calls from study personnel on Day 8, Day 15, Day 22, Day 36, and Day 43 that served both to monitor for unsolicited AEs and to monitor for symptoms of COVID-19.

Safety telephone calls and eDiary safety prompts were performed in conjunction with surveillance for COVID-19 according to the schedules of events and were intended to capture SAEs, MAAEs, AEs leading to withdrawal, concomitant medications associated with these events, receipt of nonstudy vaccinations, and pregnancy. If an eDiary prompt resulted in identification of a relevant safety event, a follow-up safety call was triggered. At each dosing visit, participants were instructed (Day 1) or reminded (Day 29) of the procedures to document and report solicited ARs in the eDiary. Solicited ARs were assessed for 7 days after each IP dose, and unsolicited AEs were assessed for 28 days after each IP dose; SAEs, MAAEs, and AEs leading to withdrawal were assessed throughout the study.

After EUA in the US was granted for mRNA-1273 (18 Dec 2020) and another mRNA COVID-19 vaccine (11 Dec 2020; Section 2.7.3.1.1.1), the open-label observational phase of the study was initiated (Part B). All participants in Part A were to proceed to Part B, starting with a participant decision visit (PDV), at which participants were given the option to be unblinded to their original group assignment or remain blinded. Unblinded participants who had received placebo in Part A had the choice to receive active vaccination with mRNA-1273 in Part B. Planned follow-up continues until Day 759 (Month 25) for assessments of safety and durability of vaccine efficacy. Safety oversight during Part A included ongoing review by the Sponsor of blinded SAE cases reported by the investigators and weekly review of medical data listings by a Protocol Safety Review Team. This team had access to blinded data only and was to escalate any concerns to an independent DSMB, which periodically reviewed blinded and unblinded data, including both safety and cases of COVID-19 at scheduled data review meetings and at 2 planned interim analyses. The DSMB also monitored for VAERD as described in Section 2.7.4.1.1.1.6. The DSMB charter is provided in Appendix 16.1.3 of the Study 301 Part A CSR.

Monitoring by the DSMB continued for Part B of the study through the generation of tables and listings for this application. During Part B, the reporting of SAEs other than deaths was reduced from weekly to monthly and the frequency of reviews with the Sponsor team was reduced. The final meeting of the DSMB was held on 18 Jun 2021; the Sponsor and the DSMB mutually agreed that there was no reason for further DSMB oversight during the open-label phase of the study.

The focus of this SCS is the safety data for the blinded portion (Part A) of the study through the PDV as presented in the Study 301 Part A CSR for the prespecified primary efficacy analysis. In order to capture at least 6 months' median safety follow-up for all participants across age cohorts, additional safety data are presented for the unblinded open-label observational phase (Part B) of the study from the PDV through the data cutoff date (26 Mar 2021) in the Study 301 CSR Addendum 1 (Part B). This includes data for participants who received at least one dose of mRNA-1273 in Part A and data for participants who received placebo in Part A and continued into Part B of the study after the PDV (regardless of whether they have received any dose of mRNA-1273).

2.7.4.1.1.2.2 Study 201

This is an ongoing 3-part Phase 2a study. Part A was a randomized, parallel, observer-blind, and placebo-controlled dose confirmation study to evaluate the safety, reactogenicity, and

immunogenicity of mRNA-1273 in adults at least 18 years of age. Two mRNA-1273 dose levels, 50 µg and 100 µg, are being evaluated.

Approximately 600 participants were randomly assigned to receive either mRNA-1273 (50 or 100 µg per vaccination) or saline placebo control according to a 1:1:1 randomization ratio within each age cohort. The study included 2 age cohorts: Cohort 1, ≥ 18 to < 55 years of age (300 participants planned); and Cohort 2, ≥ 55 years of age (300 participants planned). The study was initiated with a parallel enrollment of all 300 participants in Cohort 1 (≥ 18 to < 55 years old) and a sentinel group of 50 participants in Cohort 2 (≥ 55 years old) receiving study treatment. Before initiating study treatment of the remaining participants in Cohort 2, safety data through Day 7 from the sentinel group of Cohort 2 and all available data from Cohort 1 were reviewed by the safety monitoring committee. No safety concerns were found, and Cohort 2 enrollment continued.

The safety and reactogenicity endpoints included solicited local and systemic ARs through 7 days after each injection and until resolution, unsolicited AEs through 28 days after each injection, MAAEs, SAEs, safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only), vital sign measurements, and physical examination findings. The endpoints and data collection for immunogenicity are described in Section 2.7.3.1.1.2.

Participants received an IM injection (0.5 mL) of either mRNA-1273 or placebo on Day 1 and Day 29. At each dosing visit, participants were instructed (Day 1) or reminded (Day 29) how to document and report solicited ARs within an eDiary application and/or device provided to them. In Part A, solicited ARs were assessed for 7 days (the day of injection and the following 6 days) after each injection. If solicited ARs were entered into the eDiary on Day 7 after injection, the collection of ARs in the eDiary was automatically extended by 1 day until no ARs were reported. Unsolicited AEs were assessed for 28 days after each injection (up to Day 57); SAEs and MAAEs were assessed throughout the study (planned up to Day 394). Safety oversight was provided by an external, independent safety monitoring committee that reviewed unblinded safety data on a regular basis. Although regular meetings have ceased, the committee remains available to meet ad hoc if requested by the Sponsor.

After EUA in the US was granted for mRNA-1273 and another mRNA COVID-19 vaccine (Section 2.7.3.1.1.1), which occurred after the primary analysis for Study 201 was completed, the open-label interventional phases of the study were initiated (Parts B and C). All participants in Part A were to proceed to Part B, starting with a PDV, at which participants previously treated with placebo had the opportunity to actively request to receive 2 doses of mRNA-1273 (100 µg) vaccine. In addition, all participants who previously received 1 or 2 injections of mRNA-1273

(50 µg or 100 µg) vaccine were able to receive a single booster dose of mRNA-1273 (50 µg). Study 201 Part C enrolled consenting participants from Study 301 who had received 2 doses of mRNA-1273 at least 6 months previously for vaccination with a single booster dose of either mRNA-1273.351 (which encodes for a variant; 20 µg or 50 µg), or mRNA-1273/mRNA-1273.351 mixture (50 µg total, including 25 µg of each sequence), with a possible additional booster dose approximately 56 days after the first boost based on initial immunogenicity data. Solicited ARs were captured as for Part A, unsolicited AEs were captured from Day 1 through 28 days after each dose up to Day 57 in Part B and up to Day 29 in Part C. Both MAAEs and SAEs were captured from Day 1 throughout entire study duration (6 months after the last vaccination for Parts B and C).

The focus of this SCS is the safety data for the blinded portion of the study (Part A) as presented in the Study 201 Primary Analysis CSR (data through Day 57 [28 days after most recent injection]). Additional safety data collected through Day 209 (6 months after most recent injection) including SAEs and MAAEs are presented as reported in the Study 201 CSR Addendum 1 (End of Part A).

2.7.4.1.1.2.3 Study 101

This is an ongoing Phase 1, open-label, dose-ranging study in healthy men and nonpregnant women at least 18 years of age to assess the safety, reactogenicity, and immunogenicity of mRNA-1273. Four mRNA-1273 dose levels were evaluated: 25, 50, 100, and 250 µg. The methodology for Study 101, which was a collaborative study performed under the auspices of the US National Institutes of Health, differed from that of Studies 301 and 201.

Up to 155 participants were planned to be enrolled in up to 13 cohorts (Table 4). Based on review of available interim data, no participants were enrolled in Cohorts 6, 9, and 13 (a total of 120 participants were enrolled in the study). Participants received an IM injection (0.5 mL) of either mRNA-1273 or placebo on Day 1 and Day 29 and were followed through 12 months after the second vaccination (Day 394). There was no control group in this study.

Table 4 Study 101 Planned Study Cohorts

Cohort	Stratum (Age in Years)	mRNA-1273 Dose (µg) on Day 1 and Day 29
1	18 to 55	25
2	18 to 55	100
3	18 to 55	250
4	56 to 70	25
5	56 to 70	100
6	56 to 70	250

Cohort	Stratum (Age in Years)	mRNA-1273 Dose (µg) on Day 1 and Day 29
7	≥ 71	25
8	≥ 71	100
9	≥ 71	250
10	18 to 55	50
11	56 to 70	50
12	≥ 71	50
13	18 to 55	10

Note: No participants were enrolled in Cohorts 6, 9, or 13.

Participants received an IM injection (0.5 mL) of mRNA-1273 on Day 1 and Day 29. All participants were monitored for safety and reactogenicity at each visit, starting with the first dose at Day 1. Additional safety and reactogenicity data were solicited via telephone calls to participants 1 and 2 days after each vaccination (Days 2, 3, 30, and 31). Reactogenicity was assessed based on occurrence of solicited local (injection site) and systemic ARs from the time of each vaccination through 7 days after each vaccination. Unsolicited AEs were collected from the time of each vaccination through 28 days after each vaccination. Serious AEs, NOCMCs, and MAAEs are being collected throughout the study. Planned follow-up continues through Day 394 (one year after the second dose) for safety and immunogenicity. The endpoints and data collection for immunogenicity are described in Section 2.7.3.1.1.3. All data collection is open-label since there was no blinding in this study. Safety oversight is provided by an independent safety monitoring committee according to procedures defined in an approved charter.

The focus of this SCS is the safety data, as presented in the Study 101 Day 119 CSR, for the period through Day 119 for the 25-, 100-, and 250-µg dose levels in age cohorts 18 to 55 years, 56 to 70 years, and ≥ 71 years (Cohorts 1 through 8) and through Day 57 for the 50-µg dose level in age cohorts 18 to 55 years, 56 to 70 years, and ≥ 71 years (Cohorts 10, 11, and 12, respectively). Additional safety data (AEs leading to withdrawal from study, SAEs, NOCMCs, and MAAEs) are presented for the period through Day 209 as reported in the Study 101 CSR Addendum (Day 209).

2.7.4.1.2 Overall Extent of Exposure and Duration of Follow-up

2.7.4.1.2.1 Extent of Exposure

2.7.4.1.2.1.1 Total Exposure

Although data have not been pooled across studies, cumulative exposure is described in this section and shown in Table 5 along with data for the separate studies. In all 3 studies, 31,066 participants received at least 1 dose of mRNA-1273 (15,704 participants) or placebo

(15,362 participants). Among all participants treated with mRNA-1273 in any of these 3 studies, 14,963 participants have received the recommended mRNA-1273 vaccine regimen of 2 doses of 100 µg mRNA-1273 administered approximately 28 days apart. In addition, 12,648 participants have received at least one dose of 100 µg mRNA-1273 in Part B of Study 301 (Study 301 CSR Addendum 1 [Part B] Section 5.1).

In Study 301, 97.0% of participants who were randomly assigned to mRNA-1273 received both doses. In Study 201, 393/400 (98.3%) participants who were randomly assigned to mRNA-1273 50 or 100 µg received both doses. In Study 101, 116/120 (96.7%) of participants treated with mRNA-1273 25, 50, 100, or 250 µg received both doses.

Exposure in the post-authorization setting is summarized in Section 2.7.4.6.

Table 5 Numbers of Participants in the 3 Clinical Studies Included in the Summary of Clinical Safety

	mRNA-1273 25 µg N=35		mRNA-1273 50 µg N=235		mRNA-1273 100 µg N=15419		mRNA-1273 250 µg N=15		Placebo N=15362		All mRNA-1273 N=15704	
Study	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
301 Part A[a]	–	–	–	–	15184	14731	–	–	15162	14631	15184	14731
201	–	–	200	195	200	198	–	–	200	194	400	393
101	35	33	35	35	35	34	15	14	–	–	120	116
Total	35	33	235	230	15419	14963	15	14	15362	14825	15704	15240

Sources: Study 301 Part A CSR Table 14.1.6.2.1 (26 Mar 2021); Study 201 Primary Analysis CSR Table 7 (05 Nov 2020); Study 101 Day 119 CSR Table 4, Table 5, and Table 6 (07 Oct 2020).

[a] The table includes only exposure in Part A of Study 301. In Part B, an additional 12,648 participants have received at least one dose of 100 µg mRNA-1273.

2.7.4.1.2.1.2 Exposure by Age Cohort

Study 301 used a threshold of 65 years to designate younger and older age groups. The threshold in Studies 201 and 101 was 55 years. Study 101 additionally defined an age group for ≥ 71 years. In Study 301, 3769 participants ≥ 65 years old received at least 1 dose and 3704 participants ≥ 65 years old received both doses (Table 6). In all age groups, most participants received both planned doses; no age-related increased likelihood of missing the second dose was apparent.

Table 6 Numbers of Participants in the 3 Clinical Studies Included in the Summary of Clinical Safety by Age Group

	mRNA-1273 25 µg N=35		mRNA-1273 50 µg N=235		mRNA-1273 100 µg N=15419		mRNA-1273 250 µg N=15		Placebo N=15362		All mRNA-1273 N=15704	
Study	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
301[a]												
18 to <65	–	–	–	–	11415	11027	–	–	11411	10964	11415	11027
≥65	–	–	–	–	3769	3704	–	–	3751	3667	3769	3704
≥65 to <75	–	–	–	–	3112	3058	–	–	3010	2946	3112	3058
≥75 to <85	–	–	–	–	616	608	–	–	692	674	616	608
≥85	–	–	–	–	41	38	–	–	49	47	41	38
201												
18 to <55	–	–	100	97	100	99	–	–	100	94	200	196
≥55	–	–	100	98	100	99	–	–	100	100	200	197
101												
18 to 55	15	13	15	15	15	15	15	14	–	–	60	57
56 to 70	10	10	10	10	10	9	–	–	–	–	30	29
≥71	10	10	10	10	10	10	–	–	–	–	30	30

Sources: Study 301 Part A CSR Table 14.1.6.2.3 and Table 14.1.6.2.4 (26 Mar 2021); Study 201 Primary Analysis CSR Table 14.1.1.1 (05 Nov 2020); Study 101 Day 119 CSR Table 4, Table 5, and Table 6 (07 Oct 2020).

[a] The table includes only exposure in Part A of Study 301. In Part B, an additional 12,648 participants have received at least one dose of 100 µg mRNA-1273.

2.7.4.1.2.2 Duration of Follow-up

2.7.4.1.2.2.1 Study 301

For Study 301, the time on study, or duration of follow-up from randomization, is defined as the time from randomization to death, discontinuation from study, or the data cutoff date for database lock (26 Mar 2021), whichever occurs earlier. The median duration of follow-up after randomization for the entire period up to the data cutoff for database lock (including Part A and Part B) was 212 days (range: 1 to 243 days) (Table 7). The median duration of follow-up from randomization to the PDV/unblinding (ie, Part A) for participants who had a PDV before the data cutoff date was 148 days (range: 30 to 241 days). For participants who received both injections, the median duration of follow-up after the second injection to the data cutoff for database lock (including Part A and Part B) was 183 days (range: 1 to 218 days), or approximately 6 months. A large number of discontinuations from the study occurred in the placebo group shortly after vaccines were authorized for emergency use (details are provided in Study 301 Part A CSR Section 5.1).

To enhance the diversity of the trial population, an effort was made to increase enrollment in communities of color during the course of the study. This effort was more successfully implemented toward the end of the enrollment period and resulted in a slightly reduced median study duration for participants identifying as members of communities of color. Across communities of color, the median study duration from second injection in participants who received the second injection was approximately 5.5 months (169 days in Black or African Americans, 165 days in Asians, 169.5 days in American Indian or Alaska Natives, 169 days in Native Hawaiian or other Pacific Islanders, and 171 days in those identified as multiple race) compared with approximately 6.2 months (185 days) for White participants (Study 301 Part A CSR Table 14.1.6.2.5). Median study duration from second injection in participants who received the second injection was generally balanced between the placebo and mRNA-1273 groups within all race groups.

In participants who reported Hispanic or Latino ethnicity, the median study duration from second injection was 170 days (Study 301 Part A CSR Table 14.1.6.2.6). In participants who did not report Hispanic or Latino ethnicity, the median study duration from second injection was 185 days. Median study duration from the second injection was balanced between the placebo and mRNA-1273 groups within these ethnicity subgroups.

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Table 7 Study 301: Summary of Study Duration in Part A (Safety Set)

	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Number of subjects, n (%)			
Received first injection	15162 (100)	15184 (100)	30346 (100)
Received second injection	14631 (96.5)	14731 (97.0)	29362 (96.8)
>= 49 days since first injection	14992 (98.9)	15039 (99.0)	30031 (99.0)
>= 56 days since first injection	14960 (98.7)	15023 (98.9)	29983 (98.8)
>= 2 months since first injection	14929 (98.5)	14995 (98.8)	29924 (98.6)
< 28 days since second injection	36 (0.2)	24 (0.2)	60 (0.2)
>= 28 and < 56 days since second injection	120 (0.8)	51 (0.3)	171 (0.6)
>= 28 days since second injection	14595 (96.3)	14707 (96.9)	29302 (96.6)
>= 56 days since second injection	14475 (95.5)	14656 (96.5)	29131 (96.0)
>= 2 months since second injection	14438 (95.2)	14645 (96.5)	29083 (95.8)
>= 3 months since second injection	13927 (91.9)	14595 (96.1)	28522 (94.0)
>= 4 months since second injection	13263 (87.5)	14485 (95.4)	27748 (91.4)
>= 5 months since second injection	11636 (76.7)	12861 (84.7)	24497 (80.7)
>= 6 months since second injection	6778 (44.7)	7499 (49.4)	14277 (47.0)
Study duration from randomization (days)			
Mean (SD)	198.4 (38.90)	206.1 (31.02)	202.2 (35.38)
Median	210.0	213.0	212.0
Q1, Q3	189.0, 224.0	197.0, 226.0	193.0, 225.0
Min, Max	1, 243	1, 243	1, 243
Study duration from first injection (days)			
Mean (SD)	198.4 (38.91)	206.0 (31.02)	202.2 (35.39)
Median	210.0	213.0	212.0
Q1, Q3	189.0, 224.0	197.0, 226.0	193.0, 225.0
Min, Max	1, 243	1, 243	1, 243
Person-years from first injection [a]	8236.9	8565.5	16802.4
Study duration from second injection (days) [b]			
Mean (SD)	165.4 (46.12)	173.7 (38.95)	169.5 (42.88)
Median	180.0	183.0	182.0
Q1, Q3	157.0, 193.0	166.0, 194.0	163.0, 194.0
Min, Max	0, 218	0, 218	0, 218

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	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Study duration from second injection in subjects who received second injection (days)			
n	14631	14731	29362
Mean (SD)	171.4 (34.28)	179.0 (24.65)	175.2 (30.09)
Median	180.0	184.0	183.0
Q1, Q3	161.0, 194.0	169.0, 196.0	165.0, 194.0
Min, Max	1, 218	1, 218	1, 218
Study duration from randomization to PDV/unblinding (days) [c]			
n	14307	14537	28844
Mean (SD)	144.8 (25.46)	147.5 (25.64)	146.1 (25.59)
Median	146.0	148.0	148.0
Q1, Q3	128.0, 161.0	132.0, 163.0	131.0, 162.0
Min, Max	30, 237	44, 241	30, 241
Study duration from PDV/unblinding to study discontinuation/data cutoff date (days) [c]			
n	14307	14537	28844
Mean (SD)	58.9 (23.53)	63.2 (18.73)	61.1 (21.35)
Median	67.0	66.0	67.0
Q1, Q3	52.0, 75.0	55.0, 75.0	54.0, 75.0
Min, Max	1, 205	1, 179	1, 205

Abbreviations: PDV = Participant Decision Visit; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

1 month = 30.4375 days.

Percentages are based on the number of safety subjects.

[a] Person-years is defined as the total years from the first dose date to the earlier date of study discontinuation or data cutoff.

[b] Study duration from second injection is 0 day for subjects who did not receive second injection.

[c] Only include subjects who had PDV/unblinding on/before data cutoff date.

Source: Study 301 Part A CSR Table 14.1.6.2.1 (26 Mar 2021).

2.7.4.1.2.2.2 Study 201

The Study 201 Primary Analysis CSR reports post-injection follow-up of at least 28 days after the most recent injection (Day 57) for the 590/600 (98.3%) participants who had not discontinued from the study before Day 57 (Study 201 Primary Analysis CSR Table 14.1.1.1).

The Study 201 Day 209 CSR Addendum reports post-injection follow-up of at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 (Study 201 Day 209 CSR Addendum 1 [End of Part A] Table 14.1.1.1).

2.7.4.1.2.2.3 Study 101

The Study 101 Day 119 CSR reports post-injection follow-up of at least 90 days (3 months) after the most recent injection for Cohorts 1 through 5, 7, and 8 and at least 30 days for Cohorts 10 through 12 for the 120/120 (100%) participants who had not discontinued from the study before Day 119 (Study 101 Day 119 CSR Section 5.1). The Study 101 Day 209 CSR Addendum reports post-injection follow-up of at least 180 days (6 months) after the most recent injection (Day 209) for the 120/120 (100%) participants who had not discontinued from the study before Day 209 (Study 101 CSR Addendum 1 [Day 209] Section 5.1).

2.7.4.1.3 Demographics and Other Characteristics of Study Population

All participants were ≥ 18 years of age at the time of study enrollment. In all studies, enrollment was managed to ensure representation of particular age cohorts, in Study 301 using age- and risk-based randomization stratification factors and in Study 201 and Study 101 using age cohort-based enrollment. The 3 clinical studies for mRNA-1273 included in this application were conducted exclusively at US study sites.

Whereas Study 101 and Study 201 enrolled adults without particular risks for exposure to SARS-CoV-2 who were generally in good health, Study 301 enrolled adults considered to be at increased risk of exposure (based primarily on geographic location and occupational risk) and specifically required enrollment of those with comorbid medical conditions that were recognized to put them at increased risk of developing severe COVID-19. In Study 301, 82.5% of participants had a specified occupational risk for acquisition of SARS-CoV-2 and 41.5% participants were considered at risk for severe COVID-19 based on either older age or the presence of a pre-existing comorbid condition. (Section 2.7.4.1.3.2.1; Table 8).

Additionally, Study 301 was designed to increase the representation of racial and ethnic minorities in order to mirror the general US population more closely. In Study 301, 10.2% of participants self-reported as Black or African American and 20.5% self-reported as Hispanic or Latino (Table 8), which approaches current percentages in the US population (US Census Bureau

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2019: Black [13.4%], Hispanic or Latino [18.5%]). By contrast, in Study 201, 2.7% of participants self-reported as Black or African American and 7.8% of participants self-reported as Hispanic or Latino (Table 10). In Study 101, less than 3% of participants self-reported as Black or African American and less than 8% of participants self-reported as Hispanic or Latino (Study 101 Day 119 CSR Table 7, Table 8, and Table 9). Due to the dominant sample size of Study 301, the sample size across all 3 studies (in aggregate) approaches that of the US population with respect to the proportion of these racial and ethnic groups.

2.7.4.1.3.1 Study 301

2.7.4.1.3.1.1 Demography

Participant demographic and baseline characteristics were similar between the treatment groups (Table 8). A slightly higher proportion of males versus females (52.6% vs. 47.4%. respectively) was enrolled. The mean (range) participant age at screening was 51.4 years (18 to 95 years) with 75.2% of participants age 18 to 64 years and 24.8% of participants age 65 years and older. The majority of participants were White (79.2%). A majority reported as Not Hispanic or Latino (78.6%). Participants who did not report as White and/or who reported Hispanic or Latino ethnicity were considered to be members of communities of color and comprised 37.2% of the study population; the racial and ethnicity proportions observed in this study were generally representative of US demographics.

Randomization was stratified based on age and risk of complications of COVID-19: 41.5% of participants were considered at risk for severe COVID-19 (16.7% participants who were < 65 years old and at risk, and 24.8% participants > 65 years old) (Table 8) (the predefined medical conditions placing participants at increased risk for the complications from COVID-19 are listed in Section 2.7.4.1.1.2.1). Residence at baseline in a nursing home or assisted living facility, which may be indicative of overall frail health, was reported for 0.2% of participants in each group, including 0.4% of those ≥ 65 years old and 0.1% of those < 65 years old. Occupational risk for exposure was reported for 63.3% of those ≥ 65 years old and 88.9% of those < 65 years old.

Baseline SARS-CoV-2 status was positive for 2.3% of participants in the mRNA-1273 group and 2.2% of participants in the placebo group. Although known history of infection was an exclusion criterion, many participants were screened on the same day as they received their first dose, and screening results were not known until after that day.

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Table 8 Study 301: Baseline Demographics and Characteristics by Age Group (Safety Set)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	100 µg mRNA-1273 (N=11415)	Total (N=22826)	Placebo (N=3751)	100 µg mRNA-1273 (N=3769)	Total (N=7520)	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Age at screening (years)									
n	11411	11415	22826	3751	3769	7520	15162	15184	30346
Mean (SD)	45.0 (12.30)	45.1 (12.35)	45.0 (12.33)	70.7 (4.88)	70.4 (4.66)	70.6 (4.77)	51.3 (15.60)	51.4 (15.51)	51.4 (15.55)
Median	46.0	46.0	46.0	70.0	69.0	70.0	52.0	53.0	52.0
Min, Max	18, 64	18, 64	18, 64	65, 95	65, 95	65, 95	18, 95	18, 95	18, 95
Age group at screening, n (%)									
>=18 and <65 years	11411 (100)	11415 (100)	22826 (100)	0	0	0	11411 (75.3)	11415 (75.2)	22826 (75.2)
Mean (SD)	45.0 (12.30)	45.1 (12.35)	45.0 (12.33)				45.0 (12.30)	45.1 (12.35)	45.0 (12.33)
Median	46.0	46.0	46.0				46.0	46.0	46.0
Min, Max	18, 64	18, 64	18, 64				18, 64	18, 64	18, 64
>=65 years	0	0	0	3751 (100)	3769 (100)	7520 (100)	3751 (24.7)	3769 (24.8)	7520 (24.8)
Mean (SD)				70.7 (4.88)	70.4 (4.66)	70.6 (4.77)	70.7 (4.88)	70.4 (4.66)	70.6 (4.77)
Median				70.0	69.0	70.0	70.0	69.0	70.0
Min, Max				65, 95	65, 95	65, 95	65, 95	65, 95	65, 95

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	100 µg mRNA-1273 (N=11415)	Total (N=22826)	Placebo (N=3751)	100 µg mRNA-1273 (N=3769)	Total (N=7520)	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Age subgroup at screening, n (%)									
>=18 and <65 years	11411 (100)	11415 (100)	22826 (100)	0	0	0	11411 (75.3)	11415 (75.2)	22826 (75.2)
>=65 and <70 years	0	0	0	1817 (48.4)	1906 (50.6)	3723 (49.5)	1817 (12.0)	1906 (12.6)	3723 (12.3)
>=70 and <75 years	0	0	0	1193 (31.8)	1206 (32.0)	2399 (31.9)	1193 (7.9)	1206 (7.9)	2399 (7.9)
>=75 and <80 years	0	0	0	507 (13.5)	466 (12.4)	973 (12.9)	507 (3.3)	466 (3.1)	973 (3.2)
>=80 years	0	0	0	234 (6.2)	191 (5.1)	425 (5.7)	234 (1.5)	191 (1.3)	425 (1.4)
Age subgroup at screening, n (%)									
>=18 and <65 years	11411 (100)	11415 (100)	22826 (100)	0	0	0	11411 (75.3)	11415 (75.2)	22826 (75.2)
>=65 and <75 years	0	0	0	3010 (80.2)	3112 (82.6)	6122 (81.4)	3010 (19.9)	3112 (20.5)	6122 (20.2)
>=75 and <85 years	0	0	0	692 (18.4)	616 (16.3)	1308 (17.4)	692 (4.6)	616 (4.1)	1308 (4.3)
>=85 years	0	0	0	49 (1.3)	41 (1.1)	90 (1.2)	49 (0.3)	41 (0.3)	90 (0.3)
Age and health risk for severe COVID-19, n (%) [a]									
>=18 and <65 years and not at risk	8878 (77.8)	8890 (77.9)	17768 (77.8)	2 (<0.1)	0	2 (<0.1)	8880 (58.6)	8890 (58.5)	17770 (58.6)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	100 µg mRNA-1273 (N=11415)	Total (N=22826)	Placebo (N=3751)	100 µg mRNA-1273 (N=3769)	Total (N=7520)	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
>=18 and <65 years and at risk	2532 (22.2)	2524 (22.1)	5056 (22.2)	3 (<0.1)	6 (0.2)	9 (0.1)	2535 (16.7)	2530 (16.7)	5065 (16.7)
>=65 years	1 (<0.1)	1 (<0.1)	2 (<0.1)	3746 (99.9)	3763 (99.8)	7509 (99.9)	3747 (24.7)	3764 (24.8)	7511 (24.8)
Risk factor for severe COVID-19 at screening, n (%) [b]									
Chronic lung disease	504 (4.4)	473 (4.1)	977 (4.3)	245 (6.5)	239 (6.3)	484 (6.4)	749 (4.9)	712 (4.7)	1461 (4.8)
Significant cardiac disease	292 (2.6)	321 (2.8)	613 (2.7)	450 (12.0)	441 (11.7)	891 (11.8)	742 (4.9)	762 (5.0)	1504 (5.0)
Severe obesity	905 (7.9)	896 (7.8)	1801 (7.9)	153 (4.1)	174 (4.6)	327 (4.3)	1058 (7.0)	1070 (7.0)	2128 (7.0)
Diabetes	912 (8.0)	919 (8.1)	1831 (8.0)	545 (14.5)	541 (14.4)	1086 (14.4)	1457 (9.6)	1460 (9.6)	2917 (9.6)
Liver disease	70 (0.6)	84 (0.7)	154 (0.7)	26 (0.7)	20 (0.5)	46 (0.6)	96 (0.6)	104 (0.7)	200 (0.7)
Human immunodeficiency virus infection	75 (0.7)	77 (0.7)	152 (0.7)	16 (0.4)	17 (0.5)	33 (0.4)	91 (0.6)	94 (0.6)	185 (0.6)
At risk for severe COVID-19 at screening, n (%)									
Yes	2322 (20.3)	2320 (20.3)	4642 (20.3)	1135 (30.3)	1128 (29.9)	2263 (30.1)	3457 (22.8)	3448 (22.7)	6905 (22.8)
One risk factor for severe COVID-19	1937 (17.0)	1925 (16.9)	3862 (16.9)	878 (23.4)	866 (23.0)	1744 (23.2)	2815 (18.6)	2791 (18.4)	5606 (18.5)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	**100 µg mRNA-1273 (N=11415)**	**Total (N=22826)**	**Placebo (N=3751)**	**100 µg mRNA-1273 (N=3769)**	**Total (N=7520)**	**Placebo (N=15162)**	**100 µg mRNA-1273 (N=15184)**	**Total (N=30346)**
Two or more risk factors for severe COVID-19	385 (3.4)	395 (3.5)	780 (3.4)	257 (6.9)	262 (7.0)	519 (6.9)	642 (4.2)	657 (4.3)	1299 (4.3)
No	9089 (79.7)	9095 (79.7)	18184 (79.7)	2616 (69.7)	2641 (70.1)	5257 (69.9)	11705 (77.2)	11736 (77.3)	23441 (77.2)
Age and risk for severe COVID-19, n (%) [c]									
>=18 and <65 years and not at risk	9089 (79.7)	9095 (79.7)	18184 (79.7)	0	0	0	9089 (59.9)	9095 (59.9)	18184 (59.9)
>=18 and <65 years and at risk	2322 (20.3)	2320 (20.3)	4642 (20.3)	0	0	0	2322 (15.3)	2320 (15.3)	4642 (15.3)
>=65 years and not at risk	0	0	0	2616 (69.7)	2641 (70.1)	5257 (69.9)	2616 (17.3)	2641 (17.4)	5257 (17.3)
>=65 years and at risk	0	0	0	1135 (30.3)	1128 (29.9)	2263 (30.1)	1135 (7.5)	1128 (7.4)	2263 (7.5)
Baseline RT-PCR results, n (%)									
Negative	11269 (98.8)	11270 (98.7)	22539 (98.7)	3722 (99.2)	3747 (99.4)	7469 (99.3)	14991 (98.9)	15017 (98.9)	30008 (98.9)
Positive	85 (0.7)	81 (0.7)	166 (0.7)	10 (0.3)	7 (0.2)	17 (0.2)	95 (0.6)	88 (0.6)	183 (0.6)
Missing	57 (0.5)	64 (0.6)	121 (0.5)	19 (0.5)	15 (0.4)	34 (0.5)	76 (0.5)	79 (0.5)	155 (0.5)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	100 µg mRNA-1273 (N=11415)	Total (N=22826)	Placebo (N=3751)	100 µg mRNA-1273 (N=3769)	Total (N=7520)	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Baseline Elecsys anti-SARS-CoV-2 results, n (%)									
Negative	11122 (97.5)	11126 (97.5)	22248 (97.5)	3718 (99.1)	3725 (98.8)	7443 (99.0)	14840 (97.9)	14851 (97.8)	29691 (97.8)
Positive	274 (2.4)	276 (2.4)	550 (2.4)	29 (0.8)	33 (0.9)	62 (0.8)	303 (2.0)	309 (2.0)	612 (2.0)
Missing	15 (0.1)	13 (0.1)	28 (0.1)	4 (0.1)	11 (0.3)	15 (0.2)	19 (0.1)	24 (0.2)	43 (0.1)
Baseline SARS-CoV-2 status, n (%) [d]									
Negative	11044 (96.8)	11039 (96.7)	22083 (96.7)	3697 (98.6)	3711 (98.5)	7408 (98.5)	14741 (97.2)	14750 (97.1)	29491 (97.2)
Positive	303 (2.7)	311 (2.7)	614 (2.7)	34 (0.9)	36 (1.0)	70 (0.9)	337 (2.2)	347 (2.3)	684 (2.3)
Missing	64 (0.6)	65 (0.6)	129 (0.6)	20 (0.5)	22 (0.6)	42 (0.6)	84 (0.6)	87 (0.6)	171 (0.6)
Sex, n (%)									
Male	5955 (52.2)	5841 (51.2)	11796 (51.7)	2101 (56.0)	2077 (55.1)	4178 (55.6)	8056 (53.1)	7918 (52.1)	15974 (52.6)
Female	5456 (47.8)	5574 (48.8)	11030 (48.3)	1650 (44.0)	1692 (44.9)	3342 (44.4)	7106 (46.9)	7266 (47.9)	14372 (47.4)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	100 µg mRNA-1273 (N=11415)	Total (N=22826)	Placebo (N=3751)	100 µg mRNA-1273 (N=3769)	Total (N=7520)	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Race, n (%)									
White	8656 (75.9)	8654 (75.8)	17310 (75.8)	3342 (89.1)	3380 (89.7)	6722 (89.4)	11998 (79.1)	12034 (79.3)	24032 (79.2)
Black or African American	1316 (11.5)	1345 (11.8)	2661 (11.7)	215 (5.7)	222 (5.9)	437 (5.8)	1531 (10.1)	1567 (10.3)	3098 (10.2)
Asian	662 (5.8)	589 (5.2)	1251 (5.5)	77 (2.1)	67 (1.8)	144 (1.9)	739 (4.9)	656 (4.3)	1395 (4.6)
American Indian or Alaska Native	95 (0.8)	92 (0.8)	187 (0.8)	26 (0.7)	21 (0.6)	47 (0.6)	121 (0.8)	113 (0.7)	234 (0.8)
Native Hawaiian or other Pacific Islander	29 (0.3)	33 (0.3)	62 (0.3)	3 (<0.1)	3 (<0.1)	6 (<0.1)	32 (0.2)	36 (0.2)	68 (0.2)
Multiracial	283 (2.5)	288 (2.5)	571 (2.5)	35 (0.9)	32 (0.8)	67 (0.9)	318 (2.1)	320 (2.1)	638 (2.1)
Other	262 (2.3)	276 (2.4)	538 (2.4)	32 (0.9)	23 (0.6)	55 (0.7)	294 (1.9)	299 (2.0)	593 (2.0)
Not reported	60 (0.5)	84 (0.7)	144 (0.6)	14 (0.4)	13 (0.3)	27 (0.4)	74 (0.5)	97 (0.6)	171 (0.6)
Unknown	48 (0.4)	54 (0.5)	102 (0.4)	7 (0.2)	8 (0.2)	15 (0.2)	55 (0.4)	62 (0.4)	117 (0.4)
Ethnicity, n (%)									
Hispanic or Latino	2773 (24.3)	2768 (24.2)	5541 (24.3)	335 (8.9)	354 (9.4)	689 (9.2)	3108 (20.5)	3122 (20.6)	6230 (20.5)
Not Hispanic or Latino	8543 (74.9)	8549 (74.9)	17092 (74.9)	3375 (90.0)	3371 (89.4)	6746 (89.7)	11918 (78.6)	11920 (78.5)	23838 (78.6)
Not reported	57 (0.5)	72 (0.6)	129 (0.6)	26 (0.7)	33 (0.9)	59 (0.8)	83 (0.5)	105 (0.7)	188 (0.6)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	100 µg mRNA-1273 (N=11415)	Total (N=22826)	Placebo (N=3751)	100 µg mRNA-1273 (N=3769)	Total (N=7520)	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Unknown	38 (0.3)	26 (0.2)	64 (0.3)	15 (0.4)	11 (0.3)	26 (0.3)	53 (0.3)	37 (0.2)	90 (0.3)
Race and ethnicity group, n (%) [e]									
Minority	4069 (35.7)	4076 (35.7)	8145 (35.7)	561 (15.0)	578 (15.3)	1139 (15.1)	4630 (30.5)	4654 (30.7)	9284 (30.6)
Non-minority	7329 (64.2)	7319 (64.1)	14648 (64.2)	3177 (84.7)	3185 (84.5)	6362 (84.6)	10506 (69.3)	10504 (69.2)	21010 (69.2)
Missing	13 (0.1)	20 (0.2)	33 (0.1)	13 (0.3)	6 (0.2)	19 (0.3)	26 (0.2)	26 (0.2)	52 (0.2)
Race and ethnicity group, n (%) [f]									
White	6401 (56.1)	6459 (56.6)	12860 (56.3)	3065 (81.7)	3076 (81.6)	6141 (81.7)	9466 (62.4)	9535 (62.8)	19001 (62.6)
Communities of color	4997 (43.8)	4936 (43.2)	9933 (43.5)	673 (17.9)	687 (18.2)	1360 (18.1)	5670 (37.4)	5623 (37.0)	11293 (37.2)
Missing	13 (0.1)	20 (0.2)	33 (0.1)	13 (0.3)	6 (0.2)	19 (0.3)	26 (0.2)	26 (0.2)	52 (0.2)
Weight (kg)									
n	11351	11359	22710	3728	3740	7468	15079	15099	30178
Mean (SD)	86.75 (22.351)	86.56 (22.683)	86.66 (22.518)	83.24 (19.020)	83.10 (19.333)	83.17 (19.176)	85.88 (21.628)	85.70 (21.951)	85.79 (21.790)
Median	83.64	83.64	83.64	81.60	81.20	81.40	83.00	83.00	83.00
Min, Max	30.7, 223.0	30.3, 236.4	30.3, 236.4	34.8, 184.5	37.2, 165.0	34.8, 184.5	30.7, 223.0	30.3, 236.4	30.3, 236.4

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	**100 µg mRNA-1273 (N=11415)**	**Total (N=22826)**	**Placebo (N=3751)**	**100 µg mRNA-1273 (N=3769)**	**Total (N=7520)**	**Placebo (N=15162)**	**100 µg mRNA-1273 (N=15184)**	**Total (N=30346)**
Height (cm)									
n	11350	11359	22709	3727	3741	7468	15077	15100	30177
Mean (SD)	171.16 (9.964)	170.98 (9.902)	171.07 (9.933)	170.05 (10.223)	169.97 (10.005)	170.01 (10.114)	170.89 (10.039)	170.73 (9.937)	170.81 (9.988)
Median	171.00	170.20	170.50	170.18	170.18	170.18	170.50	170.18	170.20
Min, Max	118.0, 205.7	104.1, 221.0	104.1, 221.0	124.5, 223.5	123.0, 208.3	123.0, 223.5	118.0, 223.5	104.1, 221.0	104.1, 223.5
Body mass index (kg/m^2)									
n	11350	11356	22706	3727	3740	7467	15077	15096	30173
Mean (SD)	29.53 (6.904)	29.53 (7.120)	29.53 (7.012)	28.71 (5.891)	28.67 (5.850)	28.69 (5.870)	29.33 (6.677)	29.32 (6.837)	29.32 (6.757)
Median	28.27	28.25	28.26	27.75	27.86	27.79	28.14	28.13	28.13
Min, Max	10.3, 72.7	9.8, 86.1	9.8, 86.1	12.1, 71.1	11.2, 62.9	11.2, 71.1	10.3, 72.7	9.8, 86.1	9.8, 86.1
Body mass index subgroup, n (%)									
< 30 kg/m^2	6866 (60.2)	6860 (60.1)	13726 (60.1)	2434 (64.9)	2416 (64.1)	4850 (64.5)	9300 (61.3)	9276 (61.1)	18576 (61.2)
>=30 kg/m^2	4484 (39.3)	4496 (39.4)	8980 (39.3)	1293 (34.5)	1324 (35.1)	2617 (34.8)	5777 (38.1)	5820 (38.3)	11597 (38.2)
Missing	61 (0.5)	59 (0.5)	120 (0.5)	24 (0.6)	29 (0.8)	53 (0.7)	85 (0.6)	88 (0.6)	173 (0.6)

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	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	100 µg mRNA-1273 (N=11415)	Total (N=22826)	Placebo (N=3751)	100 µg mRNA-1273 (N=3769)	Total (N=7520)	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Occupational risk, n (%) [b]	10161 (89.0)	10123 (88.7)	20284 (88.9)	2386 (63.6)	2377 (63.1)	4763 (63.3)	12547 (82.8)	12500 (82.3)	25047 (82.5)
Healthcare workers	3337 (29.2)	3341 (29.3)	6678 (29.3)	503 (13.4)	468 (12.4)	971 (12.9)	3840 (25.3)	3809 (25.1)	7649 (25.2)
Emergency response	277 (2.4)	281 (2.5)	558 (2.4)	19 (0.5)	21 (0.6)	40 (0.5)	296 (2.0)	302 (2.0)	598 (2.0)
Retail or restaurant operations	881 (7.7)	858 (7.5)	1739 (7.6)	99 (2.6)	100 (2.7)	199 (2.6)	980 (6.5)	958 (6.3)	1938 (6.4)
Manufacturing and production operations	391 (3.4)	391 (3.4)	782 (3.4)	30 (0.8)	35 (0.9)	65 (0.9)	421 (2.8)	426 (2.8)	847 (2.8)
Warehouse shipping and fulfillment centers	163 (1.4)	181 (1.6)	344 (1.5)	12 (0.3)	9 (0.2)	21 (0.3)	175 (1.2)	190 (1.3)	365 (1.2)
Transportation and delivery services	419 (3.7)	434 (3.8)	853 (3.7)	61 (1.6)	50 (1.3)	111 (1.5)	480 (3.2)	484 (3.2)	964 (3.2)
Border protection and military personnel	63 (0.6)	65 (0.6)	128 (0.6)	6 (0.2)	3 (<0.1)	9 (0.1)	69 (0.5)	68 (0.4)	137 (0.5)
Personal care and in-home services	407 (3.6)	405 (3.5)	812 (3.6)	61 (1.6)	67 (1.8)	128 (1.7)	468 (3.1)	472 (3.1)	940 (3.1)
Hospitality and tourism workers	184 (1.6)	201 (1.8)	385 (1.7)	43 (1.1)	37 (1.0)	80 (1.1)	227 (1.5)	238 (1.6)	465 (1.5)
Pastoral, social or public health workers	364 (3.2)	386 (3.4)	750 (3.3)	140 (3.7)	149 (4.0)	289 (3.8)	504 (3.3)	535 (3.5)	1039 (3.4)
Educators and students	1387 (12.2)	1365 (12.0)	2752 (12.1)	170 (4.5)	186 (4.9)	356 (4.7)	1557 (10.3)	1551 (10.2)	3108 (10.2)
Other	3398 (29.8)	3415 (29.9)	6813 (29.8)	1432 (38.2)	1435 (38.1)	2867 (38.1)	4830 (31.8)	4850 (31.8)	9680 (31.9)

	>=18 and <65 Years			>=65 Years			Overall		
	Placebo (N=11411)	100 µg mRNA-1273 (N=11415)	Total (N=22826)	Placebo (N=3751)	100 µg mRNA-1273 (N=3769)	Total (N=7520)	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Location and living circumstances risk, n (%)[b]	9578 (83.9)	9601 (84.1)	19179 (84.0)	3107 (82.8)	3135 (83.2)	6242 (83.0)	12685 (83.7)	12736 (83.9)	25421 (83.8)
Resides in nursing home or assisted living facility	9 (<0.1)	24 (0.2)	33 (0.1)	20 (0.5)	11 (0.3)	31 (0.4)	29 (0.2)	35 (0.2)	64 (0.2)
Resides in multi-family dwelling	348 (3.0)	397 (3.5)	745 (3.3)	65 (1.7)	66 (1.8)	131 (1.7)	413 (2.7)	463 (3.0)	876 (2.9)
Resides in high density housing	1073 (9.4)	1038 (9.1)	2111 (9.2)	240 (6.4)	253 (6.7)	493 (6.6)	1313 (8.7)	1291 (8.5)	2604 (8.6)
Resides in low density, multi-family setting	1236 (10.8)	1248 (10.9)	2484 (10.9)	256 (6.8)	244 (6.5)	500 (6.6)	1492 (9.8)	1492 (9.8)	2984 (9.8)
Resides in a single family home	6146 (53.9)	6117 (53.6)	12263 (53.7)	2260 (60.3)	2285 (60.6)	4545 (60.4)	8406 (55.4)	8402 (55.3)	16808 (55.4)
Other	1647 (14.4)	1649 (14.4)	3296 (14.4)	528 (14.1)	549 (14.6)	1077 (14.3)	2175 (14.3)	2198 (14.5)	4373 (14.4)

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

Percentages are based on the number of subjects in Safety Set.

[a] Based on stratification factor from IRT, subjects who are < 65 years old are categorized as at risk for severe COVID-19 illness if they have at least 1 of the risk factors specified in the study protocol at Screening.

[b] Subjects could be under one or more categories, and are counted once at each category.

[c] Age and health risk for severe COVID-19 are derived from age and risk factors collected on case report form (CRF).

[d] Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

[e] Minority is defined as: Blacks or African Americans, Hispanics or Latinos, American Indians or Alaska Natives, Native Hawaiians, and other Pacific Islanders, and Non-Minority includes all the others whose race or ethnicity is not unknown, unreported or missing.

[f] White is defined as White and non-Hispanic; Communities of Color includes all the others whose race or ethnicity is not unknown, unreported or missing.

Source: Study 301 Part A CSR Table 14.1.3.2.2 (26 Mar 2021).

2.7.4.1.3.1.2 Medical History

In Study 301, 92.2% of participants in the mRNA-1273 group and 92.0% of participants in the placebo group reported specific conditions as part of their medical history (past and ongoing conditions). Medical history conditions were balanced between the groups. The most frequently reported (≥ 15% of participants in either group) were hypertension, seasonal allergy, postmenopause, and gastroesophageal reflux disease (Study 301 Part A CSR Table 14.1.4.1). In accordance with the planned stratification based on the 6 identified risk factors for severe COVID-19, the groups were balanced with respect to presence at baseline of chronic lung disease (4.8% of the total population), significant cardiac disease (5.0%), severe obesity (7.0%), diabetes (9.6%), liver disease (0.7%), and HIV infection (0.6%) (Table 8).

Participants with a medical history of autoimmune disorder, angioedema, anaphylaxis, or hypersensitivity were not excluded from the study. In the mRNA-1273 group, 3064 participants (20.2%) had a history of hypersensitivity, 1152 participants (7.6%) had a history of autoimmune disorder, 100 participants (0.7%) had a history of angioedema, and 23 participants (0.2%) had a history of anaphylaxis (Study 301 Part A CSR Table 14.1.4.4, Table 14.1.4.5, Table 14.1.4.6, and Table 14.1.4.7). Incidence of these conditions was balanced between the mRNA-1273 and placebo groups. After the interim analysis, participants were asked about history of dermal filler use; history of dermal filler use was reported for 325 participants (2.1%) in the mRNA-1273 group and 234 participants (1.5%) in the placebo group (Study 301 Part A CSR Section 7.3.3.3.3).

2.7.4.1.3.1.3 Concomitant Use of Medications

Overall, use of concomitant medications and/or non-study vaccination throughout the study was reported for 62.3% of participants; 72.5% of participants in the mRNA-1273 group and 52.1% of participants in the placebo group (Table 9). The imbalance generally appears to be driven by antipyretic or analgesic medication use in the mRNA-1273 group during the study. A higher proportion of participants in the mRNA-1273 group (60.0%) reported any concomitant medications or non-study vaccination within 7 days post-injection than participants in the placebo group (25.4%). An imbalance was also observed within 14 days post injection (62.8% in the mRNA-1273 group vs. 31.0% in the placebo group) and within 28 days post injection (72.3% vs. 51.7%, respectively).

Concomitant vaccine use throughout the study was reported for 23.5% of participants, with no notable differences between the mRNA-1273 group and the placebo group. Concomitant vaccine

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use within 7 days, 14 days, and 28 days post injection was reported for 0.5%, 1.7%, and 23.4% of participants, respectively, with no notable differences between the mRNA-1273 and placebo groups.

Seasonal influenza vaccine within 14 days post injection and within 28 days post injection was reported for a total of 1.5% and 23.1% participants, respectively.

Use of concomitant medication information as summarized in this section and in Table 9 is as collected from the CRF. Use of antipyretic or analgesic medication before and after injections as summarized in Section 2.7.4.2.1.2 is as collected in the eDiary.

Table 9 Study 301: Concomitant Medications (Safety Set)

	Placebo N=15162 n (%)	100 µg mRNA-1273 N=15184 n (%)	Total N=30346 n (%)
Any Concomitant Medications or Nonstudy Vaccination			
Throughout the Study	7906 (52.1)	11012 (72.5)	18918 (62.3)
Within 7 Days Post Injection	3845 (25.4)	9107 (60.0)	12952 (42.7)
Within 14 Days Post Injection	4706 (31.0)	9530 (62.8)	14236 (46.9)
Within 28 Days Post Injection	7846 (51.7)	10984 (72.3)	18830 (62.1)
Seasonal Influenza Vaccine Within 14 Days Post Injection	253 (1.7)	198 (1.3)	451 (1.5)
Seasonal Influenza Vaccine Within 28 Days Post Injection	3634 (24.0)	3364 (22.2)	6998 (23.1)
Antipyretic or Analgesic Medication Within 28 Days Post Injection	3517 (23.2)	8892 (58.6)	12409 (40.9)

Percentages are based on the number of safety participants.
Source: Study 301 Part A CSR Table 14.1.5.1.1 (26 Mar 2021).

2.7.4.1.3.2 Study 201

2.7.4.1.3.2.1 Demography

Of the 600 participants in the Safety Set in Study 201, approximately two-thirds were female (65.0%), most were White (94.8%) and not of Hispanic or Latino descent (92.0%), and the median age was 54.5 years (range: 18 to 87) (Table 10). No differences were apparent across treatment groups in the baseline demographics shown in Table 10.

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Table 10 Study 201: Baseline Demographics (Safety Set)

		mRNA-1273			
	Placebo (N=200)	**50 µg (N=200)**	**100 µg (N=200)**	**Total mRNA-1273 (N=400)**	**Overall (N=600)**
Age (years)					
n	200	200	200	400	600
Mean (SD)	50.8 (15.77)	50.6 (16.30)	51.1 (15.55)	50.8 (15.91)	50.8 (15.85)
Median	54.0	54.5	54.5	54.5	54.5
Min, Max	18, 84	18, 87	18, 87	18, 87	18, 87
Gender, n (%)					
Male	71 (35.5)	63 (31.5)	76 (38.0)	139 (34.8)	210 (35.0)
Female	129 (64.5)	137 (68.5)	124 (62.0)	261 (65.3)	390 (65.0)
Race, n (%)					
White	193 (96.5)	188 (94.0)	188 (94.0)	376 (94.0)	569 (94.8)
Black or African American	3 (1.5)	5 (2.5)	8 (4.0)	13 (3.3)	16 (2.7)
Asian	3 (1.5)	2 (1.0)	2 (1.0)	4 (1.0)	7 (1.2)
American Indian or Alaska Native	0	2 (1.0)	1 (0.5)	3 (0.8)	3 (0.5)
Native Hawaiian or Other Pacific Islander	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Multiracial	1 (0.5)	1 (0.5)	0	1 (0.3)	2 (0.3)
Other	0	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.3)
Not reported	0	0	0	0	0
Unknown	0	0	0	0	0
Ethnicity, n (%)					
Hispanic or Latino	16 (8.0)	15 (7.5)	16 (8.0)	31 (7.8)	47 (7.8)
Not Hispanic or Latino	184 (92.0)	184 (92.0)	184 (92.0)	368 (92.0)	552 (92.0)
Not reported	0	1 (0.5)	0	1 (0.3)	1 (0.2)
Unknown	0	0	0	0	0

	Placebo (N=200)	mRNA-1273 50 µg (N=200)	mRNA-1273 100 µg (N=200)	Total mRNA-1273 (N=400)	Overall (N=600)
Body mass index (kg/m²)					
n	200	200	200	400	600
Mean (SD)	25.35 (2.855)	25.60 (2.920)	25.02 (2.944)	25.31 (2.943)	25.32 (2.912)
Median	25.73	26.11	25.24	25.64	25.67
Min, Max	18.0, 30.4	17.9, 30.7	18.2, 30.1	17.9, 30.7	17.9, 30.7

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation.

Percentages are based on the number of safety participants.

Source: Study 201 Primary Analysis CSR Table 10 (05 Nov 2020).

2.7.4.1.3.2.2 Medical History

The most frequently reported medical history conditions (> 10% of participants in either the mRNA-1273 50 or 100 µg group) in Study 201 included seasonal allergy (113/400 [28.3%]), postmenopause (105/400 [26.3%]), drug hypersensitivity (69/400 [17.3%]), anxiety (49/400 [12.3%]), hysterectomy (46/400 [11.5%]), and depression (42/400 [10.5%]) (Study 201 Primary Analysis CSR Section 5.1 and Table 14.1.5.1). Medical history conditions were generally balanced across treatment groups in the Safety Set.

Among the medical history conditions reported for at least 5% of participants in any treatment group, drug hypersensitivity was reported for 69/400 (17.3%) participants treated with 50 µg or 100 µg mRNA-1273 and for 24/200 (12.0%) participants treated with placebo.

Medical history conditions that are often more prevalent in older populations were more common in Cohort 2 (≥ 55 years) than Cohort 1 (≥ 18 to < 55 years) across all treatment groups; these conditions included hypercholesterolemia, osteoarthritis, menopause/postmenopause, and hysterectomy (Study 201 Primary Analysis CSR Table 14.1.5.1).

2.7.4.1.3.2.3 Concomitant Use of Medications

In Study 201, the majority of participants received at least 1 concomitant medication during the study (336/400 [84.0%] in the mRNA-1273 total group [all participants who received 100 µg or 50 µg mRNA-1273] and 148/200 [74.0%] in the placebo group) (Study 201 Primary Analysis CSR Table 14.1.4.2). Nonstudy vaccination use was reported for 2 participants who received a nonstudy vaccine > 7 days but < 28 days after the second injection: 1 participant in the mRNA-1273 50 µg group received the influenza and shingles vaccines and 1 participant in the mRNA-1273 100 µg group received the shingles vaccine (Study 201 Primary Analysis CSR Listing 16.2.4.4).

2.7.4.1.3.3 Study 101

2.7.4.1.3.3.1 Demography

2.7.4.1.3.3.1.1 Age Group 18 to 55 Years of Age

The majority of participants were White (53/60 [88%]) and not of Hispanic or Latino ethnicity (52/60 [87%]). The median age was 32.1 years (range: 18 to 54), and 31/60 (52%) participants were male and 29/60 (48%) were female (Study 101 Day 119 CSR Table 7).

2.7.4.1.3.3.1.2 Age Group 56 to 70 Years of Age

The majority of participants were White (27/30 [90%]), and all (30/30 [100%]) were not of Hispanic or Latino ethnicity. The median age was 65.0 years (range: 56 to 70), and 13/30 (43%) participants were male and 17/30 (57%) were female (Study 101 Day 119 CSR Table 8).

2.7.4.1.3.3.1.3 Age Group 71 Years of Age and Older

The majority of participants were White (29/30 [97%]) and not of Hispanic or Latino ethnicity (28/30 [93%]). The median age was 72.9 years (range: 71 to 83), and 17/30 (57%) participants were male and 13/30 (43%) were female (Study 101 Day 119 CSR Table 9).

2.7.4.1.3.3.2 Medical History

Data for medical history were not summarized for Study 101. The eligibility criteria required participants to be in good health as determined by medical history and physical examination (Study 101 Day 119 CSR Section 3.5.1).

2.7.4.1.3.3.3 Concomitant Medications

While Study 101 participants were generally in good health, most reported use of at least 1 concomitant medication: 58/60 (97%) participants in the 18 to 55 years age group, 30/30 (100%) participants in the 56 to 70 years age group, and 30/30 (100%) participants in the ≥ 71 years age group (Study 101 Day 119 CSR Posttext Table 172, Posttext Table 173, and Posttext Table 174).

2.7.4.2 ADVERSE EVENTS

As described in Section 2.7.4.1.1.1, data from the 3 studies have not been integrated for this SCS, and the focus is on Study 301 Part A, which provides safety data from the blinded portion of the study for 30,346 participants. Analyses of solicited ARs and unsolicited AEs are presented for Study 301 Part A in Section 2.7.4.2.1, for Study 201 in Section 2.7.4.2.3, and for Study 101 in Section 2.7.4.2.4. Further safety findings including at least 6 months' median follow-up are presented for Study 301 (Part B) in Section 2.7.4.2.2.2.

2.7.4.2.1 Study 301 Part A

Part A of Study 301 is the randomized, placebo-controlled, observer-blind portion of the study. Safety data are reported for all participants from Day 1 until early unblinding, study discontinuation, the Part B PDV, or data cutoff date (26 Mar 2021), whichever was earlier. Part B of Study 301 is the open-label observational portion of the study. Safety data from Part B are reported for all participants from the time of unblinding (if applicable) until the data cutoff date (Section 2.7.4.2.2).

Observations for solicited ARs were consistent with earlier clinical trials with the mRNA-1273 vaccine. Incidence of local and systemic ARs was higher in the mRNA-1273 group than in the placebo group. In the mRNA-1273 group, incidence was higher for systemic ARs after the second injection than after the first. Most solicited ARs were grade 1 to grade 2 in severity. More events were reported at higher severity after the second dose compared with after the first.

Commonly reported unsolicited AEs were consistent with reactogenicity of the mRNA-1273 vaccine. Incidence of SAEs was similar between the mRNA-1273 and placebo groups.

Adverse event data were also assessed for potential risks based on regulatory agency requests, clinical experience with this and other vaccines for COVID-19 and other infectious diseases, reports in the literature of emerging knowledge, and theoretical concerns; ie, they were not prospectively defined, but instead have evolved over the course of the study. Supplemental summaries are provided for events in categories using SMQs and CMQs to facilitate these assessments (Section 2.7.4.1.1.1.5 and Section 2.7.4.2.1.4.5). No unexpected findings emerged from these reviews.

In addition, data about specific event terms have been evaluated separately from these summaries to elucidate whether they represent a potential effect of mRNA-1273 administration (including unsolicited AEs [Section 2.7.4.2.1.3.2] and SAEs [Section 2.7.4.2.1.4.2]). No cases were reported of myocarditis, idiopathic thrombocytopenic purpura, thrombosis with thrombocytopenia, or cerebral venous sinus thrombosis in Study 301. There was no evidence of an increased risk of pericarditis in the mRNA-1273 group. No evidence of VAERD was observed.

2.7.4.2.1.1 Solicited Adverse Reactions

Participants recorded solicited local and systemic ARs in the eDiary on the day of each IP injection and during the 7 days after each IP injection (Study 301 Part A CSR Section 3.7.1.1). If any AR was ongoing on the seventh day, the eDiary solicited entries until resolution of the ARs.

2.7.4.2.1.1.1 Incidence and Severity of Solicited Adverse Reactions Starting Within 7 Days After Injection

Incidence of solicited local ARs was higher in the mRNA-1273 group (84.2%) than in the placebo group (19.9%) after the first injection (Table 11) and after the second injection (88.7% in the mRNA-1273 group compared with 18.9% in the placebo group) (Table 12). Pain was the most commonly reported local AR in the mRNA-1273 group after both injections (83.7% after the first injection and 88.3% after the second injection). In the mRNA-1273 group, grade 3 solicited local ARs were more common after the second injection (7.0%) than after the first (3.5%). Grade 3 local ARs occurred infrequently in the placebo group after either injection. Pain was the most commonly reported grade 3 local AR in the mRNA-1273 group after both injections, and the incidence of grade 3 pain was higher after the second injection (2.7% after the first injection and 4.1% after the second injection). Grade 3 pain in the mRNA-1273 group was the only grade 3 solicited local AR reported at a frequency > 2% after either injection. No grade 4 solicited local ARs were reported.

Incidence of solicited systemic ARs was higher in the mRNA-1273 group (54.8%) than in the placebo group (42.2%) after the first injection (Table 11) and after the second injection (79.5% in the mRNA-1273 group compared with 36.7% in the placebo group) (Table 12). In the mRNA-1273 group, incidence was higher after the second injection compared with after the first. In the mRNA-1273 group, fatigue (37.2%) and headache (32.6%) were the most commonly reported systemic ARs after the first injection. This was also true after the second injection, after which the incidence was higher for fatigue (65.4%) and headache (58.8%). Incidence was also higher for myalgia (58.1%) and arthralgia (42.9%) after the second injection (compared with 22.7% for myalgia and 16.6% for arthralgia after the first). Fatigue and headache were the most commonly reported grade 3 systemic ARs in the mRNA-1273 group after the first injection (1.0% for fatigue and 1.8% for headache). This was also true after the second injection, and incidence of grade 3 fatigue (9.8%) or grade 3 headache (4.5%) was higher compared with the first injection. In addition, incidences of grade 3 myalgia (9.0%) and grade 3 arthralgia (5.3%) were higher compared with the first injection (0.6% for myalgia and 0.4% for arthralgia). In the placebo group, incidence and severity were generally not higher after the second injection compared with the first. At least one grade 4 solicited systemic AR was reported for 5 participants in the mRNA-1273 group (< 0.1%) and 6 participants in the placebo group (< 0.1%) after the first injection and for 14 (< 0.1%) and 3 (< 0.1%) participants, respectively, after the second injection. The most common grade 4 systemic AR was fever, defined as a temperature above 40°C, which was reported in 4 participants in the mRNA-1273 group and 6 participants in the placebo group after the first injection and for 13 and 3 participants, respectively, after the second injection.

Table 11 Study 301: Summary of Participants With Solicited Adverse Reactions Starting Within 7 Days After First Injection by Grade (First Injection Solicited Safety Set)

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Solicited adverse reactions - N1	15151	15166	30317
Any solicited adverse reactions	7285 (48.1)	13317 (87.8)	20602 (68.0)
95% CI	47.3, 48.9	87.3, 88.3	67.4, 68.5
Grade 1	5134 (33.9)	9329 (61.5)	14463 (47.7)
Grade 2	1782 (11.8)	3134 (20.7)	4916 (16.2)
Grade 3	363 (2.4)	849 (5.6)	1212 (4.0)
Grade 4	6 (<0.1)	5 (<0.1)	11 (<0.1)
Grade 3 or above	369 (2.4)	854 (5.6)	1223 (4.0)
Solicited local adverse reactions - N1	15147	15162	30309
Any solicited local adverse reactions	3009 (19.9)	12765 (84.2)	15774 (52.0)
95% CI	19.2, 20.5	83.6, 84.8	51.5, 52.6
Grade 1	2842 (18.8)	10725 (70.7)	13567 (44.8)
Grade 2	89 (0.6)	1511 (10.0)	1600 (5.3)
Grade 3	78 (0.5)	529 (3.5)	607 (2.0)
Grade 4	0	0	0
Grade 3 or above	78 (0.5)	529 (3.5)	607 (2.0)
Pain - N1	15147	15162	30309
Any	2665 (17.6)	12688 (83.7)	15353 (50.7)
Grade 1	2551 (16.8)	10985 (72.5)	13536 (44.7)
Grade 2	59 (0.4)	1287 (8.5)	1346 (4.4)
Grade 3	55 (0.4)	416 (2.7)	471 (1.6)
Grade 4	0	0	0
Grade 3 or above	55 (0.4)	416 (2.7)	471 (1.6)
Erythema (redness) - N1	15147	15162	30309
Any	77 (0.5)	445 (2.9)	522 (1.7)
Grade 1	57 (0.4)	281 (1.9)	338 (1.1)
Grade 2	7 (<0.1)	122 (0.8)	129 (0.4)
Grade 3	13 (<0.1)	42 (0.3)	55 (0.2)
Grade 4	0	0	0
Grade 3 or above	13 (<0.1)	42 (0.3)	55 (0.2)

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Swelling (hardness) - N1	15147	15162	30309
Any	65 (0.4)	935 (6.2)	1000 (3.3)
Grade 1	50 (0.3)	608 (4.0)	658 (2.2)
Grade 2	9 (<0.1)	245 (1.6)	254 (0.8)
Grade 3	6 (<0.1)	82 (0.5)	88 (0.3)
Grade 4	0	0	0
Grade 3 or above	6 (<0.1)	82 (0.5)	88 (0.3)
Axillary swelling or tenderness - N1	15147	15162	30309
Any	722 (4.8)	1553 (10.2)	2275 (7.5)
Grade 1	668 (4.4)	1394 (9.2)	2062 (6.8)
Grade 2	27 (0.2)	110 (0.7)	137 (0.5)
Grade 3	27 (0.2)	49 (0.3)	76 (0.3)
Grade 4	0	0	0
Grade 3 or above	27 (0.2)	49 (0.3)	76 (0.3)
Solicited systemic adverse reactions - N1	15151	15166	30317
Any solicited systemic adverse reactions	6397 (42.2)	8316 (54.8)	14713 (48.5)
95% CI	41.4, 43.0	54.0, 55.6	48.0, 49.1
Grade 1	4334 (28.6)	5358 (35.3)	9692 (32.0)
Grade 2	1746 (11.5)	2504 (16.5)	4250 (14.0)
Grade 3	311 (2.1)	449 (3.0)	760 (2.5)
Grade 4	6 (<0.1)	5 (<0.1)	11 (<0.1)
Grade 3 or above	317 (2.1)	454 (3.0)	771 (2.5)
Fever - N1	15149	15163	30312
Any	44 (0.3)	112 (0.7)	156 (0.5)
Grade 1	28 (0.2)	73 (0.5)	101 (0.3)
Grade 2	8 (<0.1)	24 (0.2)	32 (0.1)
Grade 3	2 (<0.1)	11 (<0.1)	13 (<0.1)
Grade 4	6 (<0.1)	4 (<0.1)	10 (<0.1)
Grade 3 or above	8 (<0.1)	15 (<0.1)	23 (<0.1)
Headache - N1	15146	15162	30308
Any	4026 (26.6)	4950 (32.6)	8976 (29.6)
Grade 1	3297 (21.8)	3947 (26.0)	7244 (23.9)
Grade 2	532 (3.5)	730 (4.8)	1262 (4.2)
Grade 3	197 (1.3)	273 (1.8)	470 (1.6)
Grade 4	0	0	0
Grade 3 or above	197 (1.3)	273 (1.8)	470 (1.6)

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Fatigue - N1	15146	15162	30308
Any	4133 (27.3)	5636 (37.2)	9769 (32.2)
Grade 1	2705 (17.9)	3585 (23.6)	6290 (20.8)
Grade 2	1323 (8.7)	1899 (12.5)	3222 (10.6)
Grade 3	105 (0.7)	151 (1.0)	256 (0.8)
Grade 4	0	1 (<0.1)	1 (<0.1)
Grade 3 or above	105 (0.7)	152 (1.0)	257 (0.8)
Myalgia - N1	15146	15162	30308
Any	2069 (13.7)	3442 (22.7)	5511 (18.2)
Grade 1	1560 (10.3)	2442 (16.1)	4002 (13.2)
Grade 2	462 (3.1)	909 (6.0)	1371 (4.5)
Grade 3	47 (0.3)	91 (0.6)	138 (0.5)
Grade 4	0	0	0
Grade 3 or above	47 (0.3)	91 (0.6)	138 (0.5)
Arthralgia - N1	15146	15162	30308
Any	1784 (11.8)	2510 (16.6)	4294 (14.2)
Grade 1	1333 (8.8)	1842 (12.1)	3175 (10.5)
Grade 2	413 (2.7)	607 (4.0)	1020 (3.4)
Grade 3	38 (0.3)	60 (0.4)	98 (0.3)
Grade 4	0	1 (<0.1)	1 (<0.1)
Grade 3 or above	38 (0.3)	61 (0.4)	99 (0.3)
Nausea/vomiting - N1	15146	15162	30308
Any	1075 (7.1)	1262 (8.3)	2337 (7.7)
Grade 1	887 (5.9)	1047 (6.9)	1934 (6.4)
Grade 2	175 (1.2)	205 (1.4)	380 (1.3)
Grade 3	13 (<0.1)	10 (<0.1)	23 (<0.1)
Grade 4	0	0	0
Grade 3 or above	13 (<0.1)	10 (<0.1)	23 (<0.1)

Solicited Adverse Reaction Category Grade	Placebo (N=15151) n (%)	100 µg mRNA-1273 (N=15166) n (%)	Total (N=30317) n (%)
Chills - N1	15146	15162	30308
Any	878 (5.8)	1251 (8.3)	2129 (7.0)
Grade 1	706 (4.7)	938 (6.2)	1644 (5.4)
Grade 2	158 (1.0)	289 (1.9)	447 (1.5)
Grade 3	14 (<0.1)	24 (0.2)	38 (0.1)
Grade 4	0	0	0
Grade 3 or above	14 (<0.1)	24 (0.2)	38 (0.1)

Abbreviations: CI = confidence intervals; N1 = number of exposed subjects who submitted any data for the event.

Any = Grade 1 or higher.

Percentages are based on the number of exposed subjects who submitted any data for the event (N1).

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

Severity grading for solicited adverse reactions is defined in Table 3.

Source: Study 301 Part A CSR (Table 14.3.1.1.1.1) (26 Mar 2021).

Table 12 Study 301: Summary of Participants With Solicited Adverse Reactions Starting Within 7 Days After Second Injection by Grade (Second Injection Solicited Safety Set)

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Solicited adverse reactions - N1	14578	14691	29269
Any solicited adverse reactions	6255 (42.9)	13556 (92.3)	19811 (67.7)
95% CI	42.1, 43.7	91.8, 92.7	67.1, 68.2
Grade 1	4346 (29.8)	4847 (33.0)	9193 (31.4)
Grade 2	1558 (10.7)	5800 (39.5)	7358 (25.1)
Grade 3	348 (2.4)	2895 (19.7)	3243 (11.1)
Grade 4	3 (<0.1)	14 (<0.1)	17 (<0.1)
Grade 3 or above	351 (2.4)	2909 (19.8)	3260 (11.1)
Solicited local adverse reactions - N1	14577	14688	29265
Any solicited local adverse reactions	2757 (18.9)	13029 (88.7)	15786 (53.9)
95% CI	18.3, 19.6	88.2, 89.2	53.4, 54.5
Grade 1	2594 (17.8)	8789 (59.8)	11383 (38.9)
Grade 2	88 (0.6)	3217 (21.9)	3305 (11.3)
Grade 3	75 (0.5)	1023 (7.0)	1098 (3.8)
Grade 4	0	0	0
Grade 3 or above	75 (0.5)	1023 (7.0)	1098 (3.8)

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Pain - N1	14577	14688	29265
Any	2486 (17.1)	12964 (88.3)	15450 (52.8)
Grade 1	2384 (16.4)	9508 (64.7)	11892 (40.6)
Grade 2	61 (0.4)	2850 (19.4)	2911 (9.9)
Grade 3	41 (0.3)	606 (4.1)	647 (2.2)
Grade 4	0	0	0
Grade 3 or above	41 (0.3)	606 (4.1)	647 (2.2)
Erythema (redness) - N1	14577	14687	29264
Any	68 (0.5)	1274 (8.7)	1342 (4.6)
Grade 1	48 (0.3)	456 (3.1)	504 (1.7)
Grade 2	5 (<0.1)	531 (3.6)	536 (1.8)
Grade 3	15 (0.1)	287 (2.0)	302 (1.0)
Grade 4	0	0	0
Grade 3 or above	15 (0.1)	287 (2.0)	302 (1.0)
Swelling (hardness) - N1	14577	14687	29264
Any	60 (0.4)	1807 (12.3)	1867 (6.4)
Grade 1	38 (0.3)	900 (6.1)	938 (3.2)
Grade 2	10 (<0.1)	652 (4.4)	662 (2.3)
Grade 3	12 (<0.1)	255 (1.7)	267 (0.9)
Grade 4	0	0	0
Grade 3 or above	12 (<0.1)	255 (1.7)	267 (0.9)
Axillary swelling or tenderness - N1	14577	14687	29264
Any	571 (3.9)	2092 (14.2)	2663 (9.1)
Grade 1	523 (3.6)	1735 (11.8)	2258 (7.7)
Grade 2	28 (0.2)	289 (2.0)	317 (1.1)
Grade 3	20 (0.1)	68 (0.5)	88 (0.3)
Grade 4	0	0	0
Grade 3 or above	20 (0.1)	68 (0.5)	88 (0.3)
Solicited systemic adverse reactions - N1	14577	14690	29267
Any solicited systemic adverse reactions	5343 (36.7)	11678 (79.5)	17021 (58.2)
95% CI	35.9, 37.4	78.8, 80.1	57.6, 58.7
Grade 1	3519 (24.1)	3717 (25.3)	7236 (24.7)
Grade 2	1535 (10.5)	5611 (38.2)	7146 (24.4)
Grade 3	286 (2.0)	2336 (15.9)	2622 (9.0)
Grade 4	3 (<0.1)	14 (<0.1)	17 (<0.1)
Grade 3 or above	289 (2.0)	2350 (16.0)	2639 (9.0)

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Fever - N1	14573	14682	29255
Any	43 (0.3)	2276 (15.5)	2319 (7.9)
Grade 1	33 (0.2)	1363 (9.3)	1396 (4.8)
Grade 2	5 (<0.1)	697 (4.7)	702 (2.4)
Grade 3	2 (<0.1)	203 (1.4)	205 (0.7)
Grade 4	3 (<0.1)	13 (<0.1)	16 (<0.1)
Grade 3 or above	5 (<0.1)	216 (1.5)	221 (0.8)
Headache - N1	14575	14687	29262
Any	3427 (23.5)	8637 (58.8)	12064 (41.2)
Grade 1	2740 (18.8)	4815 (32.8)	7555 (25.8)
Grade 2	522 (3.6)	3156 (21.5)	3678 (12.6)
Grade 3	165 (1.1)	666 (4.5)	831 (2.8)
Grade 4	0	0	0
Grade 3 or above	165 (1.1)	666 (4.5)	831 (2.8)
Fatigue - N1	14575	14687	29262
Any	3418 (23.5)	9607 (65.4)	13025 (44.5)
Grade 1	2181 (15.0)	3431 (23.4)	5612 (19.2)
Grade 2	1129 (7.7)	4743 (32.3)	5872 (20.1)
Grade 3	108 (0.7)	1433 (9.8)	1541 (5.3)
Grade 4	0	0	0
Grade 3 or above	108 (0.7)	1433 (9.8)	1541 (5.3)
Myalgia - N1	14575	14687	29262
Any	1824 (12.5)	8529 (58.1)	10353 (35.4)
Grade 1	1307 (9.0)	3242 (22.1)	4549 (15.5)
Grade 2	465 (3.2)	3966 (27.0)	4431 (15.1)
Grade 3	52 (0.4)	1321 (9.0)	1373 (4.7)
Grade 4	0	0	0
Grade 3 or above	52 (0.4)	1321 (9.0)	1373 (4.7)
Arthralgia - N1	14575	14687	29262
Any	1579 (10.8)	6303 (42.9)	7882 (26.9)
Grade 1	1143 (7.8)	2809 (19.1)	3952 (13.5)
Grade 2	392 (2.7)	2719 (18.5)	3111 (10.6)
Grade 3	44 (0.3)	775 (5.3)	819 (2.8)
Grade 4	0	0	0
Grade 3 or above	44 (0.3)	775 (5.3)	819 (2.8)

Solicited Adverse Reaction Category Grade	Placebo (N=14578) n (%)	100 µg mRNA-1273 (N=14691) n (%)	Total (N=29269) n (%)
Nausea/vomiting - N1	14575	14687	29262
Any	941 (6.5)	2794 (19.0)	3735 (12.8)
Grade 1	761 (5.2)	2094 (14.3)	2855 (9.8)
Grade 2	169 (1.2)	678 (4.6)	847 (2.9)
Grade 3	11 (<0.1)	21 (0.1)	32 (0.1)
Grade 4	0	1 (<0.1)	1 (<0.1)
Grade 3 or above	11 (<0.1)	22 (0.1)	33 (0.1)
Chills - N1	14575	14687	29262
Any	813 (5.6)	6500 (44.3)	7313 (25.0)
Grade 1	629 (4.3)	2907 (19.8)	3536 (12.1)
Grade 2	167 (1.1)	3402 (23.2)	3569 (12.2)
Grade 3	17 (0.1)	191 (1.3)	208 (0.7)
Grade 4	0	0	0
Grade 3 or above	17 (0.1)	191 (1.3)	208 (0.7)

Abbreviations: CI = confidence intervals; N1 = number of exposed subjects who submitted any data for the event.
Any = Grade 1 or higher.
Percentages are based on the number of exposed subjects who submitted any data for the event (N1).
95% CI is calculated using the Clopper-Pearson method.
Severity grading for solicited adverse reactions is in Table 3.
Source: Study 301 Part A CSR (Table 14.3.1.1.1.2) (26 Mar 2021).

2.7.4.2.1.1.2 Onset and Duration of Solicited Adverse Reactions

2.7.4.2.1.1.2.1 Onset and Duration of Solicited Adverse Reactions Starting Within 7 Days

Onset of solicited local and systemic ARs was mostly within the first 2 days after either injection. Local ARs most commonly had onset within the first day after either injection (in the mRNA-1273 group, 42.3% of participants after the first injection [Study 301 Part A CSR Table 14.3.1.3.1.1] and 54.8% after the second [Study 301 Part A CSR Table 14.3.1.3.1.2]). This was largely driven by pain, which was the most commonly reported local AR. Systemic ARs most commonly had onset on Day 2 after the second injection (42.3% of participants in the mRNA-1273 group); after the first injection, onset was common on Day 1 (20.0%) and on Day 2 (18.4%). This was largely driven by fatigue and headache, which were the most commonly reported systemic ARs.

The duration of solicited ARs was calculated as the cumulative number of days that the solicited AR was reported, including the day of injection. The median duration of solicited local ARs ranged from 1 to 2 days in both the mRNA-1273 and placebo groups after the first injection

(Study 301 Part A CSR Table 14.3.1.4.1.1) and ranged from 2 to 3 days in the mRNA-1273 group and was 1 day for all local ARs in the placebo group after the second injection (Study 301 Part A CSR Table 14.3.1.4.1.2). In the mRNA-1273 group, with the exception of pain, the median duration of grade 3 solicited local ARs was longer after the second injection (Study 301 Part A CSR Table 14.3.1.4.4.1 and Study 301 Part A CSR Table 14.3.1.4.4.2).

The median duration of solicited systemic ARs ranged from 1 to 2 days in both the mRNA-1273 and placebo groups after the first injection (Study 301 Part A CSR Table 14.3.1.4.1.1) and after the second injection (Study 301 Part A CSR Table 14.3.1.4.1.2). In the mRNA-1273 group, the median duration of grade 3 nausea/vomiting was 1 day after the first injection and 3 days after the second injection; the duration of other solicited systemic ARs was similar after the first and second injections (Study 301 Part A CSR Table 14.3.1.4.4.1 and Table 14.3.1.4.4.2). Grade 4 solicited systemic ARs in both groups resolved within 7 days after injection (Study 301 Part A CSR Table 14.3.1.4.5.1 and Table 14.3.1.4.5.2).

2.7.4.2.1.1.2.2 Solicited Adverse Reactions Persisting Beyond 7 Days

Solicited local ARs that persisted beyond 7 days after the first injection were reported for 2.4% of participants in the mRNA-1273 group and 0.9% of participants in the placebo group and solicited systemic ARs that persisted beyond 7 days after the first injection were reported for 5.7% and 5.6% of participants, respectively (Study 301 Part A CSR Table 14.3.1.6.1.1). Findings were similar after the second injection (Study 301 Part A CSR Table 14.3.1.6.1.2).

Grade 3 persistent local ARs were reported for 22 participants (0.1%) in the mRNA-1273 group and 4 participants (< 0.1%) in the placebo group after the first injection; incidence was higher in the mRNA-1273 group (67 participants [0.5%]) after the second injection. In both groups, axillary swelling or tenderness and pain were the most commonly reported persistent local ARs; axillary swelling or tenderness was more common after the first injection and pain was more common after the second. No individual solicited local AR term appeared more likely than others to occur at grade 3 after either injection. Grade 3 persistent systemic ARs were reported for 97 participants in the mRNA-1273 group and 91 participants in the placebo group (0.6% each); incidence was higher in the mRNA-1273 group (231 participants [1.6%]) after the second injection. Fatigue and headache were the most commonly reported persistent systemic ARs after either injection in both groups. Persistent fever was reported in 4 participants in the mRNA-1273 group and 3 participants in the placebo group after the first injection and for 2 and 1 participant(s), respectively, after the second injection. No individual systemic AR term appeared more likely than others to occur at grade 3 after the first injection. After the second injection, fatigue was more commonly reported at grade 3 than other events (1.0% of participants

in the mRNA-1273 group and 0.4% of participants in the placebo group). No grade 4 persistent solicited ARs were reported after either injection.

2.7.4.2.1.1.2.3 Solicited Local Adverse Reactions Occurring on or After Day 8

Few participants (≤ 3.4%) in both groups had local ARs on or after Day 8 after either injection (Study 301 Part A CSR Table 14.3.1.21.1.4). For most participants in both groups who reported local ARs beyond Day 7 after either injection, the reaction had begun within the first 7 days after the injection and was still ongoing. A local AR that occurred within the first 7 days but restarted on Day 8 or later was reported for 83 participants (0.5%) in the mRNA-1273 group after the first injection and for 38 participants (0.3%) after the second injection.

In the mRNA-1273 group, the incidence of local AR with delayed onset (new AR started on Day 8 or later) was higher after the first injection (80 participants [0.5%]) than after the second injection (10 participants [< 0.1%]). The most common AR that was first reported on Day 8 or later was erythema, which was reported for 68 participants (0.4%) in the mRNA-1273 group after the first injection and 6 participants (< 0.1%) in the mRNA-1273 group after the second injection (Study 301 Part A CSR Table 14.3.1.21.1.4).

2.7.4.2.1.2 Medication Use for Solicited Adverse Reactions of Pain and Fever

To further characterize potential reactogenicity of mRNA-1273, analyses were performed for participant use of medications to prevent or treat pain or fever. This analysis was based on participant-recorded use in the eDiary, wherein participants entered responses in the eDiary to questions about use of medications to treat or prevent pain or fever.

After the first injection, the use of medication for pain or fever was reported for 22.0% of participants in the mRNA-1273 group and 13.2% of participants in the placebo group (Study 301 Part A CSR Table 14.1.5.5.1). After the second injection, the use of medication for pain or fever was higher in the mRNA-1273 group (53.5%) compared with after the first injection, while no notable difference was observed in the placebo group (10.9%) (Study 301 Part A CSR Table 14.1.5.5.2). For most participants, the medication was used to treat, rather than to prevent, pain or fever. In the mRNA-1273 group after both injections, the percentage of participants who reported use of medication for pain or fever was higher in the ≥ 18 to < 65 years age group than that observed in the ≥ 65 years age group, which is consistent with the higher observed rate of reporting solicited ARs in the younger age cohort.

2.7.4.2.1.3 Unsolicited Adverse Events

Summaries of unsolicited AEs are provided for the 28-day post-injection follow-up period and with follow-up for the entire duration of Part A (the randomized, blinded part of the study). Summaries for Part A include all data up to early unblinding, study discontinuation, the Part B PDV, or the data cutoff date (26 Mar 2021), whichever was earlier, and provide accumulated safety data through a median duration of 148 days (Section 2.7.4.1.2.2.1).

2.7.4.2.1.3.1 Overview of Unsolicited Adverse Events

During the 28-day follow-up period, the incidences of unsolicited TEAEs, severe TEAEs, and MAAEs regardless of relationship to the IP were generally similar in participants who received mRNA-1273 and those who received placebo (Table 13).

At least one TEAE that was assessed by the investigator to be treatment related was reported in 13.6% and 8.2% of participants in the mRNA-1273 and placebo groups, respectively, in the 28-day follow-up period. These events were generally not severe and only rarely warranted discontinuation of treatment: the percentages of participants who had severe TEAEs that were assessed as treatment related were 0.5% and 0.2%, respectively; and 20 (0.1%) and 14 (< 0.1%) participants, respectively, discontinued treatment in response to an event. Per protocol, solicited ARs were reported as treatment-related AEs if they started or were ongoing more than 7 days after the injection, were SAEs or MAAEs, or resulted in discontinuation of treatment or withdrawal from the study (Study 301 Part A CSR Section 3.7.4.1).

Per protocol (Study 301 Part A CSR Appendix 16.1.1 Protocol Section 8.3.6), TEAEs were collected to the end of the 28-day period, while SAEs, MAAEs, and TEAEs leading to study discontinuation were collected throughout follow-up in Part A and Part B. Incidence of SAEs and MAAEs regardless of causality remained balanced between the groups (Study 301 Part A CSR Table 14.3.1.7.1.3) with follow-up throughout Part A. The incidence of MAAEs assessed by the investigator as related to IP in Part A was similar in each group to that observed in the 28-day period after each injection.

At least one unsolicited TEAE with a fatal outcome was reported for 17 participants in the mRNA-1273 group in Study 301 Part A CSR Table 14.3.1.7.1.3; however, death is reported for 16 participants in the mRNA-1273 group in Study 301 Part A CSR Table 14.3.1.23.1. This is because 1 participant had a TEAE that began during Part A (before the PDV date and during the blinded portion) but had a fatal outcome that occurred during Part B (after unblinding at the PDV). The TEAE was first reported during Part A and its outcome is thus reported in Study 301

Part A CSR Table 14.3.1.7.1.3, while the death, which did not occur until Part B, is not captured in Study 301 Part A CSR Table 14.3.1.23.1.

Table 13 Study 301: Summary of Unsolicited Treatment-Emergent Adverse Events up to 28 Days After Any Injection (Safety Set)

	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Total (N=30346) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination			
All	4338 (28.6)	4752 (31.3)	9090 (30.0)
Serious	104 (0.7)	98 (0.6)	202 (0.7)
Fatal	2 (<0.1)	2 (<0.1)	4 (<0.1)
Medically-attended	1940 (12.8)	1819 (12.0)	3759 (12.4)
Leading to discontinuation from study vaccine	92 (0.6)	61 (0.4)	153 (0.5)
Leading to discontinuation from participation in the study	6 (<0.1)	9 (<0.1)	15 (<0.1)
Severe	233 (1.5)	258 (1.7)	491 (1.6)
Unsolicited TEAEs related to study vaccination			
All	1236 (8.2)	2067 (13.6)	3303 (10.9)
Serious	3 (<0.1)	8 (<0.1)	11 (<0.1)
Fatal	0	0	0
Medically-attended	95 (0.6)	198 (1.3)	293 (1.0)
Leading to discontinuation from study vaccine	14 (<0.1)	20 (0.1)	34 (0.1)
Leading to discontinuation from participation in the study	0	1 (<0.1)	1 (<0.1)
Severe	31 (0.2)	83 (0.5)	114 (0.4)

A treatment-emergent adverse event (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.

Percentages are based on the number of safety subjects.

Source: Study 301 Part A CSR Table 14.3.1.7.1.1 (26 Mar 2021).

2.7.4.2.1.3.2 Unsolicited Adverse Events by Preferred Term

The incidence of TEAEs was similar between the mRNA-1273 and placebo treatment groups in the 28-day follow-up period (31.3% and 28.6%, respectively; Table 13) and in the full Part A follow-up period (41.6% and 43.0%, respectively) (Study 301 Part A CSR Table 14.3.1.7.1.3). Severe unsolicited TEAEs are summarized in Section 2.7.4.2.1.3.3. Unsolicited TEAEs are

summarized by causality in Section 2.7.4.2.1.3.4. Unsolicited TEAEs with onset within 30 minutes of injection are summarized in Section 2.7.4.2.1.3.5.

The most commonly reported unsolicited TEAEs in the mRNA-1273 and placebo groups, respectively, were fatigue (5.0% vs. 4.4%) and headache (4.9% vs. 4.5%) during the 28-day follow-up period (Table 14) and during the Part A period (fatigue 5.8% vs. 5.3% and headache 6.0% vs. 5.8%) (Table 14.3.1.8.1.3).

Commonly reported AEs were generally consistent with the solicited symptoms captured for the evaluation of reactogenicity. During the 28-day follow-up period, unsolicited TEAEs that were reported for ≥ 1% of participants in the mRNA-1273 group and showed higher incidence compared with placebo were lymphadenopathy (1.7% vs. 0.8%), injection site pain (1.7% vs. 0.8%), and injection site erythema (1.0% vs. 0.3%). Other TEAEs that were reported for ≥ 1% of participants in the mRNA-1273 group and did not show higher incidence compared with the placebo group were arthralgia, myalgia, diarrhea, cough, nausea, oropharyngeal pain, nasal congestion, and hypertension (arthralgia, myalgia, and nausea were solicited systemic ARs and were only reported as TEAEs if they started on Day 8, or persisted after Day 7, after the most recent injection). Observations were similar with follow-up for the duration of Part A.

Events that were less commonly reported and had higher incidence in the mRNA-1273 group compared with the placebo group during the 28-day follow-up period included other varieties of injection site reactions and other events consistent with reactogenicity, such as injection site swelling, injection site pruritus, injection site lymphadenopathy, injection site induration, injection site macule, injection site urticaria, injection site rash, injection site papule, injection site warmth, pyrexia, and erythema (Study 301 Part A CSR Table 14.3.1.8.1.1).

Assessment of TEAE incidence for other unsolicited TEAEs that were less commonly reported and less likely to be associated with reactogenicity for clinically relevant differences between the mRNA-1273 and placebo groups was performed via calculation of relative risk ratios without adjustment for multiplicity. In addition, clinical relevance and plausibility was not predefined or taken into account, so results must be interpreted cautiously. Incidence was higher for some AE terms in the mRNA-1273 group and for others in the placebo group, and this variation is likely attributable to chance in most cases. Some events that had higher incidence in the placebo group, apparently by chance, are upper respiratory tract infection (82 participants [0.5%] in the mRNA-1273 group vs. 118 [0.8%] in the placebo group), basal cell carcinoma (10 [< 0.1%] vs. 16 [0.1%]), seasonal allergy (33 [0.2%] vs. 47 [0.3%]), migraine (15 [< 0.1%] vs. 24 [0.2%]), presyncope (6 [< 0.1%] vs. 14 [< 0.1%]), sinus congestion (16 [0.1%] vs. 26 [0.2%]), and abdominal discomfort (6 [< 0.1%] vs. 13 [< 0.1%]) (Study 301 Part A CSR Table 14.3.1.8.1.1).

Some events that had higher incidence in the mRNA-1273 group, apparently by chance, are type 2 diabetes mellitus (21 [0.1%] vs. 11 [< 0.1%]), anxiety (52 [0.3%] vs. 38 [0.3%]), respiratory tract congestion (18 [0.1%] vs. 7 [< 0.1%]), epistaxis (16 [0.1%] vs. 11 [< 0.1%]), gastroesophageal reflux disease (41 [0.3%] vs. 29 [0.2%]), and abdominal pain (26 [0.2%] vs. 20 [0.1%]) (Study 301 Part A CSR Table 14.3.1.8.1.1).

A review of pericarditis and myocarditis (including possible subclinical/unreported cases; there were no reports of myocarditis) is presented in Section 2.7.4.2.1.3.2.1; a review of events for which an apparent imbalance was observed or that otherwise appeared to warrant investigation is presented in Section 2.7.4.2.1.3.2.2; stroke and thrombotic events (SAEs) are described in Section 2.7.4.2.1.4.2; anaphylactic reactions are described in Section 2.7.4.2.1.4.6; SMQ summaries are described in Section 2.7.4.2.1.4.6.

2.7.4.2.1.3.2.1 Review of Pericarditis and Myocarditis

In Part A, no cases of myocarditis were reported. Four cases of pericarditis were reported in Part A: 2 cases in the mRNA-1273 group and 2 cases in the placebo group. The cases of pericarditis in the mRNA-1273 group occurred in (i) a 59-year old female who had nonserious chest pain, dyspnea, and fatigue on Day 4 after the second dose that resolved within 2 days and subsequently presented with chest pain and syncope 68 days after the second dose leading to hospitalization and a diagnosis of pericarditis and pericardial effusion, both of which resolved (the participant had received an influenza vaccination 1 month before the events) and (ii) a 65-year-old male hospitalized with a diagnosis of pericarditis 73 days after the second dose that resolved the following day and occurred 19 days after an SAE of myocardial infarction. These SAEs (including those in the placebo group) are described in Section 2.7.4.2.1.4.2. Pericarditis and myocarditis in Part B of the study are described in Section 2.7.4.2.2.2. Pericarditis and myocarditis in the post-authorization setting are described in Section 2.7.4.6.4.2.

Because myocarditis and pericarditis are typically rare events, Moderna assessed the clinical database for evidence of individual clinical symptoms that have been associated with these events. The blinded phase of Study 301 (Part A) was assessed for TEAEs potentially associated with myocarditis or pericarditis (Study 301 Part A CSR Section 7.2.2). The TEAE data were assessed for any events mapping to PTs in the Centers for Disease Control and Prevention (CDC) working case definition diagnostic algorithm for probable and confirmed acute myocarditis and pericarditis (Gargano et al 2021). Using this approach, TEAEs were identified for the following 7 PTs that map to the relevant clinical symptoms: angina pectoris, chest discomfort, chest pain, musculoskeletal chest pain, dyspnea, palpitations, and syncope.

The TEAE database (collected for the 28 days after any injection) was assessed for the identified PTs, and the assessment further narrowed for those TEAE occurring in temporal proximity to injection (within 7 days of any injection) based on the observed epidemiology of cases of myocarditis and pericarditis (Gargano et al 2021) characterized from post-authorization data. As part of the study, the collection of unsolicited TEAEs that are nonserious do not include narrative information but rather the verbatim entries regarding the event. All TEAEs were reviewed regardless of severity or causality (as per investigator). Finally, the listing of participants reporting any of these PTs within 7 days of any injection was cross-checked to identify any participants reporting more than 1 of the targeted PTs, reflecting constellations more suggestive of a possible diagnosis of myocarditis or pericarditis.

One participant reported more than one of the target PTs: a 71-year-old male in the mRNA-1273 group with relevant history of hyperlipidemia, hypertension, folate deficiency anemia, and constipation experienced 2 nonserious, mild, ongoing, and considered unrelated TEAEs on Days 2 and 4 after the second dose, respectively, of "intermittent heart palpitations with exercising" and "intermittent chest discomfort with exercising type unknown" (verbatim terms). Other potentially relevant TEAEs reported for this participant within 7 days of these events were unrelated nonserious TEAEs of "fatigue," "generalized body aches in morning," "upper body muscle weakness," and "runny nose" (verbatim terms).

In the 28-day TEAE collection window, numerical imbalances between the mRNA-1273 and placebo groups were observed for the PT chest pain (10 in the mRNA-1273 group and 5 in the placebo group; rate ratio 2.0 [95% CI: 0.71, 5.58]). Three of these chest pain events, all in the mRNA-1273 group, occurred within the 7-day window, one was considered related, and all resolved in 1 to 2 days. In the survey of the identified PTs in the 7-day window, imbalances in the reported PTs (from the list described above) were observed for the following events:

- Dyspnea: 15 in the mRNA-1273 group and 3 in the placebo group
- Syncope: 7 in the mRNA-1273 group and 3 in the placebo group

For the PT dyspnea, 5 of the 15 events in the mRNA-1273 group were considered related, and all 18 dyspnea events resolved. For completeness, in addition to these dyspnea TEAEs, 5 participants (all in the mRNA-1273 group) reported dyspnea as an SAE, none of which were considered related and all of which occurred in participants > 50 years of age (these SAEs are described in Section 2.7.4.2.1.4.2).

For the PT syncope, 1 of the 7 events in the mRNA-1273 group was considered related, and all events resolved on the same day they occurred. For 1 of the 7 participants in the mRNA-1273

group, the syncope was an SAE: this 46-year-old Hispanic male had a previous medical history of syncopal episodes, obesity, type 2 diabetes, and hypertension and was diagnosed with osteomyelitis during admission. The syncope event was considered not related to vaccine, and a transthoracic echocardiogram during admission showed normal cardiac function.

Overall, in this assessment of the targeted PTs, 1 participant manifested more than one of the identified PT within 7 days of any injection, and the events can reasonably be attributed to other comorbid conditions. For the imbalances observed for dyspnea and syncope in the 7-day window, most resolved quickly and did not cluster with other relevant TEAEs to suggest cases of myocarditis or pericarditis.

2.7.4.2.1.3.2.2 Review of Other Events

Investigation of events for which an apparent imbalance was observed or that were otherwise of interest did not suggest safety concerns with mRNA-1273, as described below (events discussed in order per MedDRA) (Study 301 Part A CSR Section 7.2.2):

- Herpes zoster was reported for 22 participants (0.1%) in the mRNA-1273 group and 15 participants (< 0.1%) in the placebo group in the 28-day follow-up period. The overall number of reported herpes zoster cases was observed to be higher in the mRNA-1273 group than the placebo group (50 participants [0.3%] vs. 23 participants [0.2%]). The preponderance of herpes zoster cases reported in the mRNA-1273 group occurred more than 28 days after any dose (28 participants [0.1%]), while in the placebo group the preponderance of events occurred within 28 days (15 participants [< 0.1%]). This lack of case clustering is reassuring with respect to association with mRNA-1273. In addition, assuming 6 months of follow-up per participant, the observed incidence of herpes zoster among participants > 50 years of age in the mRNA-1273 group (9.28 per 1000 person-years) was within the expected incidence rate in the general population (8.46 per 1000 person-years [Johnson et al 2015]; rate ratio 1.10; 95% CI [0.69, 1.74]), while the incidence among participants > 50 years of age in the placebo group (3.45 per 1000 person-years) was below the expected incidence (rate ratio 0.41; 95% CI [0.22, 0.76]).

- Lymphadenopathy was reported during the 28-day follow-up period for 264 participants (1.7%) in the mRNA-1273 group and 127 participants (0.8%) in the placebo group; injection site lymphadenopathy was reported for 66 (0.4%) and 15 (< 0.1%) participants, respectively (Study 301 Part A CSR Table 14.3.1.8.1.1; a few participants also had events that were coded as infusion site or vaccination site lymphadenopathy). Most of these

events were localized and ipsilateral and regional to the injection site, as anticipated given the mechanism of action for this vaccine. Most events resolved within 14 days after onset. The reported characteristics of most events did not suggest generalized lymphadenopathy (ie, involving lymph nodes from multiple distant regions).

- In the 28-day period, events of paresthesia, hyperesthesia, hypoesthesia, injection site paresthesia, injection site hypoesthesia, and dysesthesia were reported in the mRNA-1273 and placebo groups, respectively, as follows: paresthesia 34 (0.2%) vs. 27 (0.2%); hyperesthesia 6 (< 0.1%) vs. 0; hypoesthesia 13 (< 0.1%) vs. 9 (< 0.1%); injection site paresthesia 6 (< 0.1%) vs. 3 (< 0.1%); injection site hypoesthesia 3 (< 0.1%) vs. 1 (< 0.1%); and dysesthesia 0 vs. 3 (< 0.1%) (Study 301 Part A CSR Table 14.3.1.8.1.1). All events in the mRNA-1273 group were nonserious; one event in the placebo group was reported as an SAE. A severe event of injection site hypoesthesia was reported for 1 participant in the mRNA-1273 group with onset on Day 3 after the first dose that was considered related to treatment and resolved on Day 5. One participant in the mRNA-1273 group who experienced paresthesia did not receive the second dose (although the action taken with study vaccine was reported as “dose not changed”); the event was described as moderate “tingling in hands” that began on Day 3 after the first dose and resolved on Day 34 and was not considered related to treatment.

- Cervical radiculopathy was reported during the 28-day follow-up for 8 participants (< 0.1%) in the mRNA-1273 group and 1 participant (< 0.1%) in the placebo group (Study 301 Part A CSR Table 14.3.1.8.1.1). The events were mild to moderate in severity and with one exception none were considered to be related to the study vaccine. Potentially relevant medical history was reported for 4 of the mRNA-1273 participants and included cervical radiculopathy, cervical spinal stenosis, intervertebral disc degeneration; compressed cervical disc, cervical radiculopathy, spinal stenosis, and osteoarthritis of the neck and shoulders; cervical radiculopathy; and intervertebral disc protrusion (C4-C7). Over the duration of Part A, cervical radiculopathy was reported for 17 participants (0.1%) in the mRNA-1273 group and 2 participants (< 0.1%) in the placebo group (Study 301 Part A CSR Table 14.3.1.8.1.3).

- In the 28-day period, facial paralysis was reported for 2 participants (< 0.1%) in the mRNA-1273 group (verbatim terms of Bell’s palsy and left side face paralysis) and 1 participant (< 0.1%) in the placebo group (verbatim term of Bell’s palsy) (Study 301 Part A CSR Table 14.3.1.8.1.1). During Part A, facial paralysis was reported for 8 participants (< 0.1%) in the mRNA-1273 group and 3 participants (< 0.1%) in the placebo group (Study 301 Part A CSR Table 14.3.1.8.1.3). One Part A event in the

mRNA-1273 group was reported as left facial palsy (the participant had mild viral infection at the time). All other events in both groups were reported as Bell's palsy. In the mRNA-1273 group, 4 of the 6 Bell's palsy events were concurrent with a TEAE of infection, and one event (mild) was considered related to treatment. One event in the mRNA-1273 group was reported as an SAE (Section 2.7.4.2.1.4.2).

There were no reports of Guillain-Barre syndrome and no imbalance was observed between the groups in the SMQ analysis for demyelination (Study 301 Part A CSR Table 14.3.1.22.6).

- Vertigo or positional vertigo was reported during the 28-day follow-up period for 30 (0.2%) vs. 19 (0.1%) participants in the mRNA-1273 and placebo groups, respectively. Over the duration of Part A, vertigo or positional vertigo was reported for 54 participants (0.4%) in the mRNA-1273 group and for 40 participants (0.3%) in the placebo group. No imbalance was observed between the groups in the SMQ analysis for hearing and vestibular disorders (Study 301 Part A CSR Table 14.3.1.22.13).

- In the 28-day period, facial bone fracture was reported for 4 participants in the mRNA-1273 group (one event was an SAE in an 80-year-old participant) and no participants in the placebo group (Study 301 Part A CSR Table 14.3.1.8.1.1). Over the duration of Part A, facial bone fracture was reported for 8 participants in the mRNA-1273 group and 1 participant in the placebo group (Study 301 Part A CSR Table 14.3.1.8.1.3). In the mRNA-1273 group, the onset day of the event relative to the start of the study ranged from Day 14 to Day 144. All events resolved and were considered not related to study vaccine by the investigator. No imbalance was observed for fractures of any kind or for falls within 28 days or during Part A.

Table 14 **Study 301: Participant Incidence of Unsolicited Treatment-Emergent Adverse Events (at Least 1% in Any Treatment Group or Rate Ratio 95% Confidence Interval Does Not Include 1, Based on Preferred Term) by System Organ Class and Preferred Term Up to 28 Days After Any Injection (Safety Set)**

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Number of subjects reporting unsolicited adverse events	4338 (28.6)	4752 (31.3)		9090 (30.0)
Number of unsolicited adverse events	8599	9541		18140
Infections and infestations	952 (6.3)	783 (5.2)		1735 (5.7)
Upper respiratory tract infection	118 (0.8)	82 (0.5)	0.69 (0.52, 0.92)	200 (0.7)
COVID-19	156 (1.0)	22 (0.1)	0.14 (0.09, 0.22)	178 (0.6)
Cystitis	11 (<0.1)	3 (<0.1)	0.27 (0.08, 0.91)	14 (<0.1)
Tonsillitis	11 (<0.1)	2 (<0.1)	0.18 (0.05, 0.73)	13 (<0.1)
Blood and lymphatic system disorders	148 (1.0)	292 (1.9)		440 (1.4)
Lymphadenopathy	127 (0.8)	264 (1.7)	2.08 (1.68, 2.56)	391 (1.3)
Nervous system disorders	881 (5.8)	1008 (6.6)		1889 (6.2)
Headache	687 (4.5)	744 (4.9)	1.08 (0.98, 1.20)	1431 (4.7)
Sinus headache	6 (<0.1)	20 (0.1)	3.33 (1.38, 8.05)	26 (<0.1)
Cervical radiculopathy	1 (<0.1)	8 (<0.1)	7.99 (1.30, 49.20)	9 (<0.1)
Eye disorders	67 (0.4)	70 (0.5)		137 (0.5)
Eye irritation	1 (<0.1)	7 (<0.1)	6.99 (1.12, 43.54)	8 (<0.1)
Ear and labyrinth disorders	83 (0.5)	81 (0.5)		164 (0.5)
Vertigo positional	1 (<0.1)	7 (<0.1)	6.99 (1.12, 43.54)	8 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Vascular disorders	204 (1.3)	198 (1.3)		402 (1.3)
Hypertension	161 (1.1)	153 (1.0)	0.95 (0.76, 1.18)	314 (1.0)
Respiratory, thoracic and mediastinal disorders	667 (4.4)	603 (4.0)		1270 (4.2)
Cough	165 (1.1)	177 (1.2)	1.07 (0.87, 1.32)	342 (1.1)
Oropharyngeal pain	232 (1.5)	158 (1.0)	0.68 (0.56, 0.83)	390 (1.3)
Nasal congestion	165 (1.1)	155 (1.0)	0.94 (0.75, 1.17)	320 (1.1)
Rhinorrhoea	145 (1.0)	130 (0.9)	0.90 (0.71, 1.13)	275 (0.9)
Respiratory tract congestion	7 (<0.1)	18 (0.1)	2.57 (1.10, 5.99)	25 (<0.1)
Gastrointestinal disorders	567 (3.7)	599 (3.9)		1166 (3.8)
Diarrhoea	199 (1.3)	204 (1.3)	1.02 (0.84, 1.24)	403 (1.3)
Nausea	164 (1.1)	162 (1.1)	0.99 (0.80, 1.22)	326 (1.1)
Skin and subcutaneous tissue disorders	235 (1.5)	295 (1.9)		530 (1.7)
Erythema	5 (<0.1)	15 (<0.1)	3.00 (1.13, 7.93)	20 (<0.1)
Musculoskeletal and connective tissue disorders	1017 (6.7)	1007 (6.6)		2024 (6.7)
Arthralgia	389 (2.6)	391 (2.6)	1.00 (0.87, 1.15)	780 (2.6)
Myalgia	388 (2.6)	387 (2.5)	1.00 (0.87, 1.14)	775 (2.6)
General disorders and administration site conditions	1065 (7.0)	1606 (10.6)		2671 (8.8)
Fatigue	666 (4.4)	752 (5.0)	1.13 (1.02, 1.25)	1418 (4.7)
Injection site pain	118 (0.8)	258 (1.7)	2.18 (1.76, 2.71)	376 (1.2)
Injection site erythema	39 (0.3)	157 (1.0)	4.02 (2.84, 5.69)	196 (0.6)
Pyrexia	62 (0.4)	118 (0.8)	1.90 (1.40, 2.58)	180 (0.6)
Injection site swelling	29 (0.2)	115 (0.8)	3.96 (2.64, 5.93)	144 (0.5)
Injection site pruritus	13 (<0.1)	88 (0.6)	6.76 (3.81, 12.00)	101 (0.3)
Injection site lymphadenopathy	15 (<0.1)	66 (0.4)	4.39 (2.53, 7.64)	81 (0.3)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Injection site induration	18 (0.1)	53 (0.3)	2.94 (1.73, 4.99)	71 (0.2)
Injection site macule	4 (<0.1)	45 (0.3)	11.23 (4.21, 30.01)	49 (0.2)
Injection site urticaria	1 (<0.1)	38 (0.3)	37.94 (6.58, 218.91)	39 (0.1)
Injection site rash	1 (<0.1)	24 (0.2)	23.97 (4.11, 139.71)	25 (<0.1)
Injection site papule	1 (<0.1)	13 (<0.1)	12.98 (2.18, 77.49)	14 (<0.1)
Injection site warmth	1 (<0.1)	7 (<0.1)	6.99 (1.12, 43.54)	8 (<0.1)
Investigations	80 (0.5)	107 (0.7)		187 (0.6)
Blood pressure diastolic increased	2 (<0.1)	10 (<0.1)	4.99 (1.23, 20.26)	12 (<0.1)

A treatment-emergent adverse event (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.

Percentages are based on the number of safety subjects. The rate ratio is calculated as the ratio of percentage of participants reporting the event in mRNA-1273 divided by that in Placebo; rate ratio is provided for TEAEs with at least 7 subjects in any vaccination group reporting the event. The 95% CI is calculated using the Miettinen and Nurminen method.

MedDRA version 23.0.

Source: Study 301 Part A CSR Table 14.3.1.8.1.1 (26 Mar 2021).

2.7.4.2.1.3.3 Unsolicited Severe Adverse Events

The incidence of severe TEAEs was similar between the mRNA-1273 and placebo treatment groups in the 28-day follow-up period (1.7% and 1.5%, respectively; Study 301 Part A CSR Table 14.3.1.17.1.1). Hypertension was reported as severe for 28 and 34 participants, respectively (0.2% in each group); no other event was reported as severe for > 0.1% of participants in either group. Events that were reported as severe for more participants in the mRNA-1273 group than in the placebo group, respectively, were fatigue (20 vs. 9), headache (14 vs. 11), myalgia (9 vs. 4), and blood pressure increased (10 vs. 6). All except the last were among the solicited systemic ARs, which were reported as TEAEs if they persisted beyond Day 7 after any injection (in which case they are counted both with solicited ARs and with unsolicited TEAEs) or started on Day 8 or later after any injection.

The incidence of severe TEAEs assessed by the investigator as related to IP was higher in the mRNA-1273 group compared with the placebo group in the 28-day follow-up period (0.5% and 0.2%, respectively; Study 301 Part A CSR Table 14.3.1.18.1.1). Events that were reported as severe and assessed by the investigator to be treatment-related for more participants in the mRNA-1273 group than in the placebo group, respectively, were fatigue (16 vs. 6) and myalgia (8 vs. 2), both of which were among the solicited systemic ARs.

2.7.4.2.1.3.4 Treatment-Related Unsolicited Adverse Events

More participants in the mRNA-1273 group (13.6%) than in the placebo group (8.2%) had unsolicited TEAEs during the 28-day follow-up that were assessed by the investigator as related to IP (Study 301 Part A CSR Table 14.3.1.11.1.1). Most of the imbalance is in events that were also solicited ARs (injection site events, headache, nausea, vomiting, pyrexia, chills) or similar to ARs (lymphadenopathy, neck pain, back pain, and musculoskeletal pain). Imbalances were also observed for less common events including diarrhea (44 vs. 32), nasal congestion (21 vs. 9), dizziness (28 vs. 13), urticaria (22 vs. 7), paresthesia (14 vs. 9), rhinorrhea (13 vs. 8), cough (13 vs. 5), rash (11 vs. 3), erythema (9 vs. 0) and insomnia (7 vs. 1).

2.7.4.2.1.3.5 Unsolicited Adverse Events Occurring Within 30 Minutes of Injection

Participants were to remain in the clinic for 15 minutes (or 30 minutes if they had a history of allergies) after each injection for observation in order to identify and address any case of anaphylaxis. No anaphylaxis was reported within 30 minutes after any injection (Study 301 Part A CSR Table 14.3.1.19.6.3). The incidence of TEAEs, severe TEAEs, and MAAEs occurring within 30 minutes after any injection, regardless of relationship to the IP, was similar

in participants who received mRNA-1273 (0.8%) and those who received placebo (0.7%) (Table 15). Few of the events were MAAEs and/or severe, none were considered SAEs, and none led to discontinuation from the study or study vaccine in the mRNA-1273 group.

At least one unsolicited TEAE that occurred within 30 minutes after the first injection was reported for 74 participants (0.5%) and 68 participants (0.4%) in the mRNA-1273 and placebo groups, respectively (Study 301 Part A CSR Table 14.3.1.19.5.1). Fewer participants experienced such events after the second injection (47 [0.3%] vs. 41 [0.3%]) (Study 301 Part A CSR Table 14.3.1.19.5.2). All reported event terms were consistent with expected physiological reactions to injections. Events assessed by the investigator to be treatment-related were reported for 28 participants (0.2%) and 24 participants (0.2%) after the first injection and 23 participants (0.2%) and 21 participants (0.1%) after the second injection. The most commonly reported events after the first injection were hypertension (13 vs. 15 participants) and tachypnea (13 vs. 16 participants) (Study 301 Part A CSR Table 14.3.1.19.6.1); after the second injection they were hypertension (6 vs. 8 participants) and dizziness (6 vs. 4 participants) (Study 301 Part A CSR Table 14.3.1.19.6.2). Events that were considered severe were reported for 4 participants in the mRNA-1273 group and 8 participants in the placebo group after the first injection and 4 and 3 participants, respectively, after the second injection. No imbalances between the groups were apparent, and no participant had a severe TEAE within 30 minutes after both injections. Only 2 events in the placebo group led to discontinuation from study vaccine; no such events were reported in the mRNA-1273 group.

Table 15 Study 301: Summary of Immediate Unsolicited Adverse Events Occurring Within 30 Minutes of Any Vaccination (Safety Set)

	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30346) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination			
All	105 (0.7)	118 (0.8)	223 (0.7)
Serious	0	0	0
Fatal	0	0	0
Medically-attended	14 (<0.1)	10 (<0.1)	24 (<0.1)
Leading to discontinuation from study vaccine	2 (<0.1)	0	2 (<0.1)
Leading to discontinuation from participation in the study	0	0	0
Severe	11 (<0.1)	8 (<0.1)	19 (<0.1)

	Placebo (N=15162) n (%)	mRNA-1273 (N=15184) n (%)	Total (N=30346) n (%)
Unsolicited TEAEs related to study vaccination			
All	44 (0.3)	50 (0.3)	94 (0.3)
Serious	0	0	0
Fatal	0	0	0
Medically-attended	5 (<0.1)	2 (<0.1)	7 (<0.1)
Leading to discontinuation from study vaccine	0	0	0
Leading to discontinuation from participation in the study	0	0	0
Severe	1 (<0.1)	2 (<0.1)	3 (<0.1)

A treatment-emergent adverse event (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.

N = Number of participants in Safety Set who received any injection

n = Number of participants who reported AEs in specified category

Source: Study 301 Part A CSR Table 14.3.1.19.5.3 (26 Mar 2021).

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

2.7.4.2.1.4.1 Deaths

A total of 32 deaths were reported in Part A, including 16 participants (0.1%) in each group (Table 16). Note that the table does not include the death of one additional participant in the mRNA-1273 group. This individual had a TEAE that was first identified during Part A of the study. The individual died due to the event during Part B [Section 2.7.4.2.1.3.1]). No trends were apparent in the timing of deaths relative to dosing or in the causes of death (Table 17). Baseline age was ≥ 65 years for 9 of the participants in the mRNA-1273 group and 6 participants in the placebo group (Study 301 Part A CSR Listing 16.2.7.14). None of the unsolicited TEAEs leading to death were considered to be related to the IP.

COVID-19 was reported as the event leading to death for 1 participant in the mRNA-1273 group and 3 participants in the placebo group. The participant in the mRNA-1273 group was 74 years old and received dose 1 but declined to receive a second dose. No TEAEs were reported as leading to discontinuation of vaccine, but the participant is noted as having “refused second injection due to side effects … consented to continue study visits” (Study 301 Part A CSR Listing 16.2.1.1). Reported TEAEs for the participant that occurred within 8 days of Day 1 were severe nausea and severe fatigue that were considered related to treatment. On Day 120, 119 days after the first dose, the participant began to experience symptoms of COVID-19. On

Day 127, the participant tested positive for SARS-CoV-2 via reverse transcriptase polymerase chain reaction (RT-PCR). The event of COVID-19 lasted for 56 days and the participant died on Day 175. This participant was not included in the Per Protocol Set due to receipt of an incomplete vaccination regimen.

Table 16 Study 301: Summary of Death in Part A (Safety Set)

	Placebo (N=15162)	mRNA-1273 (N=15184)	Total (N=30346)
Number of deaths, n (%)	16 (0.1)	16 (0.1)	32 (0.1)
From randomization up to 14 days after first injection	2	0	2
>=14 up to 21 days after first injection	0	2	2
>=21 days after first injection up to second injection	1	2	3
From second injection up to 7 days after second injection	0	0	0
>=7 up to 14 days after second injection	0	0	0
>=14 up to 28 days after second injection	0	0	0
>=28 up to 56 days after second injection	2	2	4
>=56 up to 84 days after second injection	2	4	6
>=84 up to 112 days after second injection	6	3	9
>=112 days after second injection	3	3	6

Percentages are based on the number of subjects in Safety Set.

Source: Study 301 Part A CSR Table 14.3.1.23.1 (26 Mar 2021).

Table 17 Study 301: Participants With Serious Adverse Events Resulting in Death (Safety Set)

Treatment Assignment	Preferred Term	Study Day of Death	Relationship to IP[a]
mRNA-1273	Cardiac failure congestive	145	Not related
mRNA-1273	Cardiac arrest	89	Not related
mRNA-1273	Myocardial infarction	58	Not related
mRNA-1273	Cardio-respiratory arrest	21	Not related
mRNA-1273	Hepatocellular carcinoma	107	Not related
mRNA-1273	COVID-19	175	Not related
mRNA-1273	Myocardial infarction	45	Not related
mRNA-1273	Pulmonary mass[b]	136	Not related
mRNA-1273	Cardio-respiratory arrest	155	Not related
mRNA-1273	Completed suicide	21	Not related
mRNA-1273	Death	70	Not related

Treatment Assignment	Preferred Term	Study Day of Death	Relationship to IP[a]
mRNA-1273	Gastrointestinal haemorrhage, multiple organ dysfunction syndrome, acute respiratory failure	60	Not related
mRNA-1273	Death	138	Not related
mRNA-1273	Death	54	Not related
mRNA-1273	Head injury	37	Not related
mRNA-1273	Death	110	Not related
mRNA-1273	Coronary artery disease, diabetic complication	71	Not related
Placebo	COVID-19	64	Not related
Placebo	Gastric perforation	13	Not related
Placebo	Pancreatic carcinoma stage IV	145	Not related
Placebo	Amyotrophic lateral sclerosis	86	Not related
Placebo	Myocardial infarction	29	Not related
Placebo	Myocardial infarction	103	Not related
Placebo	Myocardial infarction	47	Not related
Placebo	Cardio-pulmonary arrest	7	Not related
Placebo	Death	120	Not related
Placebo	Systemic inflammatory response syndrome	38	Not related
Placebo	COVID-19	143	Not related
Placebo	Completed suicide	87	Not related
Placebo	Myocardial infarction	86	Not related
Placebo	Death	64	Not related
Placebo	Seizure	97	Not related
Placebo	COVID-19	109	Not related

Abbreviations: COVID-19 = coronavirus disease 2019; IP = investigational product

[a] Relationship is based on investigator assessment.

[b] This participant is not counted in Table 16 because the event began during Part A but the fatal outcome occurred during Part B (Section 2.7.4.2.1.3.1).

Source: Study 301 Part A CSR Listing 16.2.7.14 (26 Mar 2021).

2.7.4.2.1.4.2 Other Serious Adverse Events

No difference was observed between the groups in the rates of reported SAEs during Part A (1.8% in the mRNA-1273 group [401 events] and 1.9% in the placebo group [439 events]) (Table 18). COVID-19 was reported as a serious TEAE for 2 (< 0.1%) participants in the mRNA-1273 group and for 40 (0.3%) participants in the placebo group. No other event was reported as an SAE in ≥ 0.1% of participants in either group. The only event for which the 95% CI for the relative risk ratio between the mRNA-1273 and placebo groups excluded 1 was chronic obstructive pulmonary disease, which was reported for 1 participant in the mRNA-1273 group and 8 participants in the placebo group (< 0.1% in each group).

At least 1 SAE that was considered related to treatment was reported for 12 participants (< 0.1%) in the mRNA-1273 group and 4 participants (< 0.1%) in the placebo group (Table 19). Swelling of the face was reported as a treatment-related SAE for 2 participants in the mRNA-1273 group and 1 participant in the placebo group (described below); no other event was reported as treatment-related for more than 1 participant in either group or overall. The other SAEs that were reported as treatment-related during Part A were B-cell small lymphocytic lymphoma, Basedow's disease, autonomic nervous system imbalance, cerebrovascular accident, multiple sclerosis, swelling of the face, nausea and vomiting, alopecia areata, angioedema, rheumatoid arthritis, and pericardial effusion and pericarditis and pleural effusion (described below) in the mRNA-1273 group and polymyalgia rheumatica; acute myocardial infarction, hypomagnesemia, acute kidney injury, and atrial fibrillation, organizing pneumonia, and respiratory failure (single participant); swelling of the face, immunization anxiety related reaction, feeling hot, and paresthesia (single participant); and procedural hemorrhage in the placebo group. The incidence of SAEs within the 28-day follow-up period was similarly balanced (0.6% in the mRNA-1273 group [140 events] and 0.7% in the placebo group [147 events]) (Study 301 Part A CSR Table 14.3.1.13.1.1).

During Part A, there were no reports of idiopathic thrombocytopenic purpura or thrombosis with thrombocytopenia (the few cases of thrombocytopenia did not occur in connection with thrombosis events) and there were no reports of cerebral venous sinus thrombosis or dural venous thrombosis. Investigation of SAEs for which an apparent imbalance was observed or that were otherwise of interest did not suggest a safety concern with mRNA-1273, as follows (Study 301 Part A CSR Section 7.3.2):

- **Dyspnea** was reported as an SAE for 5 participants in the mRNA-1273 group and 0 participants in the placebo group. The events were not considered related to treatment. All participants were ≥ 52 years of age at study entry and their baseline body mass index was ≥ 30.0 kg/m^2. None of the events were consistent with possible myocarditis or pericarditis (as discussed in detail in Section 2.7.4.2.1.3.2.1); the events occurred 13 days after the first dose and 35, 81, 88, and 137 days after the second dose; and 4 of the 5 participants had pre-existing cardiac disease.

- **Pericarditis** was reported as an SAE for 2 participants in the mRNA-1273 group (1 each male and female) and 2 in the placebo group (1 each male and female). Another participant in the placebo group had an SAE of pericardial effusion. No cases of myocarditis were reported in either group. The results of an evaluation of all TEAE data to look for possible subclinical cases of pericarditis or myocarditis are described in Section 2.7.4.2.1.3.2.1. The pericarditis events in the mRNA-1273 group were as follows:

- Grade 4 pericarditis occurred on Day 73 after the second injection in a 65-year-old male who did not have a prior history of cardiac disease but had experienced an SAE of myocardial infarction on Days 54 to 57 after the second dose and had undergone cardiac catheterization and stent placement. The pericarditis event resolved on the following day and was not considered to be related to the vaccine.

- Moderate pericarditis and grade 4 pericardial effusion occurred on Day 68 after the second injection (grade 4 pleural effusion began on the following day) in a 59-year-old female who had history of enlarged descending aorta and thoracic aorta ectasia and had experienced a sinus infection and received an influenza vaccination 1 month before the events. The events resolved on Day 166 after the second dose and were considered by the investigator to be related to study vaccine. The participant had visited an emergency department with shortness of breath and chest pain on Day 5 after the second dose (grade 4 chest pain and moderate fatigue were reported as TEAEs).

- **Stroke and thrombotic events**: Cerebrovascular accident, stroke, or transient ischemic attack were reported for 10 participants in the mRNA-1273 group and 7 participants in the placebo group. Event onset occurred within 28 days after the last dose for 3 participants in the mRNA-1273 group and 2 participants in the placebo group and more than 28 days after the last dose for 7 and 5 participants in the mRNA-1273 and placebo groups, respectively. One event of cerebrovascular accident was considered by the investigator to be related to study treatment; the event occurred on Day 67 after the first dose of mRNA-1273 (resolved on Day 82) in a 34-year-old female participant who had a patent foramen ovale and had previously experienced nonserious mild COVID-19 (the participant had only received 1 dose of the vaccine). Imaging showed acute left posterior inferior cerebellar artery territory infarct mass effect on the fourth ventricle. The locations of other cases, where specified, included the right occipital lobe, the left frontal lobe (subcortical white matter), the left middle cerebral artery, the right frontoparietal lobe, the left hemisphere (multiple locations not further specified), and the right paramedian pontine region. No cases were reported to be associated with thrombocytopenia. The age and sex distribution of the participants with these SAEs was similar between the groups, and all participants in both groups had at least one relevant risk factor for the event; these included previous stroke, hypertension, hypercholesterolemia, type 2 diabetes, heart failure, and congenital heart disease. The apparent imbalance in the summary produced for the CNS vascular disorders SMQ is due to the inclusion of subarachnoid hemorrhage and subdural hematoma that were associated with traumata (Section 2.7.4.2.1.4.6).

- Deep vein thrombosis was reported as an SAE for 4 and 1 participant(s) in the mRNA-1273 and placebo groups, respectively. The event was reported as a TEAE (regardless of seriousness) for 8 and 6 participants, and no imbalance was observed in the SMQ for embolic and thrombotic events (Study 301 Part A CSR Table 14.3.1.22.12). The SAEs in the mRNA-1273 group occurred in participants 55 years of age or older who had potentially relevant medical history (varicose veins and peroneal nerve paralysis; alpha thalassemia; hyperlipidemia; thrombophilia, thrombus, obesity, and multiple pulmonary embolisms). The events occurred at least 41 days after the most recent vaccination and were not considered related to treatment.

- Swelling of the face was reported as an SAE (and considered related to treatment) for 2 participants in the mRNA-1273 group who had reported history of dermal filler use and for 1 participant in the placebo group who did not. None of the other TEAEs within the CMQ for dermal filler reaction post vaccination were reported as SAEs, and incidence of the events did not appear to be imbalanced between the groups (Study 301 Part A CSR Section 7.3.3.3.2 [Table 14.3.1.22.11]). Nonserious swelling of the face was reported as a TEAE for 3 participants in each group in the 28-day follow-up period and for 6 participants in the mRNA-1273 group and 4 participants in the placebo group over the duration of Part A (Study 301 Part A CSR Table 14.3.1.8.1.1 and Table 14.3.1.8.1.3).

- Facial paralysis (Bell's palsy) was reported as an SAE (not considered related to treatment) for 1 participant in the mRNA-1273 group whose medical history included cerebrovascular accident, hypertension, and type 2 diabetes mellitus. The event occurred on Day 32 after the second dose and the participant had received an influenza vaccine approximately 2 weeks before the event.

  There were no reports of Guillain-Barre syndrome and no imbalance was observed in the SMQ for demyelination (Study 301 Part A CSR Table 14.3.1.22.6).

Ongoing safety monitoring includes reporting of suspected unexpected serious adverse reactions (SUSARs) to allow timely action in study conduct if concerns arise. Expectedness is determined by the list of expected events in the Investigator Brochure at the time the SAE is reported. As of the data cutoff date, SUSARs have been reported for 6 participants in Study 301 Part A. The reported SUSARs (categorized by system organ class [SOC]) were facial swelling (2 participants; general disorders and administration site conditions); pericarditis, pericardial effusion, and atrial flutter (1 participant; cardiac disorders [pleural effusion was also reported]), rheumatoid arthritis (musculoskeletal and connective tissue disorders), angioedema (skin and

subcutaneous tissue disorders), and nausea/vomiting (gastrointestinal disorders). No changes in study conduct have been required as a result of reported SUSARs.

Table 18 Study 301: Reported Incidence of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Throughout the Entire Duration of Part A (Safety Set)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Number of subjects reporting unsolicited adverse events	292 (1.9)	268 (1.8)		560 (1.8)
Number of unsolicited adverse events	439	401		840
Infections and infestations	77 (0.5)	48 (0.3)		125 (0.4)
Pneumonia	11 (<0.1)	9 (<0.1)	0.82 (0.35, 1.92)	20 (<0.1)
Appendicitis	5 (<0.1)	4 (<0.1)		9 (<0.1)
Sepsis	3 (<0.1)	4 (<0.1)		7 (<0.1)
Cellulitis	0	3 (<0.1)		3 (<0.1)
Bronchitis	0	2 (<0.1)		2 (<0.1)
COVID-19	40 (0.3)	2 (<0.1)	0.05 (0.01, 0.19)	42 (0.1)
Peritonitis	0	2 (<0.1)		2 (<0.1)
Postoperative abscess	0	2 (<0.1)		2 (<0.1)
Urosepsis	0	2 (<0.1)		2 (<0.1)
Abscess limb	0	1 (<0.1)		1 (<0.1)
Appendicitis perforated	1 (<0.1)	1 (<0.1)		2 (<0.1)
Clostridium difficile infection	0	1 (<0.1)		1 (<0.1)
Diabetic foot infection	0	1 (<0.1)		1 (<0.1)
Diverticulitis	3 (<0.1)	1 (<0.1)		4 (<0.1)
Gastroenteritis viral	0	1 (<0.1)		1 (<0.1)
Giardiasis	0	1 (<0.1)		1 (<0.1)
Hepatitis A	0	1 (<0.1)		1 (<0.1)
Liver abscess	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Lung abscess	0	1 (<0.1)		1 (<0.1)
Pneumonia mycoplasmal	0	1 (<0.1)		1 (<0.1)
Pneumonia staphylococcal	0	1 (<0.1)		1 (<0.1)
Post procedural infection	0	1 (<0.1)		1 (<0.1)
Postoperative wound infection	0	1 (<0.1)		1 (<0.1)
Pyelonephritis acute	1 (<0.1)	1 (<0.1)		2 (<0.1)
Salpingitis	0	1 (<0.1)		1 (<0.1)
Septic shock	3 (<0.1)	1 (<0.1)		4 (<0.1)
Spinal cord abscess	0	1 (<0.1)		1 (<0.1)
Toxic shock syndrome	0	1 (<0.1)		1 (<0.1)
Upper respiratory tract infection	0	1 (<0.1)		1 (<0.1)
Urinary tract infection	5 (<0.1)	1 (<0.1)		6 (<0.1)
Viral infection	0	1 (<0.1)		1 (<0.1)
Viral pharyngitis	0	1 (<0.1)		1 (<0.1)
Wound infection	0	1 (<0.1)		1 (<0.1)
COVID-19 pneumonia	8 (<0.1)	0		8 (<0.1)
Clostridium difficile colitis	1 (<0.1)	0		1 (<0.1)
Coccidioidomycosis	1 (<0.1)	0		1 (<0.1)
Enterococcal bacteraemia	1 (<0.1)	0		1 (<0.1)
Localised infection	1 (<0.1)	0		1 (<0.1)
Meningitis aseptic	1 (<0.1)	0		1 (<0.1)
Osteomyelitis	1 (<0.1)	0		1 (<0.1)
Perirectal abscess	1 (<0.1)	0		1 (<0.1)
Pharyngitis streptococcal	1 (<0.1)	0		1 (<0.1)
Pneumonia bacterial	1 (<0.1)	0		1 (<0.1)
Pneumonia klebsiella	1 (<0.1)	0		1 (<0.1)
Pyelonephritis	2 (<0.1)	0		2 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Streptococcal sepsis	1 (<0.1)	0		1 (<0.1)
Tooth abscess	1 (<0.1)	0		1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (0.2)	27 (0.2)		51 (0.2)
Prostate cancer	4 (<0.1)	5 (<0.1)		9 (<0.1)
Hepatocellular carcinoma	0	2 (<0.1)		2 (<0.1)
B-cell small lymphocytic lymphoma	0	1 (<0.1)		1 (<0.1)
Benign lung neoplasm	0	1 (<0.1)		1 (<0.1)
Cancer pain	0	1 (<0.1)		1 (<0.1)
Clear cell renal cell carcinoma	1 (<0.1)	1 (<0.1)		2 (<0.1)
Colorectal cancer	0	1 (<0.1)		1 (<0.1)
Gastric cancer	0	1 (<0.1)		1 (<0.1)
Gastrointestinal stromal tumour	0	1 (<0.1)		1 (<0.1)
Invasive lobular breast carcinoma	0	1 (<0.1)		1 (<0.1)
Liposarcoma	0	1 (<0.1)		1 (<0.1)
Malignant melanoma	0	1 (<0.1)		1 (<0.1)
Meningioma	0	1 (<0.1)		1 (<0.1)
Metastases to bone	0	1 (<0.1)		1 (<0.1)
Metastases to lung	0	1 (<0.1)		1 (<0.1)
Metastatic neoplasm	0	1 (<0.1)		1 (<0.1)
Non-Hodgkin's lymphoma	0	1 (<0.1)		1 (<0.1)
Oesophageal carcinoma	0	1 (<0.1)		1 (<0.1)
Papillary thyroid cancer	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pelvic neoplasm	0	1 (<0.1)		1 (<0.1)
Plasma cell myeloma	0	1 (<0.1)		1 (<0.1)
Renal cell carcinoma	1 (<0.1)	1 (<0.1)		2 (<0.1)
Splenic marginal zone lymphoma	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Throat cancer	0	1 (<0.1)		1 (<0.1)
Thymoma malignant	0	1 (<0.1)		1 (<0.1)
Thyroid cancer metastatic	0	1 (<0.1)		1 (<0.1)
Adenocarcinoma gastric	1 (<0.1)	0		1 (<0.1)
Breast cancer stage I	1 (<0.1)	0		1 (<0.1)
Colon cancer stage III	1 (<0.1)	0		1 (<0.1)
Endometrial cancer	3 (<0.1)	0		3 (<0.1)
Intraductal proliferative breast lesion	3 (<0.1)	0		3 (<0.1)
Invasive ductal breast carcinoma	1 (<0.1)	0		1 (<0.1)
Leiomyosarcoma metastatic	1 (<0.1)	0		1 (<0.1)
Lung adenocarcinoma	1 (<0.1)	0		1 (<0.1)
Non-small cell lung cancer	1 (<0.1)	0		1 (<0.1)
Pancreatic carcinoma stage IV	1 (<0.1)	0		1 (<0.1)
Prostate cancer metastatic	1 (<0.1)	0		1 (<0.1)
Thyroid cancer	1 (<0.1)	0		1 (<0.1)
Uterine leiomyoma	1 (<0.1)	0		1 (<0.1)
Blood and lymphatic system disorders	7 (<0.1)	3 (<0.1)		10 (<0.1)
Anaemia	2 (<0.1)	2 (<0.1)		4 (<0.1)
Blood loss anaemia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Thrombocytopenia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Anaemia macrocytic	1 (<0.1)	0		1 (<0.1)
Iron deficiency anaemia	1 (<0.1)	0		1 (<0.1)
Thrombocytosis	1 (<0.1)	0		1 (<0.1)
Immune system disorders	2 (<0.1)	0		2 (<0.1)
Anaphylactic reaction	1 (<0.1)	0		1 (<0.1)
Cytokine storm	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Endocrine disorders	0	1 (<0.1)		1 (<0.1)
Basedow's disease	0	1 (<0.1)		1 (<0.1)
Metabolism and nutrition disorders	15 (<0.1)	17 (0.1)		32 (0.1)
Dehydration	4 (<0.1)	4 (<0.1)		8 (<0.1)
Diabetic ketoacidosis	3 (<0.1)	3 (<0.1)		6 (<0.1)
Hyponatraemia	1 (<0.1)	3 (<0.1)		4 (<0.1)
Hypoglycaemia	1 (<0.1)	2 (<0.1)		3 (<0.1)
Type 2 diabetes mellitus	1 (<0.1)	2 (<0.1)		3 (<0.1)
Diabetic complication	0	1 (<0.1)		1 (<0.1)
Failure to thrive	0	1 (<0.1)		1 (<0.1)
Gout	1 (<0.1)	1 (<0.1)		2 (<0.1)
Hyperkalaemia	0	1 (<0.1)		1 (<0.1)
Hypokalaemia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Obesity	0	1 (<0.1)		1 (<0.1)
Diabetes mellitus	1 (<0.1)	0		1 (<0.1)
Diabetes mellitus inadequate control	1 (<0.1)	0		1 (<0.1)
Hypomagnesaemia	1 (<0.1)	0		1 (<0.1)
Metabolic acidosis	1 (<0.1)	0		1 (<0.1)
Psychiatric disorders	13 (<0.1)	13 (<0.1)		26 (<0.1)
Depression	2 (<0.1)	3 (<0.1)		5 (<0.1)
Alcohol withdrawal syndrome	1 (<0.1)	2 (<0.1)		3 (<0.1)
Alcohol abuse	0	1 (<0.1)		1 (<0.1)
Completed suicide	1 (<0.1)	1 (<0.1)		2 (<0.1)
Drug abuse	0	1 (<0.1)		1 (<0.1)
Intentional self-injury	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Mental status changes	1 (<0.1)	1 (<0.1)		2 (<0.1)
Schizoaffective disorder	1 (<0.1)	1 (<0.1)		2 (<0.1)
Substance-induced mood disorder	0	1 (<0.1)		1 (<0.1)
Substance-induced psychotic disorder	0	1 (<0.1)		1 (<0.1)
Suicidal ideation	0	1 (<0.1)		1 (<0.1)
Suicide attempt	0	1 (<0.1)		1 (<0.1)
Alcoholism	1 (<0.1)	0		1 (<0.1)
Anxiety	1 (<0.1)	0		1 (<0.1)
Anxiety disorder	1 (<0.1)	0		1 (<0.1)
Confusional state	1 (<0.1)	0		1 (<0.1)
Depression suicidal	1 (<0.1)	0		1 (<0.1)
Major depression	2 (<0.1)	0		2 (<0.1)
Mania	1 (<0.1)	0		1 (<0.1)
Schizophrenia	1 (<0.1)	0		1 (<0.1)
Nervous system disorders	27 (0.2)	31 (0.2)		58 (0.2)
Cerebrovascular accident	4 (<0.1)	6 (<0.1)		10 (<0.1)
Syncope	7 (<0.1)	5 (<0.1)	0.71 (0.24, 2.13)	12 (<0.1)
Seizure	1 (<0.1)	3 (<0.1)		4 (<0.1)
Subarachnoid haemorrhage	0	3 (<0.1)		3 (<0.1)
Embolic stroke	0	2 (<0.1)		2 (<0.1)
Transient ischaemic attack	2 (<0.1)	2 (<0.1)		4 (<0.1)
Aphasia	0	1 (<0.1)		1 (<0.1)
Autonomic nervous system imbalance	0	1 (<0.1)		1 (<0.1)
Carotid artery stenosis	0	1 (<0.1)		1 (<0.1)
Carotid artery thrombosis	0	1 (<0.1)		1 (<0.1)
Cauda equina syndrome	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Cervical radiculopathy	0	1 (<0.1)		1 (<0.1)
Dizziness	1 (<0.1)	1 (<0.1)		2 (<0.1)
Facial paralysis	0	1 (<0.1)		1 (<0.1)
Hemiparesis	0	1 (<0.1)		1 (<0.1)
Lumbar radiculopathy	0	1 (<0.1)		1 (<0.1)
Multiple sclerosis	1 (<0.1)	1 (<0.1)		2 (<0.1)
Optic neuritis	0	1 (<0.1)		1 (<0.1)
Spinal cord compression	0	1 (<0.1)		1 (<0.1)
Amyotrophic lateral sclerosis	1 (<0.1)	0		1 (<0.1)
Arachnoid cyst	1 (<0.1)	0		1 (<0.1)
Basal ganglia haemorrhage	1 (<0.1)	0		1 (<0.1)
Encephalopathy	2 (<0.1)	0		2 (<0.1)
Hydrocephalus	1 (<0.1)	0		1 (<0.1)
Ischaemic stroke	1 (<0.1)	0		1 (<0.1)
Loss of consciousness	1 (<0.1)	0		1 (<0.1)
Migraine	1 (<0.1)	0		1 (<0.1)
Nerve compression	1 (<0.1)	0		1 (<0.1)
Paraesthesia	1 (<0.1)	0		1 (<0.1)
Speech disorder	1 (<0.1)	0		1 (<0.1)
Eye disorders	1 (<0.1)	0		1 (<0.1)
Retinal detachment	1 (<0.1)	0		1 (<0.1)
Retinal tear	1 (<0.1)	0		1 (<0.1)
Cardiac disorders	43 (0.3)	36 (0.2)		79 (0.3)
Myocardial infarction	9 (<0.1)	7 (<0.1)	0.78 (0.30, 2.01)	16 (<0.1)
Atrial fibrillation	10 (<0.1)	6 (<0.1)	0.60 (0.23, 1.59)	16 (<0.1)
Cardiac failure congestive	3 (<0.1)	4 (<0.1)		7 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Acute coronary syndrome	0	3 (<0.1)		3 (<0.1)
Acute myocardial infarction	6 (<0.1)	3 (<0.1)		9 (<0.1)
Coronary artery disease	3 (<0.1)	3 (<0.1)		6 (<0.1)
Atrial flutter	2 (<0.1)	2 (<0.1)		4 (<0.1)
Cardio-respiratory arrest	1 (<0.1)	2 (<0.1)		3 (<0.1)
Pericarditis	2 (<0.1)	2 (<0.1)		4 (<0.1)
Acute left ventricular failure	2 (<0.1)	1 (<0.1)		3 (<0.1)
Angina unstable	0	1 (<0.1)		1 (<0.1)
Bradycardia	0	1 (<0.1)		1 (<0.1)
Cardiac arrest	0	1 (<0.1)		1 (<0.1)
Cardiac failure	2 (<0.1)	1 (<0.1)		3 (<0.1)
Cardiac failure acute	1 (<0.1)	1 (<0.1)		2 (<0.1)
Coronary artery occlusion	0	1 (<0.1)		1 (<0.1)
Pericardial effusion	1 (<0.1)	1 (<0.1)		2 (<0.1)
Stress cardiomyopathy	0	1 (<0.1)		1 (<0.1)
Supraventricular tachycardia	0	1 (<0.1)		1 (<0.1)
Ventricular extrasystoles	0	1 (<0.1)		1 (<0.1)
Angina pectoris	1 (<0.1)	0		1 (<0.1)
Arrhythmia	1 (<0.1)	0		1 (<0.1)
Atrioventricular block complete	1 (<0.1)	0		1 (<0.1)
Atrioventricular block second degree	1 (<0.1)	0		1 (<0.1)
Paroxysmal arrhythmia	1 (<0.1)	0		1 (<0.1)
Sinus tachycardia	2 (<0.1)	0		2 (<0.1)
Vascular disorders	15 (<0.1)	15 (<0.1)		30 (<0.1)
Deep vein thrombosis	1 (<0.1)	4 (<0.1)		5 (<0.1)
Haematoma	0	2 (<0.1)		2 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Hypertension	2 (<0.1)	2 (<0.1)		4 (<0.1)
Hypertensive urgency	1 (<0.1)	2 (<0.1)		3 (<0.1)
Aortic aneurysm	1 (<0.1)	1 (<0.1)		2 (<0.1)
Arteriosclerosis	0	1 (<0.1)		1 (<0.1)
Axillary vein thrombosis	0	1 (<0.1)		1 (<0.1)
Embolism venous	0	1 (<0.1)		1 (<0.1)
Hypotension	2 (<0.1)	1 (<0.1)		3 (<0.1)
Polyarteritis nodosa	0	1 (<0.1)		1 (<0.1)
Venous thrombosis limb	0	1 (<0.1)		1 (<0.1)
Aortic stenosis	1 (<0.1)	0		1 (<0.1)
Arterial haemorrhage	1 (<0.1)	0		1 (<0.1)
Fibromuscular dysplasia	1 (<0.1)	0		1 (<0.1)
Hypertensive emergency	2 (<0.1)	0		2 (<0.1)
Peripheral artery aneurysm	1 (<0.1)	0		1 (<0.1)
Peripheral artery occlusion	1 (<0.1)	0		1 (<0.1)
Thrombophlebitis superficial	1 (<0.1)	0		1 (<0.1)
Respiratory, thoracic and mediastinal disorders	35 (0.2)	25 (0.2)		60 (0.2)
Acute respiratory failure	10 (<0.1)	7 (<0.1)	0.70 (0.28, 1.77)	17 (<0.1)
Pulmonary embolism	7 (<0.1)	6 (<0.1)	0.86 (0.30, 2.43)	13 (<0.1)
Dyspnoea	0	5 (<0.1)		5 (<0.1)
Pleural effusion	2 (<0.1)	2 (<0.1)		4 (<0.1)
Respiratory failure	1 (<0.1)	2 (<0.1)		3 (<0.1)
Atelectasis	0	1 (<0.1)		1 (<0.1)
Chronic obstructive pulmonary disease	8 (<0.1)	1 (<0.1)	0.12 (0.02, 0.77)	9 (<0.1)
Emphysema	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pneumothorax	2 (<0.1)	1 (<0.1)		3 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Pulmonary mass	0	1 (<0.1)		1 (<0.1)
Acute respiratory distress syndrome	1 (<0.1)	0		1 (<0.1)
Asthma	1 (<0.1)	0		1 (<0.1)
Epistaxis	1 (<0.1)	0		1 (<0.1)
Hypoxia	3 (<0.1)	0		3 (<0.1)
Laryngeal oedema	1 (<0.1)	0		1 (<0.1)
Organising pneumonia	1 (<0.1)	0		1 (<0.1)
Pleuritic pain	1 (<0.1)	0		1 (<0.1)
Pneumonia aspiration	1 (<0.1)	0		1 (<0.1)
Pulmonary fibrosis	1 (<0.1)	0		1 (<0.1)
Pulmonary infarction	1 (<0.1)	0		1 (<0.1)
Gastrointestinal disorders	25 (0.2)	36 (0.2)		61 (0.2)
Colitis	4 (<0.1)	3 (<0.1)		7 (<0.1)
Gastrointestinal haemorrhage	2 (<0.1)	3 (<0.1)		5 (<0.1)
Nausea	3 (<0.1)	3 (<0.1)		6 (<0.1)
Small intestinal obstruction	3 (<0.1)	3 (<0.1)		6 (<0.1)
Abdominal pain	2 (<0.1)	2 (<0.1)		4 (<0.1)
Abdominal pain upper	0	2 (<0.1)		2 (<0.1)
Diarrhoea	1 (<0.1)	2 (<0.1)		3 (<0.1)
Duodenal ulcer perforation	0	2 (<0.1)		2 (<0.1)
Hiatus hernia	1 (<0.1)	2 (<0.1)		3 (<0.1)
Intestinal obstruction	0	2 (<0.1)		2 (<0.1)
Vomiting	2 (<0.1)	2 (<0.1)		4 (<0.1)
Crohn's disease	0	1 (<0.1)		1 (<0.1)
Diverticular perforation	0	1 (<0.1)		1 (<0.1)
Duodenal ulcer	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Gastritis	2 (<0.1)	1 (<0.1)		3 (<0.1)
Gastrooesophageal reflux disease	0	1 (<0.1)		1 (<0.1)
Inguinal hernia	0	1 (<0.1)		1 (<0.1)
Intra-abdominal fluid collection	0	1 (<0.1)		1 (<0.1)
Large intestine perforation	0	1 (<0.1)		1 (<0.1)
Oesophageal rupture	0	1 (<0.1)		1 (<0.1)
Oesophageal spasm	0	1 (<0.1)		1 (<0.1)
Pancreatitis	2 (<0.1)	1 (<0.1)		3 (<0.1)
Pancreatitis acute	0	1 (<0.1)		1 (<0.1)
Rectal prolapse	0	1 (<0.1)		1 (<0.1)
Retroperitoneal haemorrhage	0	1 (<0.1)		1 (<0.1)
Abdominal hernia	1 (<0.1)	0		1 (<0.1)
Abdominal pain lower	2 (<0.1)	0		2 (<0.1)
Duodenal ulcer haemorrhage	1 (<0.1)	0		1 (<0.1)
Gastric perforation	1 (<0.1)	0		1 (<0.1)
Gastric ulcer haemorrhage	1 (<0.1)	0		1 (<0.1)
Tooth socket haemorrhage	1 (<0.1)	0		1 (<0.1)
Hepatobiliary disorders	5 (<0.1)	6 (<0.1)		11 (<0.1)
Cholecystitis	3 (<0.1)	3 (<0.1)		6 (<0.1)
Bile duct stone	0	2 (<0.1)		2 (<0.1)
Cholelithiasis	0	1 (<0.1)		1 (<0.1)
Biliary dyskinesia	1 (<0.1)	0		1 (<0.1)
Cholecystitis acute	1 (<0.1)	0		1 (<0.1)
Skin and subcutaneous tissue disorders	2 (<0.1)	3 (<0.1)		5 (<0.1)
Alopecia areata	0	1 (<0.1)		1 (<0.1)
Angioedema	1 (<0.1)	1 (<0.1)		2 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Rash	0	1 (<0.1)		1 (<0.1)
Rash vesicular	0	1 (<0.1)		1 (<0.1)
Dermatitis bullous	1 (<0.1)	0		1 (<0.1)
Musculoskeletal and connective tissue disorders	28 (0.2)	24 (0.2)		52 (0.2)
Osteoarthritis	12 (<0.1)	8 (<0.1)	0.67 (0.28, 1.58)	20 (<0.1)
Intervertebral disc protrusion	2 (<0.1)	3 (<0.1)		5 (<0.1)
Back pain	0	2 (<0.1)		2 (<0.1)
Spinal stenosis	2 (<0.1)	2 (<0.1)		4 (<0.1)
Flank pain	1 (<0.1)	1 (<0.1)		2 (<0.1)
Fracture nonunion	0	1 (<0.1)		1 (<0.1)
Muscular weakness	1 (<0.1)	1 (<0.1)		2 (<0.1)
Musculoskeletal chest pain	1 (<0.1)	1 (<0.1)		2 (<0.1)
Neck pain	0	1 (<0.1)		1 (<0.1)
Rheumatoid arthritis	0	1 (<0.1)		1 (<0.1)
Spinal osteoarthritis	3 (<0.1)	1 (<0.1)		4 (<0.1)
Spondylolisthesis	0	1 (<0.1)		1 (<0.1)
Vertebral foraminal stenosis	0	1 (<0.1)		1 (<0.1)
Arthritis	1 (<0.1)	0		1 (<0.1)
Cervical spinal stenosis	1 (<0.1)	0		1 (<0.1)
Joint stiffness	1 (<0.1)	0		1 (<0.1)
Osteonecrosis	1 (<0.1)	0		1 (<0.1)
Polymyalgia rheumatica	1 (<0.1)	0		1 (<0.1)
Rhabdomyolysis	1 (<0.1)	0		1 (<0.1)
Renal and urinary disorders	11 (<0.1)	10 (<0.1)		21 (<0.1)
Acute kidney injury	6 (<0.1)	5 (<0.1)		11 (<0.1)
Nephrolithiasis	1 (<0.1)	5 (<0.1)		6 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Chronic kidney disease	2 (<0.1)	1 (<0.1)		3 (<0.1)
Renal impairment	1 (<0.1)	0		1 (<0.1)
Urinary retention	1 (<0.1)	0		1 (<0.1)
Pregnancy, puerperium and perinatal conditions	2 (<0.1)	1 (<0.1)		3 (<0.1)
Abortion spontaneous	1 (<0.1)	1 (<0.1)		2 (<0.1)
Ectopic pregnancy	1 (<0.1)	0		1 (<0.1)
Reproductive system and breast disorders	6 (<0.1)	6 (<0.1)		12 (<0.1)
Pelvic pain	0	2 (<0.1)		2 (<0.1)
Benign prostatic hyperplasia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Dysfunctional uterine bleeding	0	1 (<0.1)		1 (<0.1)
Ovarian cyst	2 (<0.1)	1 (<0.1)		3 (<0.1)
Uterine haemorrhage	0	1 (<0.1)		1 (<0.1)
Breast pain	1 (<0.1)	0		1 (<0.1)
Endometrial hyperplasia	1 (<0.1)	0		1 (<0.1)
Pelvic prolapse	1 (<0.1)	0		1 (<0.1)
Congenital, familial and genetic disorders	1 (<0.1)	0		1 (<0.1)
Talipes	1 (<0.1)	0		1 (<0.1)
General disorders and administration site conditions	12 (<0.1)	15 (<0.1)		27 (<0.1)
Death	2 (<0.1)	4 (<0.1)		6 (<0.1)
Non-cardiac chest pain	2 (<0.1)	3 (<0.1)		5 (<0.1)
Chest pain	2 (<0.1)	2 (<0.1)		4 (<0.1)
Swelling face	1 (<0.1)	2 (<0.1)		3 (<0.1)
Asthenia	0	1 (<0.1)		1 (<0.1)
Drug withdrawal syndrome	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Generalised oedema	0	1 (<0.1)		1 (<0.1)
Multiple organ dysfunction syndrome	0	1 (<0.1)		1 (<0.1)
Oedema peripheral	0	1 (<0.1)		1 (<0.1)
Feeling hot	1 (<0.1)	0		1 (<0.1)
Incarcerated hernia	2 (<0.1)	0		2 (<0.1)
Pyrexia	1 (<0.1)	0		1 (<0.1)
Systemic inflammatory response syndrome	2 (<0.1)	0		2 (<0.1)
Investigations	1 (<0.1)	3 (<0.1)		4 (<0.1)
Hepatic enzyme increased	0	2 (<0.1)		2 (<0.1)
Heart rate irregular	0	1 (<0.1)		1 (<0.1)
Transaminases increased	1 (<0.1)	0		1 (<0.1)
Injury, poisoning and procedural complications	29 (0.2)	27 (0.2)		56 (0.2)
Hip fracture	3 (<0.1)	3 (<0.1)		6 (<0.1)
Cervical vertebral fracture	0	2 (<0.1)		2 (<0.1)
Craniocerebral injury	0	2 (<0.1)		2 (<0.1)
Fall	5 (<0.1)	2 (<0.1)		7 (<0.1)
Road traffic accident	1 (<0.1)	2 (<0.1)		3 (<0.1)
Subdural haematoma	0	2 (<0.1)		2 (<0.1)
Back injury	0	1 (<0.1)		1 (<0.1)
Concussion	0	1 (<0.1)		1 (<0.1)
Facial bones fracture	0	1 (<0.1)		1 (<0.1)
Femoral neck fracture	0	1 (<0.1)		1 (<0.1)
Femur fracture	2 (<0.1)	1 (<0.1)		3 (<0.1)
Gastrointestinal procedural complication	0	1 (<0.1)		1 (<0.1)
Head injury	0	1 (<0.1)		1 (<0.1)
Humerus fracture	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Incarcerated incisional hernia	0	1 (<0.1)		1 (<0.1)
Incision site pain	0	1 (<0.1)		1 (<0.1)
Joint injury	1 (<0.1)	1 (<0.1)		2 (<0.1)
Overdose	0	1 (<0.1)		1 (<0.1)
Post procedural haemorrhage	1 (<0.1)	1 (<0.1)		2 (<0.1)
Procedural haemorrhage	1 (<0.1)	1 (<0.1)		2 (<0.1)
Rib fracture	3 (<0.1)	1 (<0.1)		4 (<0.1)
Skin laceration	1 (<0.1)	1 (<0.1)		2 (<0.1)
Superficial injury of eye	0	1 (<0.1)		1 (<0.1)
Tendon rupture	1 (<0.1)	1 (<0.1)		2 (<0.1)
Traumatic liver injury	0	1 (<0.1)		1 (<0.1)
Upper limb fracture	0	1 (<0.1)		1 (<0.1)
Wound dehiscence	0	1 (<0.1)		1 (<0.1)
Wrist fracture	0	1 (<0.1)		1 (<0.1)
Ankle fracture	1 (<0.1)	0		1 (<0.1)
Cartilage injury	1 (<0.1)	0		1 (<0.1)
Gun shot wound	1 (<0.1)	0		1 (<0.1)
Immunisation anxiety related reaction	1 (<0.1)	0		1 (<0.1)
Pelvic fracture	1 (<0.1)	0		1 (<0.1)
Post procedural fever	1 (<0.1)	0		1 (<0.1)
Post procedural haematoma	1 (<0.1)	0		1 (<0.1)
Post-traumatic pain	1 (<0.1)	0		1 (<0.1)
Sternal fracture	1 (<0.1)	0		1 (<0.1)
Thoracic vertebral fracture	1 (<0.1)	0		1 (<0.1)
Tracheal haemorrhage	1 (<0.1)	0		1 (<0.1)
Traumatic haemothorax	2 (<0.1)	0		2 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Social circumstances	1 (<0.1)	0		1 (<0.1)
Sexual abuse	1 (<0.1)	0		1 (<0.1)
Product issues	1 (<0.1)	0		1 (<0.1)
Lead dislodgement	1 (<0.1)	0		1 (<0.1)

A treatment-emergent adverse event (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.

Percentages are based on the number of safety subjects. The rate ratio is calculated as the ratio of percentage of participants reporting the event in mRNA-1273 divided by that in Placebo; rate ratio is provided for TEAEs with at least 7 subjects in any vaccination group reporting the event. The 95% CI is calculated using the Miettinen and Nurminen method.

MedDRA version 23.0.

Source: Study 301 Part A CSR Table 14.3.1.13.1.3 (26 Mar 2021).

Table 19 Study 301: Reported Incidence of Serious Treatment-Emergent Adverse Events Assessed by the Investigator as Treatment-Related by System Organ Class and Preferred Term in Part A (Safety Set)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Number of subjects reporting unsolicited adverse events	4 (<0.1)	12 (<0.1)		16 (<0.1)
Number of unsolicited adverse events	13	15		28
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (<0.1)		1 (<0.1)
B-cell small lymphocytic lymphoma	0	1 (<0.1)		1 (<0.1)
Endocrine disorders	0	1 (<0.1)		1 (<0.1)
Basedow's disease	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Metabolism and nutrition disorders	1 (<0.1)	0		1 (<0.1)
Hypomagnesaemia	1 (<0.1)	0		1 (<0.1)
Nervous system disorders	1 (<0.1)	3 (<0.1)		4 (<0.1)
Autonomic nervous system imbalance	0	1 (<0.1)		1 (<0.1)
Cerebrovascular accident	0	1 (<0.1)		1 (<0.1)
Multiple sclerosis	0	1 (<0.1)		1 (<0.1)
Paraesthesia	1 (<0.1)	0		1 (<0.1)
Cardiac disorders	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pericardial effusion	0	1 (<0.1)		1 (<0.1)
Pericarditis	0	1 (<0.1)		1 (<0.1)
Acute myocardial infarction	1 (<0.1)	0		1 (<0.1)
Atrial fibrillation	1 (<0.1)	0		1 (<0.1)
Respiratory, thoracic and mediastinal disorders	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pleural effusion	0	1 (<0.1)		1 (<0.1)
Organising pneumonia	1 (<0.1)	0		1 (<0.1)
Respiratory failure	1 (<0.1)	0		1 (<0.1)
Gastrointestinal disorders	0	1 (<0.1)		1 (<0.1)
Nausea	0	1 (<0.1)		1 (<0.1)
Vomiting	0	1 (<0.1)		1 (<0.1)
Skin and subcutaneous tissue disorders	0	2 (<0.1)		2 (<0.1)
Alopecia areata	0	1 (<0.1)		1 (<0.1)
Angioedema	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Musculoskeletal and connective tissue disorders	1 (<0.1)	1 (<0.1)		2 (<0.1)
Rheumatoid arthritis	0	1 (<0.1)		1 (<0.1)
Polymyalgia rheumatica	1 (<0.1)	0		1 (<0.1)
Renal and urinary disorders	1 (<0.1)	0		1 (<0.1)
Acute kidney injury	1 (<0.1)	0		1 (<0.1)
General disorders and administration site conditions	1 (<0.1)	2 (<0.1)		3 (<0.1)
Swelling face	1 (<0.1)	2 (<0.1)		3 (<0.1)
Feeling hot	1 (<0.1)	0		1 (<0.1)
Injury, poisoning and procedural complications	2 (<0.1)	0		2 (<0.1)
Immunisation anxiety related reaction	1 (<0.1)	0		1 (<0.1)
Procedural haemorrhage	1 (<0.1)	0		1 (<0.1)

A treatment-emergent adverse event (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.

Percentages are based on the number of safety subjects. The rate ratio is calculated as the ratio of percentage of participants reporting the event in mRNA-1273 divided by that in Placebo; rate ratio is provided for TEAEs with at least 7 subjects in any vaccination group reporting the event (no rate ratios are presented because none of the terms met the threshold). The 95% CI is calculated using the Miettinen and Nurminen method.

MedDRA version 23.0.

Source: Study 301 Part A CSR Table 14.3.1.14.1.3 (26 Mar 2021).

2.7.4.2.1.4.3 Medically Attended Treatment-Emergent Adverse Events

In Part A, the participant incidence of unsolicited MAAEs was balanced between the mRNA-1273 and placebo groups (22.8% and 27.2%, respectively) (Table 20). No additional imbalances were identified for discussion that were not already described among the nonserious TEAEs and/or SAEs. COVID-19 was the most common MAAE and was reported more frequently in the placebo group (5.9%) than in the mRNA-1273 group (0.5%). The incidence of other common (≥ 1.0% in either group) MAAEs was balanced between the groups: upper respiratory tract infection (1.2% mRNA-1273 vs. 1.4% placebo); urinary tract infection (0.9% mRNA-1273 vs. 1.2% placebo); and hypertension (1.2% mRNA-1273 vs. 1.4% placebo).

Table 20 **Study 301: Participant Incidence of Unsolicited Medically-Attended Treatment-Emergent Adverse Events (at Least 5 Participants in Any Group Based on Preferred Term) by System Organ Class and Preferred Term in Part A (Safety Set)**

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Number of subjects reporting unsolicited adverse events	4131 (27.2)	3468 (22.8)		7599 (25.0)
Number of unsolicited adverse events	7272	6145		13417
Infections and infestations	2069 (13.6)	1329 (8.8)		3398 (11.2)
Upper respiratory tract infection	209 (1.4)	177 (1.2)	0.85 (0.69, 1.03)	386 (1.3)
Urinary tract infection	180 (1.2)	137 (0.9)	0.76 (0.61, 0.95)	317 (1.0)
Suspected COVID-19	96 (0.6)	113 (0.7)	1.18 (0.90, 1.54)	209 (0.7)
Viral infection	115 (0.8)	112 (0.7)	0.97 (0.75, 1.26)	227 (0.7)
Sinusitis	99 (0.7)	108 (0.7)	1.09 (0.83, 1.43)	207 (0.7)
COVID-19	892 (5.9)	79 (0.5)	0.09 (0.07, 0.11)	971 (3.2)
Rhinovirus infection	49 (0.3)	57 (0.4)	1.16 (0.80, 1.70)	106 (0.3)
Herpes zoster	17 (0.1)	40 (0.3)	2.35 (1.34, 4.11)	57 (0.2)
Tooth abscess	39 (0.3)	30 (0.2)	0.77 (0.48, 1.23)	69 (0.2)
Tooth infection	30 (0.2)	30 (0.2)	1.00 (0.61, 1.65)	60 (0.2)
Pharyngitis streptococcal	36 (0.2)	25 (0.2)	0.69 (0.42, 1.15)	61 (0.2)
Viral upper respiratory tract infection	23 (0.2)	24 (0.2)	1.04 (0.59, 1.83)	47 (0.2)
Cellulitis	28 (0.2)	23 (0.2)	0.82 (0.48, 1.41)	51 (0.2)
Ear infection	21 (0.1)	22 (0.1)	1.05 (0.58, 1.89)	43 (0.1)
Bronchitis	30 (0.2)	20 (0.1)	0.67 (0.38, 1.16)	50 (0.2)
Gastroenteritis	20 (0.1)	19 (0.1)	0.95 (0.51, 1.76)	39 (0.1)
Pharyngitis	19 (0.1)	19 (0.1)	1.00 (0.53, 1.87)	38 (0.1)
Pneumonia	33 (0.2)	19 (0.1)	0.57 (0.33, 1.00)	52 (0.2)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Otitis media	17 (0.1)	18 (0.1)	1.06 (0.55, 2.03)	35 (0.1)
Diverticulitis	19 (0.1)	15 (<0.1)	0.79 (0.41, 1.53)	34 (0.1)
Hordeolum	16 (0.1)	13 (<0.1)	0.81 (0.40, 1.66)	29 (<0.1)
Conjunctivitis	16 (0.1)	12 (<0.1)	0.75 (0.36, 1.56)	28 (<0.1)
Otitis externa	9 (<0.1)	11 (<0.1)	1.22 (0.52, 2.87)	20 (<0.1)
Enterovirus infection	2 (<0.1)	10 (<0.1)	4.99 (1.23, 20.26)	12 (<0.1)
Fungal infection	13 (<0.1)	10 (<0.1)	0.77 (0.34, 1.71)	23 (<0.1)
Localised infection	7 (<0.1)	10 (<0.1)	1.43 (0.56, 3.62)	17 (<0.1)
Acute sinusitis	10 (<0.1)	9 (<0.1)	0.90 (0.38, 2.15)	19 (<0.1)
Onychomycosis	5 (<0.1)	9 (<0.1)	1.80 (0.63, 5.11)	14 (<0.1)
Respiratory tract infection	10 (<0.1)	9 (<0.1)	0.90 (0.38, 2.15)	19 (<0.1)
Abscess limb	2 (<0.1)	8 (<0.1)	3.99 (0.96, 16.62)	10 (<0.1)
Bacterial vaginosis	9 (<0.1)	8 (<0.1)	0.89 (0.35, 2.23)	17 (<0.1)
Herpes simplex	3 (<0.1)	8 (<0.1)	2.66 (0.77, 9.25)	11 (<0.1)
Nasopharyngitis	12 (<0.1)	8 (<0.1)	0.67 (0.28, 1.58)	20 (<0.1)
Paronychia	5 (<0.1)	8 (<0.1)	1.60 (0.55, 4.64)	13 (<0.1)
Asymptomatic COVID-19	9 (<0.1)	7 (<0.1)	0.78 (0.30, 2.01)	16 (<0.1)
Cystitis	14 (<0.1)	7 (<0.1)	0.50 (0.21, 1.20)	21 (<0.1)
Gingivitis	7 (<0.1)	7 (<0.1)	1.00 (0.37, 2.73)	14 (<0.1)
Skin infection	5 (<0.1)	7 (<0.1)	1.40 (0.47, 4.17)	12 (<0.1)
Vulvovaginal candidiasis	5 (<0.1)	7 (<0.1)	1.40 (0.47, 4.17)	12 (<0.1)
Folliculitis	12 (<0.1)	6 (<0.1)	0.50 (0.19, 1.28)	18 (<0.1)
Lyme disease	0	6 (<0.1)		6 (<0.1)
Pyelonephritis	6 (<0.1)	6 (<0.1)		12 (<0.1)
Sepsis	6 (<0.1)	6 (<0.1)		12 (<0.1)
Appendicitis	6 (<0.1)	5 (<0.1)		11 (<0.1)
Clostridium difficile infection	0	5 (<0.1)		5 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Gastroenteritis viral	6 (<0.1)	5 (<0.1)		11 (<0.1)
Kidney infection	2 (<0.1)	5 (<0.1)		7 (<0.1)
Oral candidiasis	5 (<0.1)	5 (<0.1)		10 (<0.1)
Oral herpes	7 (<0.1)	5 (<0.1)	0.71 (0.24, 2.13)	12 (<0.1)
Postoperative wound infection	3 (<0.1)	5 (<0.1)		8 (<0.1)
Staphylococcal infection	3 (<0.1)	5 (<0.1)		8 (<0.1)
Staphylococcal skin infection	1 (<0.1)	5 (<0.1)		6 (<0.1)
Eye infection	6 (<0.1)	4 (<0.1)		10 (<0.1)
Vulvovaginal mycotic infection	13 (<0.1)	4 (<0.1)	0.31 (0.11, 0.89)	17 (<0.1)
Tonsillitis	11 (<0.1)	3 (<0.1)	0.27 (0.08, 0.91)	14 (<0.1)
Otitis media acute	5 (<0.1)	2 (<0.1)		7 (<0.1)
Respiratory tract infection viral	10 (<0.1)	2 (<0.1)	0.20 (0.05, 0.81)	12 (<0.1)
COVID-19 pneumonia	16 (0.1)	0		16 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	116 (0.8)	123 (0.8)		239 (0.8)
Basal cell carcinoma	28 (0.2)	22 (0.1)	0.78 (0.45, 1.36)	50 (0.2)
Prostate cancer	5 (<0.1)	8 (<0.1)	1.60 (0.55, 4.64)	13 (<0.1)
Skin cancer	4 (<0.1)	6 (<0.1)		10 (<0.1)
Uterine leiomyoma	2 (<0.1)	6 (<0.1)		8 (<0.1)
Benign neoplasm of skin	2 (<0.1)	5 (<0.1)		7 (<0.1)
Malignant melanoma	5 (<0.1)	5 (<0.1)		10 (<0.1)
Squamous cell carcinoma	9 (<0.1)	5 (<0.1)	0.55 (0.20, 1.58)	14 (<0.1)
Squamous cell carcinoma of skin	9 (<0.1)	5 (<0.1)	0.55 (0.20, 1.58)	14 (<0.1)
Blood and lymphatic system disorders	56 (0.4)	73 (0.5)		129 (0.4)
Lymphadenopathy	29 (0.2)	38 (0.3)	1.31 (0.81, 2.11)	67 (0.2)
Anaemia	10 (<0.1)	15 (<0.1)	1.50 (0.69, 3.27)	25 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Iron deficiency anaemia	9 (<0.1)	8 (<0.1)	0.89 (0.35, 2.23)	17 (<0.1)
Immune system disorders	41 (0.3)	38 (0.3)		79 (0.3)
Seasonal allergy	25 (0.2)	23 (0.2)	0.92 (0.53, 1.61)	48 (0.2)
Drug hypersensitivity	4 (<0.1)	7 (<0.1)	1.75 (0.55, 5.58)	11 (<0.1)
Hypersensitivity	5 (<0.1)	4 (<0.1)		9 (<0.1)
Endocrine disorders	33 (0.2)	33 (0.2)		66 (0.2)
Hypothyroidism	15 (<0.1)	22 (0.1)	1.46 (0.77, 2.79)	37 (0.1)
Goitre	5 (<0.1)	2 (<0.1)		7 (<0.1)
Metabolism and nutrition disorders	222 (1.5)	191 (1.3)		413 (1.4)
Hyperlipidaemia	44 (0.3)	35 (0.2)	0.79 (0.51, 1.23)	79 (0.3)
Type 2 diabetes mellitus	25 (0.2)	33 (0.2)	1.32 (0.79, 2.20)	58 (0.2)
Vitamin D deficiency	27 (0.2)	25 (0.2)	0.92 (0.54, 1.58)	52 (0.2)
Hypercholesterolaemia	30 (0.2)	21 (0.1)	0.70 (0.40, 1.21)	51 (0.2)
Diabetes mellitus	10 (<0.1)	11 (<0.1)	1.10 (0.48, 2.52)	21 (<0.1)
Glucose tolerance impaired	10 (<0.1)	10 (<0.1)	1.00 (0.43, 2.34)	20 (<0.1)
Dehydration	14 (<0.1)	9 (<0.1)	0.64 (0.28, 1.45)	23 (<0.1)
Gout	13 (<0.1)	9 (<0.1)	0.69 (0.30, 1.58)	22 (<0.1)
Hyponatraemia	9 (<0.1)	9 (<0.1)	1.00 (0.41, 2.44)	18 (<0.1)
Hypokalaemia	16 (0.1)	5 (<0.1)	0.31 (0.12, 0.82)	21 (<0.1)
Hyperglycaemia	5 (<0.1)	4 (<0.1)		9 (<0.1)
Dyslipidaemia	5 (<0.1)	1 (<0.1)		6 (<0.1)
Hypomagnesaemia	5 (<0.1)	1 (<0.1)		6 (<0.1)
Psychiatric disorders	193 (1.3)	224 (1.5)		417 (1.4)
Depression	70 (0.5)	84 (0.6)	1.20 (0.87, 1.64)	154 (0.5)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Anxiety	67 (0.4)	81 (0.5)	1.21 (0.88, 1.66)	148 (0.5)
Insomnia	23 (0.2)	23 (0.2)	1.00 (0.56, 1.77)	46 (0.2)
Attention deficit hyperactivity disorder	21 (0.1)	19 (0.1)	0.90 (0.49, 1.66)	40 (0.1)
Bipolar disorder	7 (<0.1)	7 (<0.1)	1.00 (0.37, 2.73)	14 (<0.1)
Generalised anxiety disorder	7 (<0.1)	2 (<0.1)	0.29 (0.07, 1.21)	9 (<0.1)
Nervous system disorders	322 (2.1)	319 (2.1)		641 (2.1)
Headache	142 (0.9)	132 (0.9)	0.93 (0.73, 1.17)	274 (0.9)
Dizziness	25 (0.2)	18 (0.1)	0.72 (0.40, 1.31)	43 (0.1)
Migraine	19 (0.1)	18 (0.1)	0.95 (0.50, 1.78)	37 (0.1)
Sciatica	19 (0.1)	17 (0.1)	0.89 (0.47, 1.70)	36 (0.1)
Paraesthesia	13 (<0.1)	16 (0.1)	1.23 (0.60, 2.52)	29 (<0.1)
Syncope	24 (0.2)	16 (0.1)	0.67 (0.36, 1.24)	40 (0.1)
Cervical radiculopathy	1 (<0.1)	12 (<0.1)	11.98 (2.00, 71.83)	13 (<0.1)
Anosmia	6 (<0.1)	10 (<0.1)	1.66 (0.63, 4.40)	16 (<0.1)
Ageusia	8 (<0.1)	9 (<0.1)	1.12 (0.45, 2.82)	17 (<0.1)
Nerve compression	6 (<0.1)	8 (<0.1)	1.33 (0.48, 3.67)	14 (<0.1)
Cerebrovascular accident	3 (<0.1)	7 (<0.1)	2.33 (0.66, 8.26)	10 (<0.1)
Facial paralysis	2 (<0.1)	7 (<0.1)	3.49 (0.83, 14.79)	9 (<0.1)
Carpal tunnel syndrome	7 (<0.1)	6 (<0.1)	0.86 (0.30, 2.43)	13 (<0.1)
Hypoaesthesia	5 (<0.1)	5 (<0.1)		10 (<0.1)
Lumbar radiculopathy	1 (<0.1)	5 (<0.1)		6 (<0.1)
Seizure	6 (<0.1)	5 (<0.1)		11 (<0.1)
Presyncope	5 (<0.1)	3 (<0.1)		8 (<0.1)
Restless legs syndrome	6 (<0.1)	2 (<0.1)		8 (<0.1)
Neuropathy peripheral	5 (<0.1)	0		5 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Eye disorders	70 (0.5)	80 (0.5)		150 (0.5)
Cataract	9 (<0.1)	13 (<0.1)	1.44 (0.63, 3.29)	22 (<0.1)
Dry eye	7 (<0.1)	8 (<0.1)	1.14 (0.43, 3.03)	15 (<0.1)
Retinal detachment	3 (<0.1)	7 (<0.1)	2.33 (0.66, 8.26)	10 (<0.1)
Glaucoma	5 (<0.1)	6 (<0.1)		11 (<0.1)
Ear and labyrinth disorders	71 (0.5)	61 (0.4)		132 (0.4)
Vertigo	13 (<0.1)	22 (0.1)	1.69 (0.86, 3.31)	35 (0.1)
Ear pain	10 (<0.1)	10 (<0.1)	1.00 (0.43, 2.34)	20 (<0.1)
Tinnitus	8 (<0.1)	7 (<0.1)	0.87 (0.33, 2.32)	15 (<0.1)
Vertigo positional	3 (<0.1)	7 (<0.1)	2.33 (0.66, 8.26)	10 (<0.1)
Meniere's disease	2 (<0.1)	5 (<0.1)		7 (<0.1)
Ear canal erythema	5 (<0.1)	1 (<0.1)		6 (<0.1)
Tympanic membrane perforation	6 (<0.1)	1 (<0.1)		7 (<0.1)
Cardiac disorders	114 (0.8)	118 (0.8)		232 (0.8)
Atrial fibrillation	27 (0.2)	25 (0.2)	0.92 (0.54, 1.58)	52 (0.2)
Palpitations	6 (<0.1)	14 (<0.1)	2.33 (0.93, 5.86)	20 (<0.1)
Ventricular extrasystoles	4 (<0.1)	10 (<0.1)	2.50 (0.83, 7.52)	14 (<0.1)
Coronary artery disease	8 (<0.1)	8 (<0.1)	1.00 (0.39, 2.57)	16 (<0.1)
Angina pectoris	9 (<0.1)	6 (<0.1)	0.67 (0.25, 1.79)	15 (<0.1)
Cardiac failure congestive	9 (<0.1)	6 (<0.1)	0.67 (0.25, 1.79)	15 (<0.1)
Myocardial infarction	8 (<0.1)	6 (<0.1)	0.75 (0.27, 2.06)	14 (<0.1)
Sinus tachycardia	7 (<0.1)	6 (<0.1)	0.86 (0.30, 2.43)	13 (<0.1)
Tachycardia	11 (<0.1)	6 (<0.1)	0.54 (0.21, 1.42)	17 (<0.1)
Acute myocardial infarction	6 (<0.1)	4 (<0.1)		10 (<0.1)
Arrhythmia	6 (<0.1)	2 (<0.1)		8 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Vascular disorders	264 (1.7)	222 (1.5)		486 (1.6)
Hypertension	218 (1.4)	176 (1.2)	0.81 (0.66, 0.98)	394 (1.3)
Haematoma	4 (<0.1)	8 (<0.1)	2.00 (0.64, 6.23)	12 (<0.1)
Deep vein thrombosis	6 (<0.1)	7 (<0.1)	1.16 (0.41, 3.30)	13 (<0.1)
Hypotension	6 (<0.1)	3 (<0.1)		9 (<0.1)
Respiratory, thoracic and mediastinal disorders	409 (2.7)	329 (2.2)		738 (2.4)
Cough	122 (0.8)	112 (0.7)	0.92 (0.71, 1.18)	234 (0.8)
Nasal congestion	91 (0.6)	91 (0.6)	1.00 (0.75, 1.33)	182 (0.6)
Rhinorrhoea	75 (0.5)	76 (0.5)	1.01 (0.74, 1.39)	151 (0.5)
Oropharyngeal pain	104 (0.7)	73 (0.5)	0.70 (0.52, 0.94)	177 (0.6)
Dyspnoea	46 (0.3)	41 (0.3)	0.89 (0.59, 1.35)	87 (0.3)
Asthma	28 (0.2)	20 (0.1)	0.71 (0.41, 1.26)	48 (0.2)
Chronic obstructive pulmonary disease	18 (0.1)	10 (<0.1)	0.55 (0.26, 1.18)	28 (<0.1)
Sinus congestion	12 (<0.1)	9 (<0.1)	0.75 (0.32, 1.73)	21 (<0.1)
Respiratory tract congestion	10 (<0.1)	8 (<0.1)	0.80 (0.33, 1.96)	18 (<0.1)
Acute respiratory failure	14 (<0.1)	7 (<0.1)	0.50 (0.21, 1.20)	21 (<0.1)
Rhinitis allergic	12 (<0.1)	7 (<0.1)	0.58 (0.24, 1.43)	19 (<0.1)
Upper-airway cough syndrome	6 (<0.1)	7 (<0.1)	1.16 (0.41, 3.30)	13 (<0.1)
Pulmonary embolism	7 (<0.1)	6 (<0.1)	0.86 (0.30, 2.43)	13 (<0.1)
Sinus pain	1 (<0.1)	6 (<0.1)		7 (<0.1)
Pleural effusion	5 (<0.1)	5 (<0.1)		10 (<0.1)
Sneezing	2 (<0.1)	5 (<0.1)		7 (<0.1)
Respiratory disorder	5 (<0.1)	4 (<0.1)		9 (<0.1)
Sleep apnoea syndrome	6 (<0.1)	4 (<0.1)		10 (<0.1)
Epistaxis	5 (<0.1)	2 (<0.1)		7 (<0.1)
Hypoxia	6 (<0.1)	2 (<0.1)		8 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Pharyngeal erythema	6 (<0.1)	2 (<0.1)		8 (<0.1)
Wheezing	5 (<0.1)	2 (<0.1)		7 (<0.1)
Pleuritic pain	6 (<0.1)	1 (<0.1)		7 (<0.1)
Gastrointestinal disorders	371 (2.4)	382 (2.5)		753 (2.5)
Nausea	65 (0.4)	69 (0.5)	1.06 (0.76, 1.48)	134 (0.4)
Diarrhoea	60 (0.4)	61 (0.4)	1.02 (0.71, 1.45)	121 (0.4)
Gastrooesophageal reflux disease	37 (0.2)	51 (0.3)	1.38 (0.90, 2.09)	88 (0.3)
Abdominal pain	21 (0.1)	25 (0.2)	1.19 (0.67, 2.11)	46 (0.2)
Dental caries	29 (0.2)	23 (0.2)	0.79 (0.46, 1.36)	52 (0.2)
Toothache	27 (0.2)	20 (0.1)	0.74 (0.42, 1.31)	47 (0.2)
Vomiting	21 (0.1)	19 (0.1)	0.90 (0.49, 1.66)	40 (0.1)
Constipation	16 (0.1)	16 (0.1)	1.00 (0.51, 1.97)	32 (0.1)
Abdominal pain upper	10 (<0.1)	15 (<0.1)	1.50 (0.69, 3.27)	25 (<0.1)
Inguinal hernia	5 (<0.1)	11 (<0.1)	2.20 (0.80, 6.05)	16 (<0.1)
Large intestine polyp	9 (<0.1)	10 (<0.1)	1.11 (0.46, 2.65)	19 (<0.1)
Hiatus hernia	5 (<0.1)	9 (<0.1)	1.80 (0.63, 5.11)	14 (<0.1)
Irritable bowel syndrome	3 (<0.1)	8 (<0.1)	2.66 (0.77, 9.25)	11 (<0.1)
Abdominal pain lower	8 (<0.1)	7 (<0.1)	0.87 (0.33, 2.32)	15 (<0.1)
Colitis	9 (<0.1)	7 (<0.1)	0.78 (0.30, 2.01)	16 (<0.1)
Dyspepsia	6 (<0.1)	7 (<0.1)	1.16 (0.41, 3.30)	13 (<0.1)
Gastritis	10 (<0.1)	6 (<0.1)	0.60 (0.23, 1.59)	16 (<0.1)
Gastric ulcer	6 (<0.1)	5 (<0.1)		11 (<0.1)
Tooth impacted	6 (<0.1)	5 (<0.1)		11 (<0.1)
Food poisoning	7 (<0.1)	3 (<0.1)	0.43 (0.12, 1.52)	10 (<0.1)
Abdominal discomfort	5 (<0.1)	2 (<0.1)		7 (<0.1)
Dysphagia	5 (<0.1)	2 (<0.1)		7 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Hepatobiliary disorders	17 (0.1)	27 (0.2)		44 (0.1)
Cholelithiasis	7 (<0.1)	13 (<0.1)	1.85 (0.76, 4.51)	20 (<0.1)
Cholecystitis	3 (<0.1)	7 (<0.1)	2.33 (0.66, 8.26)	10 (<0.1)
Skin and subcutaneous tissue disorders	180 (1.2)	155 (1.0)		335 (1.1)
Urticaria	17 (0.1)	21 (0.1)	1.23 (0.66, 2.31)	38 (0.1)
Dermatitis contact	20 (0.1)	17 (0.1)	0.85 (0.45, 1.60)	37 (0.1)
Rash	20 (0.1)	13 (<0.1)	0.65 (0.33, 1.29)	33 (0.1)
Eczema	7 (<0.1)	10 (<0.1)	1.43 (0.56, 3.62)	17 (<0.1)
Acne	17 (0.1)	9 (<0.1)	0.53 (0.24, 1.16)	26 (<0.1)
Actinic keratosis	5 (<0.1)	7 (<0.1)	1.40 (0.47, 4.17)	12 (<0.1)
Pruritus	8 (<0.1)	7 (<0.1)	0.87 (0.33, 2.32)	15 (<0.1)
Rosacea	3 (<0.1)	6 (<0.1)		9 (<0.1)
Dermatitis	8 (<0.1)	4 (<0.1)	0.50 (0.16, 1.56)	12 (<0.1)
Dermal cyst	5 (<0.1)	3 (<0.1)		8 (<0.1)
Rash pruritic	6 (<0.1)	1 (<0.1)		7 (<0.1)
Musculoskeletal and connective tissue disorders	467 (3.1)	484 (3.2)		951 (3.1)
Arthralgia	65 (0.4)	68 (0.4)	1.04 (0.75, 1.46)	133 (0.4)
Back pain	73 (0.5)	62 (0.4)	0.85 (0.61, 1.19)	135 (0.4)
Osteoarthritis	57 (0.4)	52 (0.3)	0.91 (0.63, 1.32)	109 (0.4)
Myalgia	60 (0.4)	50 (0.3)	0.83 (0.57, 1.21)	110 (0.4)
Musculoskeletal pain	20 (0.1)	29 (0.2)	1.45 (0.83, 2.54)	49 (0.2)
Neck pain	14 (<0.1)	25 (0.2)	1.78 (0.94, 3.39)	39 (0.1)
Muscle spasms	25 (0.2)	22 (0.1)	0.88 (0.50, 1.55)	47 (0.2)
Pain in extremity	26 (0.2)	22 (0.1)	0.84 (0.48, 1.48)	48 (0.2)
Rotator cuff syndrome	19 (0.1)	20 (0.1)	1.05 (0.57, 1.95)	39 (0.1)
Intervertebral disc protrusion	10 (<0.1)	17 (0.1)	1.70 (0.79, 3.64)	27 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Bursitis	11 (<0.1)	14 (<0.1)	1.27 (0.59, 2.75)	25 (<0.1)
Tendonitis	16 (0.1)	13 (<0.1)	0.81 (0.40, 1.66)	29 (<0.1)
Arthritis	10 (<0.1)	12 (<0.1)	1.20 (0.53, 2.71)	22 (<0.1)
Spinal osteoarthritis	8 (<0.1)	8 (<0.1)	1.00 (0.39, 2.57)	16 (<0.1)
Trigger finger	5 (<0.1)	8 (<0.1)	1.60 (0.55, 4.64)	13 (<0.1)
Musculoskeletal chest pain	10 (<0.1)	7 (<0.1)	0.70 (0.28, 1.77)	17 (<0.1)
Periarthritis	4 (<0.1)	7 (<0.1)	1.75 (0.55, 5.58)	11 (<0.1)
Joint swelling	1 (<0.1)	6 (<0.1)		7 (<0.1)
Osteoporosis	6 (<0.1)	6 (<0.1)		12 (<0.1)
Muscular weakness	1 (<0.1)	5 (<0.1)		6 (<0.1)
Osteopenia	5 (<0.1)	5 (<0.1)		10 (<0.1)
Flank pain	5 (<0.1)	4 (<0.1)		9 (<0.1)
Intervertebral disc degeneration	5 (<0.1)	4 (<0.1)		9 (<0.1)
Exostosis	6 (<0.1)	2 (<0.1)		8 (<0.1)
Foot deformity	6 (<0.1)	2 (<0.1)		8 (<0.1)
Synovial cyst	5 (<0.1)	1 (<0.1)		6 (<0.1)
Renal and urinary disorders	78 (0.5)	71 (0.5)		149 (0.5)
Nephrolithiasis	30 (0.2)	23 (0.2)	0.77 (0.45, 1.31)	53 (0.2)
Acute kidney injury	12 (<0.1)	7 (<0.1)	0.58 (0.24, 1.43)	19 (<0.1)
Chronic kidney disease	6 (<0.1)	6 (<0.1)		12 (<0.1)
Haematuria	7 (<0.1)	5 (<0.1)	0.71 (0.24, 2.13)	12 (<0.1)
Hypertonic bladder	3 (<0.1)	5 (<0.1)		8 (<0.1)
Urinary retention	4 (<0.1)	5 (<0.1)		9 (<0.1)
Reproductive system and breast disorders	100 (0.7)	85 (0.6)		185 (0.6)
Benign prostatic hyperplasia	20 (0.1)	8 (<0.1)	0.40 (0.18, 0.89)	28 (<0.1)
Ovarian cyst	6 (<0.1)	6 (<0.1)		12 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Prostatitis	6 (<0.1)	6 (<0.1)		12 (<0.1)
Breast cyst	3 (<0.1)	5 (<0.1)		8 (<0.1)
Erectile dysfunction	8 (<0.1)	5 (<0.1)	0.62 (0.21, 1.81)	13 (<0.1)
Pelvic pain	2 (<0.1)	5 (<0.1)		7 (<0.1)
Prostatomegaly	5 (<0.1)	5 (<0.1)		10 (<0.1)
Breast mass	5 (<0.1)	2 (<0.1)		7 (<0.1)
General disorders and administration site conditions	240 (1.6)	265 (1.7)		505 (1.7)
Fatigue	104 (0.7)	104 (0.7)	1.00 (0.76, 1.31)	208 (0.7)
Pain	45 (0.3)	40 (0.3)	0.89 (0.58, 1.35)	85 (0.3)
Chills	34 (0.2)	29 (0.2)	0.85 (0.52, 1.39)	63 (0.2)
Pyrexia	33 (0.2)	28 (0.2)	0.85 (0.51, 1.39)	61 (0.2)
Injection site pain	6 (<0.1)	15 (<0.1)	2.50 (1.00, 6.23)	21 (<0.1)
Non-cardiac chest pain	12 (<0.1)	12 (<0.1)	1.00 (0.46, 2.18)	24 (<0.1)
Chest pain	7 (<0.1)	9 (<0.1)	1.28 (0.50, 3.32)	16 (<0.1)
Oedema peripheral	12 (<0.1)	9 (<0.1)	0.75 (0.32, 1.73)	21 (<0.1)
Injection site lymphadenopathy	2 (<0.1)	8 (<0.1)	3.99 (0.96, 16.62)	10 (<0.1)
Chest discomfort	14 (<0.1)	7 (<0.1)	0.50 (0.21, 1.20)	21 (<0.1)
Injection site erythema	2 (<0.1)	7 (<0.1)	3.49 (0.83, 14.79)	9 (<0.1)
Injection site induration	0	7 (<0.1)		7 (<0.1)
Injection site rash	0	7 (<0.1)		7 (<0.1)
Injection site swelling	0	7 (<0.1)		7 (<0.1)
Peripheral swelling	7 (<0.1)	6 (<0.1)	0.86 (0.30, 2.43)	13 (<0.1)
Asthenia	6 (<0.1)	4 (<0.1)		10 (<0.1)
Cyst	5 (<0.1)	3 (<0.1)		8 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Investigations	85 (0.6)	88 (0.6)		173 (0.6)
Blood cholesterol increased	8 (<0.1)	9 (<0.1)	1.12 (0.45, 2.82)	17 (<0.1)
Blood pressure increased	17 (0.1)	8 (<0.1)	0.47 (0.21, 1.06)	25 (<0.1)
Hepatic enzyme increased	4 (<0.1)	7 (<0.1)	1.75 (0.55, 5.58)	11 (<0.1)
Prostatic specific antigen increased	1 (<0.1)	5 (<0.1)		6 (<0.1)
Blood pressure systolic increased	7 (<0.1)	4 (<0.1)	0.57 (0.18, 1.82)	11 (<0.1)
Injury, poisoning and procedural complications	425 (2.8)	392 (2.6)		817 (2.7)
Skin laceration	47 (0.3)	34 (0.2)	0.72 (0.47, 1.12)	81 (0.3)
Ligament sprain	22 (0.1)	32 (0.2)	1.45 (0.85, 2.48)	54 (0.2)
Fall	25 (0.2)	26 (0.2)	1.04 (0.60, 1.79)	51 (0.2)
Muscle strain	24 (0.2)	25 (0.2)	1.04 (0.60, 1.81)	49 (0.2)
Procedural pain	34 (0.2)	22 (0.1)	0.65 (0.38, 1.10)	56 (0.2)
Tooth fracture	30 (0.2)	22 (0.1)	0.73 (0.43, 1.26)	52 (0.2)
Foot fracture	18 (0.1)	20 (0.1)	1.11 (0.59, 2.08)	38 (0.1)
Meniscus injury	19 (0.1)	18 (0.1)	0.95 (0.50, 1.78)	37 (0.1)
Animal bite	15 (<0.1)	15 (<0.1)	1.00 (0.50, 2.01)	30 (<0.1)
Arthropod bite	16 (0.1)	13 (<0.1)	0.81 (0.40, 1.66)	29 (<0.1)
Limb injury	11 (<0.1)	13 (<0.1)	1.18 (0.54, 2.58)	24 (<0.1)
Joint injury	7 (<0.1)	12 (<0.1)	1.71 (0.70, 4.22)	19 (<0.1)
Road traffic accident	9 (<0.1)	11 (<0.1)	1.22 (0.52, 2.87)	20 (<0.1)
Concussion	5 (<0.1)	10 (<0.1)	2.00 (0.71, 5.58)	15 (<0.1)
Rib fracture	9 (<0.1)	10 (<0.1)	1.11 (0.46, 2.65)	19 (<0.1)
Contusion	11 (<0.1)	9 (<0.1)	0.82 (0.35, 1.92)	20 (<0.1)
Facial bones fracture	1 (<0.1)	8 (<0.1)	7.99 (1.30, 49.20)	9 (<0.1)
Post-traumatic pain	10 (<0.1)	7 (<0.1)	0.70 (0.28, 1.77)	17 (<0.1)
Head injury	2 (<0.1)	6 (<0.1)		8 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Clavicle fracture	1 (<0.1)	5 (<0.1)		6 (<0.1)
Corneal abrasion	5 (<0.1)	5 (<0.1)		10 (<0.1)
Humerus fracture	2 (<0.1)	5 (<0.1)		7 (<0.1)
Ligament rupture	5 (<0.1)	5 (<0.1)		10 (<0.1)
Muscle rupture	2 (<0.1)	5 (<0.1)		7 (<0.1)
Stress fracture	7 (<0.1)	5 (<0.1)	0.71 (0.24, 2.13)	12 (<0.1)
Upper limb fracture	1 (<0.1)	5 (<0.1)		6 (<0.1)
Ankle fracture	10 (<0.1)	4 (<0.1)	0.40 (0.13, 1.20)	14 (<0.1)
Cartilage injury	5 (<0.1)	4 (<0.1)		9 (<0.1)
Epicondylitis	5 (<0.1)	4 (<0.1)		9 (<0.1)
Skin abrasion	10 (<0.1)	4 (<0.1)	0.40 (0.13, 1.20)	14 (<0.1)
Wrist fracture	6 (<0.1)	4 (<0.1)		10 (<0.1)
Arthropod sting	5 (<0.1)	3 (<0.1)		8 (<0.1)
Bone contusion	5 (<0.1)	2 (<0.1)		7 (<0.1)
Tendon rupture	9 (<0.1)	2 (<0.1)	0.22 (0.05, 0.91)	11 (<0.1)
Radius fracture	6 (<0.1)	1 (<0.1)		7 (<0.1)
Wound	6 (<0.1)	1 (<0.1)		7 (<0.1)

A treatment-emergent adverse event (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.

Percentages are based on the number of safety subjects. The rate ratio is calculated as the ratio of percentage of participants reporting the event in mRNA-1273 divided by that in Placebo; rate ratio is provided for TEAEs with at least 7 subjects in any vaccination group reporting the event. The 95% CI is calculated using the Miettinen and Nurminen method.

MedDRA version 23.0.

Source: Study 301 Part A CSR Table 14.3.1.19.1.3 (26 Mar 2021).

2.7.4.2.1.4.4 Discontinuation From Study Vaccine or Study Participation

At least one unsolicited TEAE that was reported as leading to discontinuation from study injections in Part A was reported for 74 participants (0.5%) in the mRNA-1273 group and 109 participants (0.7%) in the placebo group (Table 21). The most frequently reported TEAE leading to discontinuation from the study vaccine was symptomatic COVID-19 (14 participants [< 0.1%] in the mRNA-1273 group vs. 53 participants [0.3%] in the placebo group). Urticaria was reported as leading to discontinuation of vaccine for 5 participants who received mRNA-1273 and 2 participants who received placebo (< 0.1% each); no other unsolicited TEAE (PT) leading to discontinuation from the study vaccine was reported by more than 3 participants in either group. Follow-up for safety observations continued for all participants remaining on the study including those who were reported as having a TEAE resulting in discontinuation of vaccine that occurred after they had completed the 2-dose series.

At least one unsolicited TEAE leading to discontinuation from participation in Part A was reported for 26 participants (0.2%) in the mRNA-1273 group and 23 participants (0.2%) in the placebo group (Study 301 Part A CSR Table 14.3.1.16.1.3). Events in the cardiac disorders SOC that led to discontinuation were reported for 3 participants in the mRNA-1273 group and 6 participants in the placebo group (< 0.1% for each). Myocardial infarction was reported for 2 participants in the mRNA-1273 group and 4 participants in the placebo group, and COVID-19 was reported for 1 participant in the mRNA-1273 group and 3 participants in the placebo group (< 0.1% each); no other unsolicited TEAE (PT) leading to discontinuation from participation in the study was reported by more than 2 participants in either group. In addition, events coded as “death” without further specification were reported for 4 participants in the mRNA-1273 group and 2 participants in the placebo group.

Table 21 Study 301: Participant Incidence of Unsolicited Treatment-Emergent Adverse Events Leading to Discontinuation from Study Vaccine by System Organ Class and Preferred Term for Part A (Safety Set)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Number of subjects reporting unsolicited adverse events	109 (0.7)	74 (0.5)		183 (0.6)
Number of unsolicited adverse events	123	87		210
Infections and infestations	61 (0.4)	25 (0.2)		86 (0.3)
COVID-19	53 (0.3)	14 (<0.1)	0.26 (0.15, 0.47)	67 (0.2)
Asymptomatic COVID-19	0	3 (<0.1)		3 (<0.1)
Pneumonia	1 (<0.1)	2 (<0.1)		3 (<0.1)
Hepatitis A	0	1 (<0.1)		1 (<0.1)
Herpes simplex	0	1 (<0.1)		1 (<0.1)
Herpes zoster	0	1 (<0.1)		1 (<0.1)
Liver abscess	0	1 (<0.1)		1 (<0.1)
Lung abscess	0	1 (<0.1)		1 (<0.1)
Suspected COVID-19	0	1 (<0.1)		1 (<0.1)
Viral infection	0	1 (<0.1)		1 (<0.1)
Cholecystitis infective	1 (<0.1)	0		1 (<0.1)
Diverticulitis	1 (<0.1)	0		1 (<0.1)
Escherichia bacteraemia	1 (<0.1)	0		1 (<0.1)
Osteomyelitis	1 (<0.1)	0		1 (<0.1)
Pyelonephritis acute	1 (<0.1)	0		1 (<0.1)
Septic shock	1 (<0.1)	0		1 (<0.1)
Upper respiratory tract infection	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Urinary tract infection	1 (<0.1)	0		1 (<0.1)
Urinary tract infection enterococcal	1 (<0.1)	0		1 (<0.1)
Varicella zoster virus infection	1 (<0.1)	0		1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	3 (<0.1)		4 (<0.1)
Colorectal cancer	0	1 (<0.1)		1 (<0.1)
Gastric cancer	0	1 (<0.1)		1 (<0.1)
Metastases to lung	0	1 (<0.1)		1 (<0.1)
Throat cancer	0	1 (<0.1)		1 (<0.1)
Colon cancer stage III	1 (<0.1)	0		1 (<0.1)
Blood and lymphatic system disorders	0	2 (<0.1)		2 (<0.1)
Lymphadenopathy	0	2 (<0.1)		2 (<0.1)
Psychiatric disorders	6 (<0.1)	4 (<0.1)		10 (<0.1)
Bipolar disorder	0	1 (<0.1)		1 (<0.1)
Drug abuse	0	1 (<0.1)		1 (<0.1)
Schizoaffective disorder	0	1 (<0.1)		1 (<0.1)
Substance abuse	0	1 (<0.1)		1 (<0.1)
Anxiety	2 (<0.1)	0		2 (<0.1)
Confusional state	1 (<0.1)	0		1 (<0.1)
Depression	2 (<0.1)	0		2 (<0.1)
Depression suicidal	1 (<0.1)	0		1 (<0.1)
Nervous system disorders	6 (<0.1)	6 (<0.1)		12 (<0.1)
Ageusia	0	1 (<0.1)		1 (<0.1)
Anosmia	0	1 (<0.1)		1 (<0.1)
Cervical radiculopathy	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Headache	2 (<0.1)	1 (<0.1)		3 (<0.1)
Idiopathic intracranial hypertension	0	1 (<0.1)		1 (<0.1)
Neuropathy peripheral	0	1 (<0.1)		1 (<0.1)
Seizure	0	1 (<0.1)		1 (<0.1)
Amnesia	1 (<0.1)	0		1 (<0.1)
Ischaemic stroke	1 (<0.1)	0		1 (<0.1)
Migraine	1 (<0.1)	0		1 (<0.1)
Paraesthesia	1 (<0.1)	0		1 (<0.1)
Speech disorder	1 (<0.1)	0		1 (<0.1)
Eye disorders	2 (<0.1)	0		2 (<0.1)
Eye swelling	1 (<0.1)	0		1 (<0.1)
Retinal detachment	1 (<0.1)	0		1 (<0.1)
Ear and labyrinth disorders	2 (<0.1)	0		2 (<0.1)
Vertigo	2 (<0.1)	0		2 (<0.1)
Cardiac disorders	6 (<0.1)	3 (<0.1)		9 (<0.1)
Cardiac failure congestive	1 (<0.1)	1 (<0.1)		2 (<0.1)
Coronary artery disease	0	1 (<0.1)		1 (<0.1)
Myocardial infarction	0	1 (<0.1)		1 (<0.1)
Acute myocardial infarction	1 (<0.1)	0		1 (<0.1)
Atrial fibrillation	2 (<0.1)	0		2 (<0.1)
Tachycardia	1 (<0.1)	0		1 (<0.1)
Ventricular extrasystoles	1 (<0.1)	0		1 (<0.1)
Vascular disorders	4 (<0.1)	4 (<0.1)		8 (<0.1)
Hypertension	3 (<0.1)	3 (<0.1)		6 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Orthostatic hypotension	0	1 (<0.1)		1 (<0.1)
Deep vein thrombosis	1 (<0.1)	0		1 (<0.1)
Respiratory, thoracic and mediastinal disorders	6 (<0.1)	3 (<0.1)		9 (<0.1)
Dyspnoea	0	1 (<0.1)		1 (<0.1)
Pulmonary embolism	1 (<0.1)	1 (<0.1)		2 (<0.1)
Respiratory failure	1 (<0.1)	1 (<0.1)		2 (<0.1)
Acute respiratory failure	1 (<0.1)	0		1 (<0.1)
Chronic obstructive pulmonary disease	1 (<0.1)	0		1 (<0.1)
Oropharyngeal pain	1 (<0.1)	0		1 (<0.1)
Pleurisy	1 (<0.1)	0		1 (<0.1)
Gastrointestinal disorders	2 (<0.1)	3 (<0.1)		5 (<0.1)
Abdominal pain lower	0	1 (<0.1)		1 (<0.1)
Pancreatitis acute	0	1 (<0.1)		1 (<0.1)
Swollen tongue	0	1 (<0.1)		1 (<0.1)
Duodenal ulcer haemorrhage	1 (<0.1)	0		1 (<0.1)
Retching	1 (<0.1)	0		1 (<0.1)
Hepatobiliary disorders	1 (<0.1)	0		1 (<0.1)
Cholecystitis acute	1 (<0.1)	0		1 (<0.1)
Cholelithiasis	1 (<0.1)	0		1 (<0.1)
Skin and subcutaneous tissue disorders	4 (<0.1)	9 (<0.1)		13 (<0.1)
Urticaria	2 (<0.1)	5 (<0.1)		7 (<0.1)
Psoriasis	0	2 (<0.1)		2 (<0.1)
Angioedema	1 (<0.1)	1 (<0.1)		2 (<0.1)
Pruritus	0	1 (<0.1)		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Rash macular	0	1 (<0.1)		1 (<0.1)
Rash pruritic	1 (<0.1)	1 (<0.1)		2 (<0.1)
Musculoskeletal and connective tissue disorders	4 (<0.1)	3 (<0.1)		7 (<0.1)
Arthralgia	1 (<0.1)	1 (<0.1)		2 (<0.1)
Arthritis	0	1 (<0.1)		1 (<0.1)
Fracture nonunion	0	1 (<0.1)		1 (<0.1)
Rheumatoid arthritis	0	1 (<0.1)		1 (<0.1)
Back pain	1 (<0.1)	0		1 (<0.1)
Polymyalgia rheumatica	1 (<0.1)	0		1 (<0.1)
Synovitis	1 (<0.1)	0		1 (<0.1)
Pregnancy, puerperium and perinatal conditions	1 (<0.1)	0		1 (<0.1)
Pregnancy	1 (<0.1)	0		1 (<0.1)
Reproductive system and breast disorders	0	1 (<0.1)		1 (<0.1)
Breast mass	0	1 (<0.1)		1 (<0.1)
General disorders and administration site conditions	3 (<0.1)	6 (<0.1)		9 (<0.1)
Injection site erythema	0	2 (<0.1)		2 (<0.1)
Injection site swelling	0	2 (<0.1)		2 (<0.1)
Induration	0	1 (<0.1)		1 (<0.1)
Injection site macule	0	1 (<0.1)		1 (<0.1)
Injection site urticaria	0	1 (<0.1)		1 (<0.1)
Incarcerated hernia	1 (<0.1)	0		1 (<0.1)
Non-cardiac chest pain	1 (<0.1)	0		1 (<0.1)
Systemic inflammatory response syndrome	1 (<0.1)	0		1 (<0.1)

System Organ Class Preferred Term	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)	Rate Ratio (95% CI)	Total (N=30346) n (%)
Investigations	3 (<0.1)	3 (<0.1)		6 (<0.1)
Hepatic enzyme increased	0	2 (<0.1)		2 (<0.1)
Blood pressure diastolic increased	1 (<0.1)	1 (<0.1)		2 (<0.1)
Blood pressure increased	1 (<0.1)	0		1 (<0.1)
Heart rate irregular	1 (<0.1)	0		1 (<0.1)
Injury, poisoning and procedural complications	5 (<0.1)	4 (<0.1)		9 (<0.1)
Head injury	0	1 (<0.1)		1 (<0.1)
Hip fracture	1 (<0.1)	1 (<0.1)		2 (<0.1)
Overdose	0	1 (<0.1)		1 (<0.1)
Road traffic accident	0	1 (<0.1)		1 (<0.1)
Femur fracture	1 (<0.1)	0		1 (<0.1)
Immunisation anxiety related reaction	1 (<0.1)	0		1 (<0.1)
Joint injury	1 (<0.1)	0		1 (<0.1)
Post procedural bile leak	1 (<0.1)	0		1 (<0.1)
Ulnar nerve injury	1 (<0.1)	0		1 (<0.1)
Product issues	0	1 (<0.1)		1 (<0.1)
Device dislocation	0	1 (<0.1)		1 (<0.1)

A treatment-emergent adverse event (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.

Percentages are based on the number of safety subjects. Percentages are based on the number of safety subjects. The rate ratio is calculated as the ratio of percentage of participants reporting the event in mRNA-1273 divided by that in Placebo; rate ratio is provided for TEAEs with at least 7 subjects in any vaccination group reporting the event. The 95% CI is calculated using the Miettinen and Nurminen method.

MedDRA version 23.0.

Source: Study 301 Part A CSR Table 14.3.1.15.1 (26 Mar 2021).

2.7.4.2.1.4.5 Vaccine-Associated Enhanced Respiratory Disease: COVID-19 and Severe COVID-19

The DSMB continuously monitored case counts of COVID-19 and severe COVID-19 based on prespecified criteria for any indication of higher disease incidence and/or severity in the mRNA-1273 group compared with the placebo group that might suggest a risk of vaccine harm in the form of VAERD (Section 2.7.4.1.1.1.6; Study 301 Part A CSR Section 7.3.3.4). The prespecified criteria for VAERD have not been met at any time during the study. Fewer cases of severe COVID-19 (Study 301 Part A CSR Table 14.2.2.2.3.1.1) or COVID-19 of any severity (Study 301 Part A CSR Table 14.2.2.1.3.1.1) have been observed in participants who received mRNA-1273 than in those who received placebo.

In contrast to the a priori hypothetical concern for risk of more severe disease (VAERD) being observed in vaccine recipients, participants who received mRNA-1273 and experienced COVID-19 had milder disease compared with participants who received placebo and experienced COVID-19 (based on symptom scores during the 28 days after onset; Study 301 Part A CSR Table 14.2.3.3.1). A reduced level of viral replication (reduced viral load) was found in COVID-19 cases in vaccine recipients compared with placebo recipients. This was consistent with the reduced symptomatology in these participants. In addition, as a further sign of the absence of VAERD, the point estimates for vaccine efficacy tended to be highest for severe disease, lower for any disease, and lowest for asymptomatic infection (Summary of Clinical Efficacy Module 2.7.3 Table 6; Study 301 Part A CSR Table S-1). Based on these investigations, monitoring for VAERD in Study 301 by the DSMB has been discontinued in Part B of the study by mutual agreement of the Sponsor and the DSMB.

The absence of VAERD has been further supported by data from post-authorization use (described as vaccine-associated enhanced disease [VAED]; Section 2.7.4.6.4.4.1).

2.7.4.2.1.4.6 Adverse Events of Interest

In addition to thorough analyses of AEs as described in the foregoing sections, assessments have been performed using SMQs and CMQs (Section 2.7.4.1.1.1.5; Section 2.7.4.2.1). The queries for which potential imbalances were observed or are otherwise of interest were as follows (presented in alphabetical order):

- Anaphylaxis: Nine events were reported for 5 participants (< 0.1%) in the mRNA-1273 group and 18 events were reported for 8 participants (< 0.1%) in the placebo group (Study 301 Part A CSR Table 14.3.1.22.8). Anaphylactic reaction was reported as an SAE

for 2 participants in the placebo group on Days 11 and 10 after the first injection; one event was severe and one was grade 4 in severity; both were considered not related to IP and resolved on the same day with concomitant medications. Anaphylactic reaction of unknown cause was reported for 2 participants in the mRNA-1273 group as nonserious moderate events approximately 2 months after the second dose; both were considered not related to IP and resolved on the same day with concomitant medications. Among the other terms in the SMQ, reported events in the mRNA-1273 group were all nonserious and described as follows: mild cough and mild eye pruritus for one participant on Day 47 after the second dose (not considered related); mild tachypnea on Day 29 after the first dose (which was reported on the day of the second dose), severe tachypnea on Day 1 after the second dose (which was the same day; event resolved on Day 64), and moderate urticaria beginning 30 minutes after the second dose and resolved in 1 hour with concomitant medication (all events considered related) for one participant; and moderate dyspnea (considered related; reported as resolving) and severe swelling face (not considered related; resolving with prednisone) beginning on Day 34 after the second dose for one participant (Study 301 Part A CSR Listing 16.2.7.28). Events in the placebo group were also nonserious and included hypotension and cough; dyspnea, hypotension, and edema; dyspnea and pruritus; hypotension and wheezing; urticaria and asthma; tachypnea (participant later had grade 4 serious anaphylactic reaction); and asthma.

- Central nervous system vascular disorders: A total of 32 participants (0.1%) experienced at least one TEAE in the CNS vascular disorders SMQ (21 participants [0.1%] in the mRNA-1273 group and 11 participants [< 0.1%] in the placebo group) (Study 301 Part A CSR Table 14.3.1.22.10). The following events were reported for more participants in the mRNA-1273 group than in the placebo group: cerebrovascular accident (7 vs. 4), carotid artery stenosis (2 vs. 0), and embolic stroke (2 vs. 0). No cases involved cerebral venous sinus thrombosis; details about locations of thrombosis are in Section 2.7.4.2.1.4.2. No cases of thrombosis with thrombocytopenia syndrome were reported. For all events in the category, the difference between the mRNA-1273 and placebo groups was more pronounced among participants ≥ 65 years of age (11 vs. 4) than among participants ≥ 18 to < 65 years of age (10 vs. 7). The age distribution and the overall incidence in the mRNA-1273 group is consistent with general epidemiology of these types of vascular events, and the timing of the events is also not consistent with an attribution to mRNA-1273 (7 of 10 events occurred more than 28 days after the last dose). Imbalances were also noted for subarachnoid hemorrhage (4 vs. 0) and subdural hematoma (3 vs. 0), but these events were related to trauma (with precipitating events not considered related to mRNA-1273) and are not indicative of a vascular disorder.

- Demyelination: No imbalance was observed for the demyelination SMQ (Study 301 Part A CSR Table 14.3.1.22.6) and there were no reports of Guillain-Barre syndrome (Study 301 Part A CSR Table 14.3.1.8.1.3).

- Dermal filler reaction post vaccination: A total of 34 participants (0.1%) reported at least one TEAE in the dermal filler post-vaccination CMQ (20 participants [0.1%] in the mRNA-1273 group and 14 participants [< 0.1%] in the placebo group) and no imbalance was apparent for any individual PT (Study 301 Part A CSR Table 14.3.1.22.11). The event was considered related to treatment for 4 participants in the mRNA-1273 group and 3 participants in the placebo group. The worst severity of the event was mild for 13 participants in the mRNA-1273 group and 7 participants in the placebo group. The event was reported as an SAE for 2 participants in the mRNA-1273 group and 1 participant in the placebo group (Section 2.7.4.2.1.4.2). None of the participants who experienced this TEAE in this study had reported dermal filler reaction post vaccination in their medical history. When prompted post-baseline for this information, 325 participants (2.1%) in the mRNA-1273 group and 234 participants (1.5%) in the placebo group reported history of dermal filler use (Study 301 Part A CSR Section 7.3.3.3.3).

- Hematopoietic cytopenias: Thrombocytopenia was reported for 5 participants in the mRNA-1273 group and 1 participant in the placebo group (Study 301 Part A CSR Table 14.3.1.22.15); these events were not associated with thrombosis (Section 2.7.4.2.1.4.2) and none were considered related to IP. One participant in each group had an SAE of grade 4 thrombocytopenia: the event occurred on Day 68 (approximately 40 days after the second dose) for the participant in the mRNA-1273 group. At the same time, the participant (who was 72 years old) had severe bacterial pyelonephritis, acute renal failure (SAE), and nephrolithiasis (SAE). The event occurred on Day 131 for the participant in the placebo group, who also had COVID-19 infection and cytokine storm and several other grade 4 SAEs. The thrombocytopenia TEAEs in the mRNA-1273 group were all mild and occurred on Days 25, 57, 60 (concurrent with moderate periorbital hematoma, mild periorbital hemorrhage, grade 4 serious alcohol withdrawal syndrome, and multiple other events), and 153. No imbalance was evident for the other terms included in the SMQ for hematopoietic cytopenias.

- Hypersensitivity: A total of 614 participants (2.0%) reported at least one hypersensitivity event (336 participants [2.2%] in the mRNA-1273 group and 278 participants [1.8%] in the placebo group) (Study 301 Part A CSR Table 14.3.1.22.2). Hypersensitivity events for which larger imbalances between the groups were observed were consistent with

reactogenicity of the vaccine. Injection site urticaria was reported for 38 participants (0.3%) overall in the mRNA-1273 group vs. 1 participant (< 0.1%) in the placebo group; this imbalance was noted in the older age group but not in the younger age group. Injection site rash was reported for 25 participants [0.2%] overall in the mRNA-1273 group vs. 1 participant (< 0.1%) in the placebo group; this imbalance was noted the younger age group but not in the older age group). No imbalance was apparent for events in the angioedema SMQ (82 vs. 71 participants [0.5% for each] in the mRNA-1273 and placebo groups, respectively [Study 301 Part A CSR Table 14.3.1.22.4]).

Data for all queries are referenced in Study Part A CSR Section 7.3.3.3.

2.7.4.2.2 Study 301 Part B

The Study 301 CSR Addendum 1 (Part B) includes data from the PDV through the data cutoff (26 Mar 2021) for participants who completed the PDV. Unblinding was performed at this visit and any subsequent treatment was open label. Safety data were collected during this period for SAEs, MAAEs, TEAEs leading to discontinuation from study participation, and pregnancies. The Part B data provide at least 6 months' median follow-up time for participants treated with mRNA-1273 in Part A and initial safety data for participants treated with mRNA-1273 in Part B (Section 2.7.4.2.2.1). The additional safety data are consistent with findings in Part A; no new safety signals were detected. Events of interest that were analyzed in the Study 301 Part A CSR that also occurred in Part B were investigated and not found to be indicative of a potential safety concern with the mRNA-1273 vaccine.

2.7.4.2.2.1 Participant Follow-up and Crossover Status at Participant Decision Visit

Of the 28,964 participants who started Part B, 1698 participants received placebo in Part A and chose not to receive mRNA-1273 in Part B (they remain in the placebo group); 12,648 participants received placebo in Part A, chose to receive mRNA-1273 in Part B (placebo–mRNA-1273 group), and received at least 1 dose of the vaccine; and 14,618 participants received mRNA-1273 in Part A (Study 301 CSR Addendum 1 [Part B] Table 14.1.1.1.5.5). The median duration of follow-up from the PDV to the data cutoff date was 67 days (range: 1 to 205 days) (Study 301 Part A CSR Table 14.1.6.2.1; the maximum duration is higher than expected because of a few participants who were unblinded earlier in the study). As described in Section 2.7.4.1.2.2.1, the median duration of follow-up for Part A and Part B was 183 days (range: 1 to 218 days) or approximately 6 months. Comparisons of the mRNA-1273 and placebo groups in Part B are of limited value because of the small number of participants who opted to

remain in the placebo group, which created an imbalance in follow-up between the groups (Study 301 CSR Addendum 1 [Part B] Table 14.1.1.1.5.5).

2.7.4.2.2.2 Safety Data

Safety data from Study 301 Part B were consistent with results in Part A.

2.7.4.2.2.2.1 Deaths

A total of 12 participants died in Part B (Study 301 CSR Addendum 1 [Part B] Table 14.3.1.36.1.1): 1 participant in the placebo group (9 days after the PDV), 3 participants in the placebo–mRNA-1273 group (median time from PDV: 54.0 days), and 8 participants in the mRNA-1273 group (median time from PDV: 46.5 days; for one of these participants, the AE that caused death began during Part A [Section 2.7.4.2.1.4.1]). Serious AEs resulting in death are summarized in Table 22.

Table 22 Study 301 Open-Label Phase: Participants With Serious Adverse Events Resulting in Death (Safety Set)

Treatment Assignment	Preferred Term	Study Day of Death	Relationship to IP[a]
mRNA-1273	Sudden death	182	Not related
mRNA-1273	Cardiac arrest	155	Not related
mRNA-1273	Myocardial infarction	95	Not related
mRNA-1273	Acute myocardial infarction	184	Not related
mRNA-1273	Cerebrovascular accident	212	Not related
mRNA-1273	Head injury	180	Not related
mRNA-1273	Pulmonary embolism, pulseless electrical activity, gastrointestinal hemorrhage	138	Not related
mRNA-1273	Pulmonary mass[b]	136	Not related
Placebo–mRNA-1273	Cardiac failure congestive, gastrointestinal hemorrhage, anticoagulation drug level above therapeutic	27[c]	Not related
Placebo–mRNA-1273	Accidental overdose	10[c]	Not related
Placebo–mRNA-1273	Cerebrovascular accident	44[c]	Not related
Placebo	Ventricular arrhythmia	128	Not related

Abbreviation: IP = investigational product

[a] Relationship is based on investigator assessment.

[b] This participant is not included in Study 301 CSR Addendum 1 (Part B) Listing 16.2.7.9.3 because the event began during Part A (Study 301 Part A CSR Listing 16.2.7.14).

[c] This is the number of days since the first dose of mRNA-1273 in Part B.

Source: Study 301 CSR Addendum 1 (Part B) Listing 16.2.7.9.3 (26 Mar 2021).

2.7.4.2.2.2.2 Other Serious Adverse Events

At least 1 SAE was reported for 296 participants (1.0%) (Study 301 CSR Addendum 1 [Part B] Table 14.3.1.32.1.1). Serious AEs that were considered related to open-label treatment were reported only in the placebo–mRNA-1273 group and included severe paresthesia that occurred on Day 9 and resolved on Day 11 (the participant also had swelling, redness, and tenderness at the injection site; participant was premedicated with antihistamines before the second dose), severe muscular weakness (lower extremities) that occurred on Day 1 and resolved on Day 3 after the second dose of mRNA-1273 and co-occurred with pyrexia, spontaneous abortion that occurred/resolved on Day 11 (positive home pregnancy test 6 days after expected menses and 10 days after first dose of mRNA-1273; bleeding from 11 to 17 days after vaccination), and moderate autoimmune thyroiditis that occurred on Day 27 and was ongoing (participant had family history of Hashimoto's thyroiditis) (Study 301 CSR Addendum 1 [Part B] Listing 16.2.7.10.3). Anaphylactic reaction was reported for 2 participants in the placebo–mRNA-1273 group (1 participant had a reaction to a steroid shot in the shoulder that occurred over 2 months after the second dose of mRNA-1273 and 1 participant had an allergic reaction to an unknown allergen 18 days after the first dose of mRNA-1273) and 1 participant in the mRNA-1273 group (anaphylaxis occurred over 4 months after the second dose of mRNA-1273 during antigen challenge allergy testing).

Six participants in the placebo–mRNA-1273 group discontinued the study vaccine due to a serious TEAE (one each of arthritis bacterial, pancreatic carcinoma metastatic, prostate cancer, anaphylactic reaction, brain stem infarction, and spontaneous abortion); none of the events were considered related to study vaccine (Study 301 CSR Addendum 1 [Part B] Listing 16.2.7.9.3). As of the data cutoff date, 2 SUSARs have been reported for Study 301 Part B: muscular weakness (musculoskeletal and connective tissue disorders) and pericardial effusion (cardiac disorders); this was consistent with Part A events.

Thrombotic Events

Incidence of thrombotic events in Part B was consistent with observations in Part A (Study 301 CSR Addendum 1 [Part B] Section 7.3.2). In the placebo-mRNA group, 7 participants experienced an SAE of stroke. Four of these were > 65 years old (68 to 84 years of age) and 4 were males. Time to onset was between 1 day to approximately 2 months after vaccination. In the mRNA group, 3 participants experienced an SAE of stroke (including 1 fatal event) and 1 serious transient ischemic attack. All occurred approximately 6 months after the vaccination, were considered unrelated to the vaccine, and occurred in participants with risk factors for cerebrovascular accident including hyperlipidemia, type 2 diabetes, atherosclerosis, or aortic stenosis. All events were considered unrelated to vaccination.

2.7.4.2.2.2.3 Pericarditis and Myocarditis

Adverse event data from Part B were assessed for clinical symptoms that have been associated with myocarditis and pericarditis as described for Part A (Section 2.7.4.2.1.3.2.1). In Part B, no cases of myocarditis were reported. One case of acute pericarditis (verbatim: “acute infective pericarditis”) was reported as an SAE in a 63-year-old male in the placebo group; the event occurred 24 days after a COVID-19 diagnosis. In addition, one case of pericardial effusion was reported as an SAE (resolving) in a 23-year-old male in the placebo–mRNA-1273 group. The participant had experienced bradycardia relative to baseline for over 1 month before seeking medical attention from a cardiologist (outpatient clinic), and the diagnosis of pericardial effusion was made 19 days after the second dose of mRNA-1273. The event was expected to resolve without treatment. The investigator considered the event to be related to study vaccine.

Because myocarditis and pericarditis are typically rare events, Moderna assessed the clinical database for evidence of individual clinical symptoms that have been associated with these events (Study 301 CSR Addendum 1 [Part B] Section 7.3.2). The open-label phase of Study 301 (Part B) was assessed for TEAEs potentially associated with myocarditis or pericarditis. The TEAE data were assessed for any events mapping to PTs in the CDC working case definition diagnostic algorithm for acute myocarditis and pericarditis. Using this approach, TEAEs were identified for the following 7 PTs: angina pectoris, chest discomfort, chest pain, musculoskeletal chest pain, dyspnea, palpitations, and syncope.

The TEAE database (collected for the 28 days after any injection) was assessed for the identified PTs, and the assessment further narrowed for those TEAEs occurring in temporal proximity to injection (within 7 days of any injection) based on the observed epidemiology of cases of myocarditis and pericarditis characterized from post-authorization data. As part of the study, the collection of unsolicited TEAE that are nonserious do not include narrative information but rather the verbatim entries regarding the event. All TEAEs were reviewed regardless of severity or causality (as per investigator). Finally, the listing of participants reporting any of these PTs within 7 days of any injection was cross-checked to identify any participants reporting more than 1 of the targeted PTs, reflecting constellations more suggestive of a possible diagnosis of myocarditis or pericarditis.

Only 1 participant reported more than one of the target PTs: a 66-year-old male experienced 2 nonserious, moderate, and considered unrelated TEAEs of chest discomfort and dyspnea on Day 5 after the second dose. Both TEAEs resolved, the chest discomfort within 6 days and the dyspnea within 2 days. Other potentially relevant TEAEs reported for this participant within 7 days of these events were unrelated nonserious TEAEs of rhinorrhea, cough, fatigue, decreased appetite, and headache.

In this assessment of the targeted PTs, 1 participant manifested more than 1 of the identified PTs within 7 days of any injection. Other TEAEs identified in this analysis were predominantly short in duration, resolved, and did not cluster with other relevant TEAEs to suggest cases of myocarditis or pericarditis.

2.7.4.2.3 Study 201

Safety results for Study 201 (approximately 400 participants in mRNA-1273 groups and approximately 200 participants in the placebo group) were consistent with those for Study 301 Part A (approximately 15,000 participants in each group). The bulk of the data presented in this section are from the Study 201 Primary Analysis CSR (data collected through Day 57). Findings from the Study 201 CSR Addendum 1 (End of Part A) immunogenicity and safety addendum are described in Section 2.7.4.2.3.4.

2.7.4.2.3.1 Solicited Adverse Reactions

2.7.4.2.3.1.1 Incidence and Severity of Solicited Adverse Reactions

The incidence of solicited local and systemic ARs within 7 days after any injection was higher for participants in the mRNA-1273 total group (all participants who received 50 µg or 100 µg mRNA-1273) (356/400 [89.0%] and 315/400 [78.8%] for local and systemic, respectively) than for those who received placebo (38/200 [19.0%] and 91/200 [45.5%]) (Study 201 Primary Analysis CSR Table 13). Incidence differed between the 50 µg and 100 µg mRNA-1273 dose levels, respectively, by 5.0 percentage points for solicited ARs (91.0% vs. 96.0%), 7.0 percentage points for solicited local ARs (85.5% vs. 92.5%), and 9.5 percentage points for solicited systemic ARs (74.0% vs. 83.5%). No grade 4 solicited ARs, local or systemic, were reported after any injection.

The incidence of solicited local ARs after the first injection appeared to be dose-dependent (131/200 participants [65.5%] in the 50 µg mRNA-1273 group and 168/200 participants [84.0%] in the 100 µg mRNA-1273 group); this was because of the dose-dependent incidence of pain (131/200 participants [65.5%] in the 50 µg group and 166/199 participants [83.4%] in the 100 µg group) (Table 23). Few participants reported local ARs other than pain. Findings were similar after the second injection, except that differences between mRNA-1273 dose levels were smaller (Table 24). Grade 3 pain was reported for 1 participant each in the 50 µg and 100 µg mRNA-1273 groups (0.5%) after the first injection; all other local ARs were grade 2 or lower in severity (Study 201 Primary Analysis CSR Table 14). After the second injection, erythema was

reported at grade 3 only among participants treated with 100 µg mRNA-1273 (5/198 [2.5%]) (Study 201 Primary Analysis CSR Table 15).

The incidence of solicited systemic ARs after the first injection was similar in the 50 µg and 100 µg mRNA-1273 groups (172/399 participants [43.1%] in the mRNA-1273 total group) and higher than in the placebo group (64/199 participants [32.2%]) (Table 23). Incidence of all solicited systemic ARs was higher in the mRNA-1273 groups after the second injection than after the first, and dose-dependent differences were observed, especially for chills, fatigue, and myalgia (Table 24). Incidence of systemic ARs in the placebo group after the second injection was essentially the same as after the first. The most common solicited systemic ARs in the mRNA-1273 total group were headache (101/399 [25.3%]) and fatigue (98/399 [24.6%]) after the first injection and fatigue (232/393 [59.0%]), headache (200/393 [50.9%]), and myalgia (185/393 [47.1%]) after the second injection (Table 23 and Table 24). Grade 3 solicited systemic ARs were reported after the first injection for 5 participants who received mRNA-1273 (4 at 50 µg and 1 at 100 µg) and 4 participants who received placebo. After the second injection, grade 3 systemic ARs were reported for 45/393 participants (11.5%) in the mRNA-1273 total group (incidence was similar between dose levels) and 2/194 participants (1.0%) in the placebo group. Fatigue was the event most frequently reported at grade 3 (18/198 participants [9.1%] in the 100 µg mRNA-1273 group and 11/195 participants [5.6%] in the 50 µg mRNA-1273 group).

Table 23 Study 201: Solicited Adverse Reactions Within 7 Days After First Injection by Grade (First Injection Solicited Safety Set)

Solicited Adverse Reaction Category Grade	Placebo (N=199) n (%)	mRNA-1273 50 µg (N=200) n (%)	mRNA-1273 100 µg (N=200) n (%)	mRNA-1273 Total (N=400) n (%)
Solicited adverse reactions - N1	199	200	200	400
Any solicited adverse reactions	77 (38.7)	142 (71.0)	176 (88.0)	318 (79.5)
95% CI	31.9, 45.8	64.2, 77.2	82.7, 92.2	75.2, 83.4
Grade 1	55 (27.6)	105 (52.5)	149 (74.5)	254 (63.5)
Grade 2	15 (7.5)	30 (15.0)	24 (12.0)	54 (13.5)
Grade 3	4 (2.0)	5 (2.5)	2 (1.0)	7 (1.8)
Grade 4	0	0	0	0
Solicited local adverse reactions - N1	199	200	200	400
Any solicited local adverse reactions	27 (13.6)	131 (65.5)	168 (84.0)	299 (74.8)
95% CI	9.1, 19.1	58.5, 72.1	78.2, 88.8	70.2, 78.9
Grade 1	26 (13.1)	124 (62.0)	157 (78.5)	281 (70.3)
Grade 2	1 (0.5)	6 (3.0)	10 (5.0)	16 (4.0)
Grade 3	0	1 (0.5)	1 (0.5)	2 (0.5)
Grade 4	0	0	0	0
Pain - N1	199	200	199	399
Any	21 (10.6)	131 (65.5)	166 (83.4)	297 (74.4)
Grade 1	21 (10.6)	125 (62.5)	155 (77.9)	280 (70.2)
Grade 2	0	5 (2.5)	10 (5.0)	15 (3.8)
Grade 3	0	1 (0.5)	1 (0.5)	2 (0.5)
Grade 4	0	0	0	0
Erythema (redness) - N1	199	200	199	399
Any	1 (0.5)	5 (2.5)	5 (2.5)	10 (2.5)
Grade 1	1 (0.5)	5 (2.5)	5 (2.5)	10 (2.5)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0

Solicited Adverse Reaction Category Grade	Placebo (N=199) n (%)	mRNA-1273 50 µg (N=200) n (%)	mRNA-1273 100 µg (N=200) n (%)	mRNA-1273 Total (N=400) n (%)
Swelling (hardness)- N1	199	200	200	400
Any	1 (0.5)	8 (4.0)	8 (4.0)	16 (4.0)
Grade 1	1 (0.5)	7 (3.5)	8 (4.0)	15 (3.8)
Grade 2	0	1 (0.5)	0	1 (0.3)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Lymphadenopathy - N1[a]	199	200	199	399
Any	5 (2.5)	10 (5.0)	18 (9.0)	28 (7.0)
Grade 1	4 (2.0)	10 (5.0)	16 (8.0)	26 (6.5)
Grade 2	1 (0.5)	0	2 (1.0)	2 (0.5)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Solicited systemic adverse reactions - N1	199	200	199	399
Any solicited systemic adverse reactions	64 (32.2)	83 (41.5)	89 (44.7)	172 (43.1)
95% CI	25.7, 39.1	34.6, 48.7	37.7, 51.9	38.2, 48.1
Grade 1	42 (21.1)	50 (25.0)	69 (34.7)	119 (29.8)
Grade 2	15 (7.5)	26 (13.0)	18 (9.0)	44 (11.0)
Grade 3	4 (2.0)	4 (2.0)	1 (0.5)	5 (1.3)
Grade 4	0	0	0	0
Fever - N1	199	200	199	399
Any	0	0	1 (0.5)	1 (0.3)
Grade 1	0	0	0	0
Grade 2	0	0	1 (0.5)	1 (0.3)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Headache - N1	199	200	199	399
Any	36 (18.1)	58 (29.0)	43 (21.6)	101 (25.3)
Grade 1	30 (15.1)	42 (21.0)	35 (17.6)	77 (19.3)
Grade 2	2 (1.0)	13 (6.5)	8 (4.0)	21 (5.3)
Grade 3	4 (2.0)	3 (1.5)	0	3 (0.8)
Grade 4	0	0	0	0

Solicited Adverse Reaction Category Grade	Placebo (N=199) n (%)	mRNA-1273 50 µg (N=200) n (%)	mRNA-1273 100 µg (N=200) n (%)	mRNA-1273 Total (N=400) n (%)
Fatigue - N1	199	200	199	399
Any	35 (17.6)	48 (24.0)	50 (25.1)	98 (24.6)
Grade 1	25 (12.6)	30 (15.0)	38 (19.1)	68 (17.0)
Grade 2	10 (5.0)	17 (8.5)	11 (5.5)	28 (7.0)
Grade 3	0	1 (0.5)	1 (0.5)	2 (0.5)
Grade 4	0	0	0	0
Myalgia - N1	199	200	199	399
Any	14 (7.0)	21 (10.5)	28 (14.1)	49 (12.3)
Grade 1	12 (6.0)	14 (7.0)	23 (11.6)	37 (9.3)
Grade 2	2 (1.0)	7 (3.5)	4 (2.0)	11 (2.8)
Grade 3	0	0	1 (0.5)	1 (0.3)
Grade 4	0	0	0	0
Arthralgia - N1	199	200	199	399
Any	10 (5.0)	18 (9.0)	18 (9.0)	36 (9.0)
Grade 1	7 (3.5)	14 (7.0)	15 (7.5)	29 (7.3)
Grade 2	3 (1.5)	4 (2.0)	2 (1.0)	6 (1.5)
Grade 3	0	0	1 (0.5)	1 (0.3)
Grade 4	0	0	0	0
Nausea/vomiting - N1	199	200	199	399
Any	10 (5.0)	11 (5.5)	6 (3.0)	17 (4.3)
Grade 1	5 (2.5)	10 (5.0)	5 (2.5)	15 (3.8)
Grade 2	5 (2.5)	1 (0.5)	0	1 (0.3)
Grade 3	0	0	1 (0.5)	1 (0.3)
Grade 4	0	0	0	0
Chills - N1	199	200	199	399
Any	6 (3.0)	13 (6.5)	10 (5.0)	23 (5.8)
Grade 1	5 (2.5)	10 (5.0)	6 (3.0)	16 (4.0)
Grade 2	1 (0.5)	3 (1.5)	3 (1.5)	6 (1.5)
Grade 3	0	0	1 (0.5)	1 (0.3)
Grade 4	0	0	0	0

Solicited Adverse Reaction Category Grade	Placebo (N=199) n (%)	mRNA-1273 50 µg (N=200) n (%)	mRNA-1273 100 µg (N=200) n (%)	mRNA-1273 Total (N=400) n (%)
Rash - N1	199	200	199	399
Any	5 (2.5)	6 (3.0)	5 (2.5)	11 (2.8)

Abbreviations: CI = confidence intervals; N1 = number of exposed participants who submitted any data for the event.

Percentages are based on the number of exposed participants who submitted any data for the event (N1).

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

[a] Adverse reaction grading is described in Table 3.

[b] Study 201 tables reported localized axillary swelling or tenderness ipsilateral to the vaccination arm under the term lymphadenopathy.

Source: Study 201 Primary Analysis CSR Table 14 (05 Nov 2020).

Table 24 Study 201: Solicited Adverse Reactions Within 7 Days After Second Injection (Second Injection Solicited Safety Set)

Solicited Adverse Reaction Category Grade	Placebo (N=194) n (%)	mRNA-1273 50 µg (N=195) n (%)	mRNA-1273 100 µg (N=198) n (%)	mRNA-1273 Total (N=393) n (%)
Solicited adverse reactions - N1	194	195	198	393
Any solicited adverse reactions	66 (34.0)	171 (87.7)	178 (89.9)	349 (88.8)
95% CI	27.4, 41.2	82.2, 92.0	84.8, 93.7	85.3, 91.7
Grade 1	53 (27.3)	90 (46.2)	64 (32.3)	154 (39.2)
Grade 2	10 (5.2)	60 (30.8)	83 (41.9)	143 (36.4)
Grade 3	2 (1.0)	21 (10.8)	31 (15.7)	52 (13.2)
Grade 4	0	0	0	0
Solicited local adverse reactions - N1	194	195	198	393
Any solicited local adverse reactions	16 (8.2)	156 (80.0)	170 (85.9)	326 (83.0)
95% CI	4.8, 13.0	73.7, 85.4	80.2, 90.4	78.9, 86.5
Grade 1	16 (8.2)	127 (65.1)	129 (65.2)	256 (65.1)
Grade 2	0	27 (13.8)	34 (17.2)	61 (15.5)
Grade 3	0	2 (1.0)	7 (3.5)	9 (2.3)
Grade 4	0	0	0	0

Solicited Adverse Reaction Category Grade	Placebo (N=194) n (%)	mRNA-1273 50 µg (N=195) n (%)	mRNA-1273 100 µg (N=198) n (%)	mRNA-1273 Total (N=393) n (%)
Pain - N1	194	195	198	393
Any	15 (7.7)	155 (79.5)	169 (85.4)	324 (82.4)
Grade 1	15 (7.7)	131 (67.2)	140 (70.7)	271 (69.0)
Grade 2	0	22 (11.3)	28 (14.1)	50 (12.7)
Grade 3	0	2 (1.0)	1 (0.5)	3 (0.8)
Grade 4	0	0	0	0
Erythema (redness) - N1	194	195	198	393
Any	0	10 (5.1)	15 (7.6)	25 (6.4)
Grade 1	0	5 (2.6)	7 (3.5)	12 (3.1)
Grade 2	0	5 (2.6)	3 (1.5)	8 (2.0)
Grade 3	0	0	5 (2.5)	5 (1.3)
Grade 4	0	0	0	0
Swelling (hardness)- N1	194	195	198	393
Any	1 (0.5)	12 (6.2)	21 (10.6)	33 (8.4)
Grade 1	1 (0.5)	6 (3.1)	14 (7.1)	20 (5.1)
Grade 2	0	6 (3.1)	6 (3.0)	12 (3.1)
Grade 3	0	0	1 (0.5)	1 (0.3)
Grade 4	0	0	0	0
Lymphadenopathy - N1[a]	194	195	198	393
Any	1 (0.5)	19 (9.7)	20 (10.1)	39 (9.9)
Grade 1	1 (0.5)	12 (6.2)	17 (8.6)	29 (7.4)
Grade 2	0	7 (3.6)	3 (1.5)	10 (2.5)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Solicited systemic adverse reactions - N1	194	195	198	393
Any solicited systemic adverse reactions	58 (29.9)	135 (69.2)	153 (77.3)	288 (73.3)
95% CI	23.5, 36.9	62.2, 75.6	70.8, 82.9	68.6, 77.6
Grade 1	45 (23.2)	55 (28.2)	56 (28.3)	111 (28.2)
Grade 2	10 (5.2)	58 (29.7)	72 (36.4)	130 (33.1)
Grade 3	2 (1.0)	20 (10.3)	25 (12.6)	45 (11.5)
Grade 4	0	0	0	0

Solicited Adverse Reaction Category Grade	Placebo (N=194) n (%)	mRNA-1273 50 µg (N=195) n (%)	mRNA-1273 100 µg (N=198) n (%)	mRNA-1273 Total (N=393) n (%)
Fever - N1	194	195	198	393
Any	1 (0.5)	12 (6.2)	26 (13.1)	38 (9.7)
Grade 1	1 (0.5)	7 (3.6)	19 (9.6)	26 (6.6)
Grade 2	0	3 (1.5)	3 (1.5)	6 (1.5)
Grade 3	0	2 (1.0)	4 (2.0)	6 (1.5)
Grade 4	0	0	0	0
Headache - N1	194	195	198	393
Any	33 (17.0)	96 (49.2)	104 (52.5)	200 (50.9)
Grade 1	33 (17.0)	65 (33.3)	56 (28.3)	121 (30.8)
Grade 2	0	22 (11.3)	39 (19.7)	61 (15.5)
Grade 3	0	9 (4.6)	9 (4.5)	18 (4.6)
Grade 4	0	0	0	0
Fatigue - N1	194	195	198	393
Any	41 (21.1)	104 (53.3)	128 (64.6)	232 (59.0)
Grade 1	33 (17.0)	44 (22.6)	44 (22.2)	88 (22.4)
Grade 2	6 (3.1)	49 (25.1)	66 (33.3)	115 (29.3)
Grade 3	2 (1.0)	11 (5.6)	18 (9.1)	29 (7.4)
Grade 4	0	0	0	0
Myalgia - N1	194	195	198	393
Any	15 (7.7)	81 (41.5)	104 (52.5)	185 (47.1)
Grade 1	12 (6.2)	36 (18.5)	35 (17.7)	71 (18.1)
Grade 2	3 (1.5)	35 (17.9)	54 (27.3)	89 (22.6)
Grade 3	0	10 (5.1)	15 (7.6)	25 (6.4)
Grade 4	0	0	0	0
Arthralgia - N1	194	195	198	393
Any	13 (6.7)	68 (34.9)	77 (38.9)	145 (36.9)
Grade 1	11 (5.7)	32 (16.4)	32 (16.2)	64 (16.3)
Grade 2	2 (1.0)	29 (14.9)	37 (18.7)	66 (16.8)
Grade 3	0	7 (3.6)	8 (4.0)	15 (3.8)
Grade 4	0	0	0	0
Nausea/vomiting - N1	194	195	198	393
Any	2 (1.0)	25 (12.8)	41 (20.7)	66 (16.8)
Grade 1	2 (1.0)	18 (9.2)	25 (12.6)	43 (10.9)

Solicited Adverse Reaction Category Grade	Placebo (N=194) n (%)	mRNA-1273 50 µg (N=195) n (%)	mRNA-1273 100 µg (N=198) n (%)	mRNA-1273 Total (N=393) n (%)
Grade 2	0	7 (3.6)	16 (8.1)	23 (5.9)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Chills - N1	194	195	198	393
Any	5 (2.6)	49 (25.1)	78 (39.4)	127 (32.3)
Grade 1	4 (2.1)	22 (11.3)	30 (15.2)	52 (13.2)
Grade 2	1 (0.5)	24 (12.3)	47 (23.7)	71 (18.1)
Grade 3	0	3 (1.5)	1 (0.5)	4 (1.0)
Grade 4	0	0	0	0
Rash - N1	194	195	198	393
Any	1 (0.5)	10 (5.1)	6 (3.0)	16 (4.1)

Abbreviations: CI = confidence intervals; N1 = number of exposed participants who submitted any data for the event.

Percentages are based on the number of exposed participants who submitted any data for the event (N1).

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

[a] Adverse reaction grading is described in Table 3.

[b] Study 201 tables reported localized axillary swelling or tenderness ipsilateral to the vaccination arm under the term lymphadenopathy.

Source: Study 201 Primary Analysis CSR Table 15 (05 Nov 2020).

2.7.4.2.3.1.2 Onset, Duration and Persistence of Solicited Adverse Reactions

In all groups, participants most often reported solicited local and systemic ARs within the first 3 days after the first or second injection, particularly on Day 2 (Study 201 Primary Analysis CSR Table 14.3.1.2.1 and Table 14.3.1.2.2).

The mean duration of solicited local and systemic ARs (first reported within the 7 days after any injection) was 2.9 and 3.1 days, respectively, in the mRNA-1273 total group and 2.0 and 2.4 days, respectively, in the placebo group (Study 201 Primary Analysis CSR Table 16).

Solicited ARs that were ongoing 7 days after any injection and reported as TEAEs were reported for 28/400 participants (7.0%) in the mRNA-1273 total group and 8/200 participants (4.0%) in the placebo group (Study 201 Primary Analysis CSR Section 7.1.2); these were not events with initial onset after 7 or more days. No solicited AR met SAE criteria. The persistent events with highest incidence in the mRNA-1273 total group were fatigue (14/400 [3.5%]), headache (11/400 [2.8%]), and arthralgia and myalgia (both 7/400 [1.8%]); most events were reported for ≤ 3 participants in any treatment group.

2.7.4.2.3.1.3 Medication Use for Solicited Adverse Reactions of Pain and Fever

After any injection, medication to treat or prevent pain and fever was reported by 79/200 (39.5%) and 103/200 (51.5%) participants in the 50 µg and 100 µg mRNA-1273 groups, respectively, and 29/200 (14.5%) participants in the placebo group (Study 201 Primary Analysis CSR Table 14.1.4.4.2.3). After the first injection, use of medication to treat or prevent pain and fever was reported by 30/200 [15%] participants each in the 50 µg and 100 µg mRNA-1273 groups and 21/199 [10.6%] participants in the placebo group (Study 201 Primary Analysis CSR Table 14.1.4.4.2.1), and all of this use occurred within 7 days after injection (Study 201 Primary Analysis CSR Table 14.1.4.4.1.1). After the second injection, use of medication to treat or prevent pain and fever was reported by 69/195 [35.4%] and 97/198 [49.0%] participants in the 50 µg and 100 µg mRNA-1273 groups, respectively, and (13/194 [6.7%] participants in the placebo group (Study 201 Primary Analysis CSR Table 14.1.4.4.2.2) and all of this use occurred primarily within 7 days after the second injection (Study 201 Primary Analysis CSR Table 14.1.4.4.1.2). These results, summarized from participant entries in the eDiary, were consistent with analgesic/antipyretic use reported on the concomitant medication use CRF (Study 201 Primary Analysis CSR Section 7.1.7).

2.7.4.2.3.2 Unsolicited Adverse Events

2.7.4.2.3.2.1 Summary of Unsolicited Adverse Events

The incidence of unsolicited TEAEs up to the Day 57 visit was similar between the mRNA-1273 total group (120/400 [30.0%]) and the placebo group (55/200 [27.5%]), and no dose-dependent increase was observed in the mRNA-1273 groups (mRNA-1273 50 µg: 61/200 [30.5%] and mRNA-1273 100 µg: 59/200 [29.5%]) (Table 25). Treatment-related TEAEs were more commonly reported by participants who received mRNA-1273 (either dose) (43/400 [10.8%]) than by those who received placebo (13/200 [6.5%]).

One SAE of pneumonia, which was not considered by the investigator to be related to IP, occurred in the mRNA-1273 50 µg group. A case narrative for this participant is provided in Study 201 Primary Analysis CSR Section 15. No fatal SAEs occurred up to the Day 57 visit.

The incidence of MAAEs was 42/400 (10.5%) in the mRNA-1273 total group and 19/200 (9.5%) in the placebo group. Few participants in any group had MAAEs considered related to IP; the highest incidence was in the mRNA-1273 100 µg group (5/200 [2.5%]).

One participant each in the mRNA-1273 50 µg (1/200 [0.5%]; pneumonia SAE) and placebo (1/200 [0.5%]; COVID-19) groups had a TEAE that led to discontinuation of study vaccine. No participants had an unsolicited TEAE that led to study discontinuation. (Study 201 Primary Analysis CSR Listing 16.2.7.9).

The incidence of unsolicited severe TEAEs up to the Day 57 visit regardless of relationship was low in each group (13/400 [3.3%] in the mRNA-1273 total group and 4/200 [2.0%] in the placebo group). For the mRNA-1273 and placebo groups, approximately half of the reported unsolicited severe TEAEs were considered related to IP.

Table 25 Study 201: Unsolicited Treatment-Emergent Adverse Events From Day 1 to Day 57 Visit (Safety Set)

Category	Placebo (N=200) n (%)	mRNA-1273 50 µg (N=200) n (%)	mRNA-1273 100 µg (N=200) n (%)	mRNA-1273 Total mRNA-1273 (N=400) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination				
All	55 (27.5)	61 (30.5)	59 (29.5)	120 (30.0)
Serious	0	1 (0.5)	0	1 (0.3)
Fatal	0	0	0	0
Medically attended	19 (9.5)	24 (12.0)	18 (9.0)	42 (10.5)
Leading to discontinuation from study vaccine	1 (0.5)	1 (0.5)	0	1 (0.3)
Leading to study discontinuation	0	0	0	0
Severe	4 (2.0)	8 (4.0)	5 (2.5)	13 (3.3)
Unsolicited TEAEs related to study vaccination				
All	13 (6.5)	16 (8.0)	27 (13.5)	43 (10.8)
Serious	0	0	0	0
Fatal	0	0	0	0
Medically attended	1 (0.5)	1 (0.5)	5 (2.5)	6 (1.5)
Leading to discontinuation from study vaccine	0	0	0	0
Leading to study discontinuation	0	0	0	0
Severe	2 (1.0)	4 (2.0)	2 (1.0)	6 (1.5)

Abbreviations: TEAE = treatment-emergent adverse event.

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

Percentages are based on the number of safety participants.

Source: Study 201 Primary Analysis CSR Table 14.3.1.7.2 (05 Nov 2020).

2.7.4.2.3.2.2 Most Common Unsolicited Adverse Events by System Organ Class and Preferred Term

In the mRNA-1273 total and placebo groups, the unsolicited TEAE incidence in each SOC was < 10%. The SOCs with the highest incidence of unsolicited TEAEs (incidence > 5%) in the mRNA-1273 total or placebo groups were general disorders and administration site conditions (36/400 [9.0%] and 10/200 [5.0%], respectively), musculoskeletal and connective tissue disorders (28/400 [7.0%] and 9/200 [4.5%], respectively), nervous system disorders (28/400 [7.0%] and 7/200 [3.5%], respectively), and infections and infestations (15/400 [3.8%] and 13/200 [6.5%], respectively) (Table 26).

The incidence of the most common unsolicited TEAEs was similar between the mRNA-1273 total and placebo groups; frequently reported events were those typically associated with

reactogenicity. The common unsolicited TEAEs with the highest incidence (≥ 2%) in the mRNA-1273 total group or placebo group (by decreasing incidence in the mRNA-1273 total group) were headache (18/400 [4.5%] and 6/200 [3.0%], respectively), fatigue (15/400 [3.8%] and 6/200 [3.0%], respectively), COVID-19 (2/400 [0.5%] and 5/200 [2.5%], respectively), arthralgia (9/400 [2.3%] and 4/200 [2.0%], respectively), and myalgia (8/400 [2.0%] and 3/200 [1.5%], respectively) (Table 26).

Two participants (1.0%) in the mRNA-1273 50 µg group and 5 participants (2.5%) in the placebo group had unsolicited TEAEs of COVID-19 infection up to the Day 57 visit (Table 26). For one of the participants in the mRNA-1273 50 µg group, the onset of COVID-19 occurred on Day 10 after the first injection. Both cases of COVID-19 in the mRNA-1273 50 µg group were mild in severity (one participant remained asymptomatic).

Table 26 Study 201: Common Unsolicited Treatment-Emergent Adverse Events From Day 1 to Day 57 Visit (1% or More in Any Treatment Group Based on Preferred Term) by System Organ Class and Preferred Term (Safety Set)

		mRNA-1273		
System Organ Class Preferred Term	**Placebo (N=200) n (%)**	**50 µg (N=200) n (%)**	**100 µg (N=200) n (%)**	**Total mRNA-1273 (N=400) n (%)**
Number of participants reporting unsolicited adverse events	55 (27.5)	61 (30.5)	59 (29.5)	120 (30.0)
Number of unsolicited adverse events	87	118	94	212
Infections and infestations	13 (6.5)	8 (4.0)	7 (3.5)	15 (3.8)
Urinary tract infection	1 (0.5)	3 (1.5)	1 (0.5)	4 (1.0)
COVID-19	5 (2.5)	2 (1.0)	0	2 (0.5)
Upper respiratory tract infection	2 (1.0)	1 (0.5)	0	1 (0.3)
Immune system disorders	1 (0.5)	1 (0.5)	2 (1.0)	3 (0.8)
Seasonal allergy	0	1 (0.5)	2 (1.0)	3 (0.8)
Psychiatric disorders	0	2 (1.0)	3 (1.5)	5 (1.3)
Depression	0	0	2 (1.0)	2 (0.5)
Nervous system disorders	7 (3.5)	15 (7.5)	13 (6.5)	28 (7.0)
Headache	6 (3.0)	10 (5.0)	8 (4.0)	18 (4.5)
Syncope	0	2 (1.0)	1 (0.5)	3 (0.8)
Respiratory, thoracic and mediastinal disorders	7 (3.5)	5 (2.5)	4 (2.0)	9 (2.3)
Rhinorrhea	0	1 (0.5)	3 (1.5)	4 (1.0)
Oropharyngeal pain	2 (1.0)	2 (1.0)	1 (0.5)	3 (0.8)
Cough	3 (1.5)	1 (0.5)	0	1 (0.3)

System Organ Class Preferred Term	Placebo (N=200) n (%)	mRNA-1273 50 µg (N=200) n (%)	mRNA-1273 100 µg (N=200) n (%)	Total mRNA-1273 (N=400) n (%)
Sinus congestion	2 (1.0)	0	0	0
Gastrointestinal disorders	6 (3.0)	9 (4.5)	7 (3.5)	16 (4.0)
Nausea	0	2 (1.0)	2 (1.0)	4 (1.0)
Diarrhea	1 (0.5)	3 (1.5)	0	3 (0.8)
Toothache	1 (0.5)	2 (1.0)	0	2 (0.5)
Skin and subcutaneous tissue disorders	8 (4.0)	11 (5.5)	6 (3.0)	17 (4.3)
Dermatitis contact	3 (1.5)	5 (2.5)	2 (1.0)	7 (1.8)
Rash	2 (1.0)	3 (1.5)	0	3 (0.8)
Musculoskeletal and connective tissue disorders	9 (4.5)	16 (8.0)	12 (6.0)	28 (7.0)
Arthralgia	4 (2.0)	5 (2.5)	4 (2.0)	9 (2.3)
Myalgia	3 (1.5)	6 (3.0)	2 (1.0)	8 (2.0)
Back pain	1 (0.5)	2 (1.0)	1 (0.5)	3 (0.8)
General disorders and administration site conditions	10 (5.0)	19 (9.5)	17 (8.5)	36 (9.0)
Fatigue	6 (3.0)	12 (6.0)	3 (1.5)	15 (3.8)
Injection site pain	1 (0.5)	3 (1.5)	3 (1.5)	6 (1.5)
Injection site erythema	1 (0.5)	1 (0.5)	3 (1.5)	4 (1.0)
Injection site induration	0	1 (0.5)	3 (1.5)	4 (1.0)
Injection site swelling	1 (0.5)	0	4 (2.0)	4 (1.0)
Axillary pain	0	1 (0.5)	2 (1.0)	3 (0.8)
Injection site bruising	2 (1.0)	1 (0.5)	0	1 (0.3)
Investigations	5 (2.5)	3 (1.5)	4 (2.0)	7 (1.8)
Blood pressure increased	2 (1.0)	1 (0.5)	1 (0.5)	2 (0.5)
Heart rate decreased	2 (1.0)	0	0	0
Injury, poisoning and procedural complications	5 (2.5)	4 (2.0)	4 (2.0)	8 (2.0)
Arthropod bite	1 (0.5)	2 (1.0)	1 (0.5)	3 (0.8)
Skin laceration	2 (1.0)	0	0	0

Abbreviation: TEAE = treatment-emergent adverse event.

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.

Percentages are based on the number of safety participants.

Medical Dictionary for Regulatory Activities version 23.0.

Source: Study 201 Primary Analysis CSR Table 14.3.1.8.2 (05 Nov 2020).

2.7.4.2.3.2.3 Severe Unsolicited Adverse Events by System Organ Class and Preferred Term

Most unsolicited TEAEs reported up to the Day 57 visit in the mRNA-1273 total and placebo groups were mild or moderate in severity (Study 201 Primary Analysis CSR Table 14.3.1.10.2). Few participants reported severe unsolicited TEAEs up to the Day 57 visit: 13/400 [3.3%]

participants in the mRNA-1273 total group and 4/200 [2.0%] participants in the placebo group. No severe COVID-19 TEAEs were reported from Day 1 through Day 57 (Study 201 Primary Analysis CSR Table 14.3.1.16.2). The incidence of severe TEAEs was similar in the mRNA-1273 50 and 100 µg groups (8/200 [4.0%] and 5/200 [2.5%], respectively).

Few participants had severe unsolicited treatment-related TEAEs: 6/400 (1.5%) participants in the mRNA-1273 total group and 2/200 (1.0%) participants in the placebo group (Study 201 Primary Analysis CSR Table 14.3.1.12.2).

2.7.4.2.3.2.4 Unsolicited Adverse Events by Relationship to Study Vaccine

More participants had unsolicited TEAEs assessed by the investigator as treatment-related up to Day 57 in the mRNA-1273 total group (43/400 [10.8%] participants with 80 events) than in the placebo group (13/200 [6.5%] participants with 18 events) (Study 201 Primary Analysis CSR Table 14.3.1.11.2).

The treatment-related TEAEs with the highest incidence (> 1%) in the mRNA-1273 total group or the placebo group (by decreasing incidence in the mRNA-1273 total group) were consistent with the solicited ARs that were collected to assess reactogenicity: fatigue (13/400 [3.3%] and 6/200 [3.0%], respectively), headache (12/400 [3.0%] and 1/200 [0.5%], respectively), arthralgia (7/400 [1.8%] and 4/200 [2.0%], respectively), myalgia (7/400 [1.8%] and 2/200 [1.0%], respectively), and injection site pain (5/400 [1.3%] and 1/200 [0.5%], respectively).

The incidence of treatment-related TEAEs was higher in the mRNA 1273 100 µg group than in the 50 µg group (27/200 [13.5%] vs. 16/200 [8.0%], respectively). The higher incidence of treatment-related TEAEs reported by participants who received mRNA-1273 at 100 µg was attributed to the higher frequency of injection site reactions (eg, injection site pain, erythema, induration, swelling) that were reported as unsolicited TEAEs.

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

2.7.4.2.3.3.1 Deaths

At the time of the database lock for the primary analysis, no participants had died during Study 201 (Study 201 Primary Analysis CSR Table 7).

2.7.4.2.3.3.2 Other Serious Adverse Events

At the time of the database lock for the primary analysis, 1 SAE (PT pneumonia) was reported in a 65-year-old participant in the mRNA-1273 50 µg group (Study 201 Primary Analysis CSR Section 7.3.2). The participant experienced symptoms including headache, cough, body aches, weakness, and fever beginning shortly before the scheduled second injection, which was delayed and later cancelled. Multiple tests during the participant's illness were negative for COVID-19 or SARS-CoV-2. A case narrative for this participant is provided in Study 201 Primary Analysis CSR Section 15.

2.7.4.2.3.3.3 Other Clinically Meaningful Unsolicited Adverse Events

2.7.4.2.3.3.3.1 Unsolicited Adverse Events Leading to Discontinuation from Vaccine or Study

At the time of the database lock for the primary analysis, 2 participants had discontinued study vaccine due to an unsolicited TEAE (1 each in the mRNA-1273 50 µg [pneumonia SAE] and placebo [COVID-19] groups) (Study 201 Primary Analysis CSR Listing 16.2.7.9).

2.7.4.2.3.3.3.2 Medically Attended Adverse Events

The incidence of MAAEs up to 28 days after any injection was similar in the mRNA-1273 total group (39/400 [9.8%]) and placebo group (17/200 [8.5%]) (Study 201 Primary Analysis CSR Table 25).

Most MAAEs were reported by one participant each in either the mRNA-1273 total or placebo groups. The MAAEs with an incidence > 0.5% in the mRNA-1273 total group or the placebo group (by decreasing incidence in the mRNA-1273 total group) were contact dermatitis (4/400 [1.0%] and 1/200 [0.5%], respectively), urinary tract infection (3/400 [0.8%] and 1/200 [0.5%], respectively), headache (3/400 [0.8%] and 0, respectively), and skin laceration (0 and 2/100 [1.0%], respectively).

The incidence of MAAEs from Day 1 to Day 57 was similar to the results in the 28-day follow-up: 42/400 (10.5%) participants in the mRNA-1273 total group and 19/200 (9.5%) participants in the placebo group reported MAAEs up to Day 57 (Study 201 Primary Analysis CSR Table 14.3.1.18.2).

2.7.4.2.3.3.3.3 Analysis of Adverse Events of Interest

Section 2.7.4.1.1.1.5 provides an overview and rationale for analysis of AEs of interest.

No participants had AEs of interest in the SMQs of vasculitis (Study 201 Primary Analysis CSR Table 14.3.1.22.1), peripheral neuropathy (Study 201 Primary Analysis CSR Table 14.3.1.22.5), demyelination (Study 201 Primary Analysis CSR Table 14.3.1.22.6), or convulsions (Study 201 Primary Analysis CSR Table 14.3.1.22.7).

One participant (0.5%) had an AE that was captured in the arthritis SMQ: the participant received mRNA-1273 100 µg and had a TEAE of gout that occurred from Day 7 to 16 after the first injection and was not considered to be related to study vaccine (Study 201 Primary Analysis CSR Table 14.3.1.22.3, Listing 16.2.7.7).

The incidence of hypersensitivity was similar between the mRNA-1273 total group (11/400 [2.8%]) and placebo group (6/200 [3.0%]) (Table 27). More participants in the mRNA-1273 50 µg group (9/200 [4.5%]) reported hypersensitivity TEAEs than did so in the mRNA-1273 100 µg group (2/200 [1.0%]). Only the angioedema AE of interest in the placebo group was considered related to IP (Study 201 Primary Analysis CSR Table 14.3.1.12.2).

Table 27 Study 201: Unsolicited Adverse Event of Interest – Hypersensitivity (Safety Set)

		mRNA-1273		
Preferred Term	**Placebo (N=200) n (%)**	**50 µg (N=200) n (%)**	**100 µg (N=200) n (%)**	**Total mRNA-1273 (N=400) n (%)**
Number of participants reporting hypersensitivity	6 (3.0)	9 (4.5)	2 (1.0)	11 (2.8)
Number of hypersensitivity adverse events	6	9	2	11
Angioedema	1 (0.5)	0	0	0
Dermatitis	0	1 (0.5)	0	1 (0.3)
Dermatitis contact	3 (1.5)	5 (2.5)	2 (1.0)	7 (1.8)
Rash	2 (1.0)	3 (1.5)	0	3 (0.8)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Hypersensitivity was identified through the selected Standardized MedDRA Query.
Percentages are based on the number of safety participants.
Medical Dictionary for Regulatory Activities version 23.0.
Source: Study 201 Primary Analysis CSR Ad hoc Table 14.3.1.22.2 (05 Nov 2020).

2.7.4.2.3.4 Study 201 Data Collected Through Day 209

The Study 201 CSR Addendum 1 (End of Part A) includes open-label data through the PDV (end of blinded Part A of the study) to provide updated results including SAEs, MAAEs, TEAEs leading to discontinuation from study participation, and pregnancies. No long-term safety concerns were apparent from the extended follow-up for both the 100 µg and 50 µg doses of mRNA-1273, and there was no evidence to suggest any difference in the safety profile of the 100 µg dose compared with the 50 µg dose.

No participants died during Study 201 Part A (Study 201 CSR Addendum 1 [End of Part A] Table 14.3.1.7.2). At least one SAE was reported for 5 participants in the 50 µg mRNA-1273 group and 2 participants in the 100 µg mRNA-1273 group (Study 201 CSR Addendum 1 [End of Part A] Table 14.3.1.13.2); none of the SAEs were considered related to treatment (Study 201 CSR Addendum 1 [End of Part A] Table 14.3.1.14.2). At least one MAAE was reported for 112 participants (28.0%) in the combined mRNA-1273 groups (including 74 [37.0%] for 50 µg and 38 [19.0%] for 100 µg) and 64 participants [32.0%]) in the placebo group and no imbalances were observed in the types of events reported (Study 201 CSR Addendum 1 [End of Part A] Table 14.3.1.18.2). No unsolicited TEAE led to study discontinuation in any group (Study 201 CSR Addendum 1 [End of Part A] Table 14.3.1.15.2). The SMQ summaries did not differ appreciably from those reported for Day 57 (Study 201 CSR Addendum 1 [End of Part A] Section 7.3.3.3; Section 2.7.4.2.3.3.3.3).

2.7.4.2.4 Study 101

Safety results for Study 101 (approximately 120 participants exposed to mRNA-1273) were consistent with those for Study 301 Part A (approximately 15,000 participants exposed to mRNA-1273). The bulk of the data presented in this section are from the Study 101 Day 119 CSR. Findings from the Study 101 CSR Addendum 1 (Day 209) immunogenicity and safety addendum are described in Section 2.7.4.2.4.4.

2.7.4.2.4.1 Solicited Adverse Reactions

In Study 101, 3 mRNA-1273 dose levels (25, 100, and 50 µg) administered twice 28 days apart were assessed in participants 18 to 55 years, 56 to 70 years, and ≥ 71 years of age. A 250 µg dose was also administered twice 28 days apart to participants 18 to 55 years of age. The mRNA-1273 250-µg dose was not evaluated in participants 56 to 70 years and ≥ 71 years of age due to reactogenicity (severe reactions) observed in the 18 to 55 years of age cohort treated with 250 µg (Table 28 and Table 29): solicited systemic ARs occurred in all 14 participants treated with the 250-µg dose, and 3 of those participants had one or more severe events (Jackson et al 2020).

The incidence of solicited local ARs in all age cohorts was similar after the first injection and after the second injection and severity was predominantly mild or moderate (Study 101 Day 119 CSR Section 7.1.3). Overall, injection site pain was the most commonly reported solicited local AR; no severe injection site pain was reported in any of the age cohorts (Table 28). Most solicited local ARs had onset within 2 days after vaccination and lasted a median of 2 days or less (Study 101 Day 119 CSR Section 7.1.4 and Section 7.1.5).

The incidence and severity of solicited systemic ARs were generally dose dependent in all age cohorts but to a lesser extent in the 56 to 70 years age group (Study 101 Day 119 CSR Section 7.1.2), and incidence and severity were generally higher after the second injection than after the first, particularly at the highest (250 µg) dose. Solicited systemic ARs were predominantly mild or moderate in severity. Fatigue and headache were the most commonly reported solicited systemic ARs after the first injection, and fatigue, headache, myalgia, and feverishness (reported by participants as “chills”) were most commonly reported solicited systemic ARs after the second injection. Most of the solicited systemic ARs had onset within 2 days after vaccination, and the median duration of solicited systemic ARs was 1 day (Study 101 Day 119 CSR Section 7.1.4 and Section 7.1.5). All severe solicited systemic ARs resolved within 1 to 2 days (Study 101 Day 119 CSR Listing 10 and Listing 11).

Table 28 Study 101: Solicited Local Adverse Reactions (All Participants 18 to 55 Years of Age)

Severity, n (%)	mRNA-1273 Dose Level								All Participants (N=60)	
	25 µg (N=15)		50 µg (N=15)		100 µg (N=15)		250 µg (N=15)			
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Any Local Reaction	10 (67)	10 (77)	13 (87)	14 (93)	14 (93)	15 (100)	15 (100)	14 (100)	52 (87)	53 (93)
Severe	–	–	–	–	1 (7)	1 (7)	1 (7)	1 (7)	2 (3)	2 (4)
Any Erythema Redness	–	1 (8)	1 (7)	4 (27)	2 (13)	2 (13)	2 (13)	3 (21)	5 (8)	10 (18)
Severe	–	–	–	–	–	–	–	–	–	–
Any Erythema Redness Measurement (mm)	–	–	–	–	2 (13)	2 (13)	1 (7)	3 (21)	3 (5)	5 (9)
Severe	–	–	–	–	1 (7)	1 (7)	1 (7)	1 (7)	2 (3)	2 (4)
Any Induration/Swelling	–	–	3 (20)	–	3 (20)	1 (7)	4 (27)	3 (21)	10 (17)	4 (7)
Severe	–	–	–	–	–	–	–	–	–	–
Any Induration/Swelling Measurement (mm)	–	–	1 (7)	–	2 (13)	1 (7)	3 (20)	3 (21)	6 (10)	4 (7)
Severe	–	–	–	–	–	–	1 (7)	–	1 (2)	–
Any Pain	10 (67)	10 (77)	13 (87)	13 (87)	14 (93)	15 (100)	15 (100)	14 (100)	52 (87)	52 (91)
Severe	–	–	–	–	–	–	–	–	–	–

Note: Severity is the maximum severity reported over all solicited symptoms after dosing for each participant.

Total number of participants for solicited adverse reaction after Dose 2 included the participants who received the second vaccination.
Source: Study 101 Day 119 CSR Table 16 (07 Oct 2020).

Table 29 Study 101: Solicited Systemic Adverse Reactions (All Participants 18 to 55 Years of Age)

Severity, n (%)	mRNA-1273 Dose Level								All Participants (N=60)	
	25 µg (N=15)		50 µg (N=15)		100 µg (N=15)		250 µg (N=15)			
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
Any Systemic Reaction	5 (33)	7 (54)	9 (60)	13 (87)	10 (67)	15 (100)	8 (53)	14 (100)	32 (53)	49 (86)
Severe	–	–	–	1 (7)	–	-	–	3 (21)	–	4 (7)
Any Arthralgia	–	2 (15)	2 (13)	2 (13)	2 (13)	2 (13)	1 (7)	8 (57)	5 (8)	14 (25)
Severe	–	–	–	–	–	–	–	–	–	–
Any Fatigue	4 (27)	5 (38)	8 (53)	10 (67)	4 (27)	12 (80)	5 (33)	10 (71)	21 (35)	37 (65)
Severe	–	–	–	–	–	–	–	2 (14)	–	2 (4)
Any Fever[a]	–	–	–	1 (7)	–	6 (40)	–	8 (57)	–	15 (26)
Severe	–	–	–	–	–	–	–	1 (7)	–	1 (7)
Any Feverishness[b]	–	1 (8)	–	3 (20)	1 (7)	12 (80)	2 (13)	12 (86)	3 (5)	28 (49)
Severe	–	–	–	–	–	–	–	3 (21)	–	3 (5)
Any Headache	3 (20)	3 (23)	3 (20)	10 (67)	4 (27)	9 (60)	7 (47)	14 (100)	17 (28)	36 (63)
Severe	–	–	–	1 (7)	–	–	–	1 (7)	–	2 (4)
Any Myalgia	1 (7)	3 (23)	2 (13)	6 (40)	1 (7)	8 (53)	4 (27)	13 (93)	8 (13)	30 (53)
Severe	–	–	–	–	–	–	–	1 (7)	–	1 (2)
Any Nausea	1 (7)	1 (8)	1 (7)	2 (13)	–	7 (47)	1 (7)	4 (29)	3 (5)	14 (25)
Severe	–	–	–	–	–	–	–	1 (7)	–	1 (2)

Note: Severity is the maximum severity reported over all solicited symptoms after dosing for each participant.

Total number of participants for solicited adverse reaction after Dose 2 included the participants who received the second vaccination.

[a] Fever percentages reflect the number of participants with at least 1 measurement available in the data system as the denominator. This denominator may differ from other systemic symptoms, which are solicited in-clinic at the post-dose assessment.

[b] Feverishness was reported by participants as “chills.”

Source: Study 101 Day 119 CSR Table 13 (07 Oct 2020).

2.7.4.2.4.2 Unsolicited Adverse Events

2.7.4.2.4.2.1 Overall Summary

The incidence of unsolicited AEs was similar across the vaccination groups and age groups (18 to 55 years of age [Table 30], 56 to 70 years of age [Table 31], and ≥ 71 years of age [Table 32]). Most unsolicited AEs were mild or moderate in severity. All unsolicited AEs related to mRNA-1273 were mild or moderate in severity, except for 2 severe AEs (dizziness and syncope both occurring on Day 1 after the second injection) that were reported in 1 participant in the 18 to 55 years age group (250 µg group). All AEs related to mRNA-1273 resolved.

Adverse events leading to treatment discontinuation were reported in 3 participants. Of these, 1 AE of mild urticaria (25 µg group, age group: 18 to 55 years) was related to mRNA-1273. The other events (unrelated to treatment) that led to treatment discontinuation were mild oropharyngeal pain (250 µg group, age group: 18 to 55 years) and moderate rash maculo-papular (100 µg group, age group: 56 to 70 years) (Study 101 Day 119 CSR Listing 2). All MAAEs reported during the study were not related to mRNA-1273.

Table 30 Study 101: Overall Summary of Unsolicited Adverse Events (All Participants 18 to 55 Years of Age)

	mRNA-1273 Dose Level				
	25 µg (N=15)	**50 µg (N=15)**	**100 µg (N=15)**	**250 µg (N=15)**	**All Participants (N=60)**
Unsolicited AEs regardless of relationship to study vaccine, n (%)					
All	12 (80)	10 (67)	11 (73)	11 (73)	44 (73)
Serious	–	–	–	–	–
Fatal	–	–	–	–	–
MAAE	4 (27)	3 (20)	2 (13)	4 (27)	13 (22)
NOCMC	–	–	–	–	–
Leading to discontinuation from study vaccine	1 (7)	–	–	1 (7)	2 (3)
Leading to discontinuation from study	–	–	–	–	–
Severe	–	–	–	1 (7)	1 (2)
Unsolicited AEs related to study vaccine, n (%)					
All	4 (27)	6 (40)	3 (20)	7 (47)	20 (33)
Serious	–	–	–	–	–
Fatal	–	–	–	–	–
MAAE	–	–	–	1 (7)	1 (2)
NOCMC	–	–	–	–	–
Leading to discontinuation from study vaccine	1 (7)	–	–	–	1 (2)
Leading to discontinuation from study	–	–	–	–	–
Severe	–	–	–	1 (7)	1 (2)

Abbreviations: AE = adverse event; MAAE = medically attended adverse events; NOCMC = new-onset chronic medical conditions.

Note: Participants were counted once for each category regardless of the number of events.

Source: Study 101 Day 119 CSR Table 28 (07 Oct 2020).

Table 31 Study 101: Overall Summary of Unsolicited Adverse Events (All Participants 56 to 70 Years of Age)

	mRNA-1273 Dose Level			
	25 µg (N=10)	50 µg (N=10)	100 µg (N=10)	All Participants (N=30)
Unsolicited AEs regardless of relationship to study vaccine, n (%)				
All	7 (70)	7 (70)	8 (80)	22 (73)
Serious	–	–	–	–
Fatal	–	–	–	–
MAAE	2 (20)	3 (30)	1 (10)	6 (20)
NOCMC	1 (10)	–	–	1 (3)
Leading to discontinuation from study vaccine	–	–	1 (10)	1 (10)
Leading to discontinuation from study	–	–	–	–
Severe	–	1 (10)	1 (10)	2 (7)
Unsolicited AEs related to study vaccine, n (%)				
All	2 (20)	1 (10)	1 (10)	4 (13)
Serious	–	–	–	–
Fatal	–	–	–	–
MAAE	–	–	–	–
NOCMC	–	–	–	–
Leading to discontinuation from study vaccine	–	–	–	–
Leading to discontinuation from study	–	–	–	–
Severe	–	–	–	–

Abbreviations: AE = adverse event; MAAE = medically attended adverse events; NOCMC = new-onset chronic medical conditions.

Participants were counted once for each category regardless of the number of events.

Source: Study 101 Day 119 CSR Table 29 (07 Oct 2020).

Table 32 Study 101: Overall Summary of Unsolicited Adverse Events (All Participants ≥ 71 Years of Age)

	mRNA-1273 Dose Level			
	25 µg (N=10)	50 µg (N=10)	100 µg (N=10)	All Participants (N=30)
Unsolicited AEs regardless of relationship to study vaccine, n (%)				
All	9 (90)	6 (60)	8 (80)	23 (77)
Serious	–	–	–	–
Fatal	–	–	–	–
MAAE	1 (10)	1 (10)	3 (30)	5 (17)
NOCMC	–	–	–	–
Leading to discontinuation from study vaccine	–	–	–	–
Leading to discontinuation from study	–	–	–	–
Severe	–	–	–	–
Unsolicited AEs regardless related to study vaccine, n (%)				
All	4 (40)	–	3 (70)	7 (23)
Serious	–	–	–	–
Fatal	–	–	–	–
MAAE	–	–	–	–
NOCMC	–	–	–	–
Leading to discontinuation from study vaccine	–	–	–	–
Leading to discontinuation from study	–	–	–	–
Severe	–	–	–	–

Abbreviations: AE = adverse event; MAAE = medically attended adverse events; NOCMC = new-onset chronic medical conditions.

Participants were counted once for each category regardless of the number of events.

Source: Study 101 Day 119 CSR Table 30 (07 Oct 2020).

2.7.4.2.4.2.2 Most Common Unsolicited Adverse Events

No clinically relevant dose-dependent trends were noted in the incidence of unsolicited AEs among the vaccination groups or age groups, including participants 18 to 55 years of age (Table 33), 56 to 70 years of age (Table 34), and ≥ 71 years of age (Table 35).

Among 18 to 55 year old participants, the most commonly reported (> 2 participants overall) unsolicited AEs were bradycardia, vomiting, vessel puncture site bruise, muscle strain, decreased appetite, and oropharyngeal pain (4 participants [7%] each) and injection site bruising, injection site pruritus, contusion, and skin abrasion (3 participants [5%] each) (Table 33).

Among 56 to 70 year old participants, no unsolicited AEs were reported in more than 2 participants (Table 34).

Among participants ≥ 71 years of age, the most commonly reported (> 2 participants overall) unsolicited AEs were skin abrasion (6 participants [20%]) and injection site bruising, vessel puncture site bruise, and dizziness (3 participants each [10%]) (Table 35).

Table 33 Study 101: Unsolicited Adverse Events (All Participants 18 to 55 Years of Age)

System Organ Class Preferred Term	mRNA-1273 Dose Level				All Participants (N=60)
	25 µg (N=15)	50 µg (N=15)	100 µg (N=15)	250 µg (N=15)	
Number of unsolicited AEs	31	24	28	40	123
Participants with any unsolicited AE, n (%)	12 (80)	10 (67)	11 (73)	11 (73)	44 (73)
Blood and lymphatic system disorders	–	1 (7)	–	–	1 (2)
Lymphadenopathy	–	1 (7)	–	–	1 (2)
Cardiac disorders	–	2 (13)	1 (7)	1 (7)	4 (7)
Bradycardia	–	2 (13)	1 (7)	1 (7)	4 (7)
Ear and labyrinth disorders	–	1 (7)	-	-	1 (2)
Vertigo	–	1 (7)	-	-	1 (2)
Eye disorders	–	–	1 (7)	1 (7)	2 (3)
Eye irritation	–	–	1 (7)	-	1 (2)
Scintillating scotoma	–	–	–	1 (7)	1 (2)
Gastrointestinal disorders	4 (27)	3 (20)	2 (13)	6 (40)	15 (25)
Abdominal discomfort	–	–	1 (7)	1 (7)	2 (3)
Abdominal pain	–	1 (7)	1 (7)	–	2 (3)
Abdominal pain upper	–	–	–	1 (7)	1 (2)
Anal fissure	–	–	–	1 (7)	1 (2)
Diarrhea	–	1 (7)	–	–	1 (2)
Dyspepsia	–	1 (7)	–	1 (7)	2 (3)
Feces discolored	–	–	1 (7)	–	1 (2)
Flatulence	1 (7)	–	–	–	1 (2)
Lip disorder	–	–	–	1 (7)	1 (2)
Tooth impacted	–	1 (7)	–	–	1 (2)
Vomiting	3 (20)	–	–	1 (7)	4 (7)
General disorders and administration site conditions	4 (27)	3 (20)	4 (27)	3 (20)	14 (23)
Fatigue	1 (7)	–	–	–	1 (2)
Feeling jittery	–	–	1 (7)	–	1 (2)

System Organ Class Preferred Term	mRNA-1273 Dose Level 25 µg (N=15)	 50 µg (N=15)	 100 µg (N=15)	 250 µg (N=15)	All Participants (N=60)
Injection site bruising	–	–	3 (20)	–	3 (5)
Injection site erythema	–	–	–	2 (13)	2 (3)
Injection site irritation	1 (7)	–	–	–	1 (2)
Injection site pruritus	–	–	2 (13)	1 (7)	3 (5)
Malaise	–	–	–	1 (7)	1 (2)
Vaccination site movement impairment	–	1 (7)	–	–	1 (2)
Vessel puncture site bruise	2 (13)	1 (7)	–	1 (7)	4 (7)
Vessel puncture site hemorrhage	–	1 (7)	–	–	1 (2)
Immune system disorders	–	1 (7)	–	–	1 (2)
Seasonal allergy	–	1 (7)	–	–	1 (2)
Infections and infestations	2 (13)	1 (7)	2 (13)	2 (13)	7 (12)
Epididymitis	–	–	–	1 (7)	1 (2)
Gastroenteritis	–	–	1 (7)	–	1 (2)
Hordeolum	1 (7)	–	–	–	1 (2)
Infected cyst	–	–	1 (7)	–	1 (2)
Pustule	1 (7)	–	–	–	1 (2)
Upper respiratory tract infection	–	1 (7)	–	–	1 (2)
Urinary tract infection	–	–	–	1 (7)	1 (2)
Injury, poisoning and procedural complications	5 (33)	2 (13)	3 (20)	–	10 (17)
Contusion	3 (20)	–	–	–	3 (5)
Muscle strain	2 (13)	–	2 (13)	–	4 (7)
Skin abrasion	1 (7)	2 (13)	–	–	3 (5)
Skin laceration	1 (7)	–	–	–	1 (2)
Thermal burn	–	–	1 (7)	–	1 (2)
Wound	1 (7)	–	–	–	1 (2)
Investigations	–	1 (7)	1 (7)	–	2 (3)
Blood glucose decreased	–	1 (7)	–	–	1 (2)
Heart rate increased	–	–	1 (7)	–	1 (2)
Metabolism and nutrition disorders	–	–	1 (7)	4 (27)	5 (8)
Decreased appetite	–	–	1 (7)	3 (20)	4 (7)
Hypoglycemia	–	–	–	1 (7)	1 (2)
Musculoskeletal and connective tissue disorders	2 (13)	2 (13)	1 (7)	4 (27)	9 (15)
Arthralgia	–	–	–	1 (7)	1 (2)
Muscle spasms	–	1 (7)	–	1 (7)	2 (3)

System Organ Class Preferred Term	mRNA-1273 Dose Level				All Participants (N=60)
	25 µg (N=15)	50 µg (N=15)	100 µg (N=15)	250 µg (N=15)	
Muscle strain	–	–	–	1 (7)	1 (2)
Muscular weakness	1 (7)	–	–	–	1 (2)
Myalgia	–	1 (7)	–	–	1 (2)
Neck pain	–	–	1 (7)	–	1 (2)
Pain in extremity	–	–	–	1 (7)	1 (2)
Pain in jaw	1 (7)	–	–	–	1 (2)
Nervous system disorders	1 (7)	–	1 (7)	3 (20)	5 (8)
Dizziness	–	–	1 (7)	1 (7)	2 (3)
Headache	–	–	–	2 (13)	2 (3)
Presyncope	1 (7)	–	–	–	1 (2)
Syncope	–	–	–	1 (7)	1 (2)
Psychiatric disorders	–	–	1 (7)	1 (7)	2 (3)
Anxiety	–	–	–	1 (7)	1 (2)
Attention deficit hyperactivity disorder	–	–	1 (7)	–	1 (2)
Insomnia	–	–	–	1 (7)	1 (2)
Reproductive system and breast disorders	–	–	1 (7)	3 (20)	4 (7)
Breast pain	–	–	1 (7)	–	1 (2)
Vaginal hemorrhage	–	–	–	1 (7)	1 (2)
Vulvovaginal pruritus	–	–	–	2 (13)	2 (3)
Respiratory, thoracic and mediastinal disorders	2 (13)	2 (13)	3 (20)	1 (7)	8 (13)
Diaphragmatic spasm	–	–	1 (7)	–	1 (2)
Dyspnea exertional	1 (7)	–	–	–	1 (2)
Nasal congestion	–	1 (7)	1 (7)	–	2 (3)
Oropharyngeal pain	1 (7)	1 (7)	1 (7)	1 (7)	4 (7)
Upper airway cough syndrome	–	1 (7)	–	–	1 (2)
Skin and subcutaneous tissue disorders	4 (27)	1 (7)	–	2 (13)	7 (12)
Dermatitis contact	1 (7)	–	–	–	1 (2)
Erythema	1 (7)	–	–	–	1 (2)
Hyperhidrosis	–	–	–	1 (7)	1 (2)
Night sweats	–	–	–	1 (7)	1 (2)
Petechiae	1 (7)	–	–	–	1 (2)
Rash	–	1 (7)	–	–	1 (2)
Urticaria	1 (7)	–	–	–	1 (2)
Vascular disorders	1 (7)	–	1 (7)	2 (13)	4 (7)
Hypertension	–	–	–	1 (7)	1 (2)

System Organ Class Preferred Term	mRNA-1273 Dose Level 25 µg (N=15)	 50 µg (N=15)	 100 µg (N=15)	 250 µg (N=15)	All Participants (N=60)
Hypotension	–	–	–	1 (7)	1 (2)
Systolic hypertension	1 (7)	–	–	–	1 (2)
Vasodilatation	–	–	1 (7)	–	1 (2)

Abbreviation: AE = adverse event.

A participant was counted once per preferred term.

Source: Study 101 Day 119 CSR Table 31 (07 Oct 2020).

Table 34 Study 101: Unsolicited Adverse Events (All Participants 56 to 70 Years of Age)

System Organ Class Preferred Term	mRNA-1273 Dose Level 25 µg (N=10)	 50 µg (N=10)	 100 µg (N=10)	All Participants (N=30)
Number of unsolicited AEs	13	8	11	32
Participants with any unsolicited AE, n (%)	7 (70)	7 (70)	8 (80)	22 (73)
Cardiac disorders	–	2 (20)	–	2 (7)
Bradycardia	–	2 (20)	–	2 (7)
Ear and labyrinth disorders	–	–	1 (10)	1 (3)
Vertigo	–	–	1 (10)	1 (3)
Gastrointestinal disorders	–	1 (10)	1 (10)	2 (7)
Abdominal discomfort	–	1 (10)	–	1 (3)
Hemorrhoids	–	–	1 (10)	1 (3)
General disorders and administration site conditions	2 (20)	–	–	2 (7)
Injection site bruising	2 (20)	–	–	2 (7)
Infections and infestations	1 (10)	2 (20)	1 (10)	4 (13)
Onychomycosis	1 (10)	–	–	1 (3)
Paronychia	–	–	1 (10)	1 (3)
Urinary tract infection	–	1 (10)	–	1 (3)
Viral infection	–	1 (10)	–	1 (3)
Injury, poisoning and procedural complications	2 (20)	3 (30)	1 (10)	6 (20)
Arthropod sting	–	–	1 (10)	1 (3)
Exposure via inhalation	1 (10)	–	–	1 (3)
Limb injury	1 (10)	–	–	1 (3)
Muscle strain	–	1 (10)	–	1 (3)
Skin laceration	–	1 (10)	–	1 (3)
Tooth fracture	–	1 (10)	–	1 (3)
Investigations	1 (10)	–	–	1 (3)
Bone density decreased	1 (10)	–	–	1 (3)

System Organ Class Preferred Term	mRNA-1273 Dose Level 25 µg (N=10)	 50 µg (N=10)	 100 µg (N=10)	All Participants (N=30)
Metabolism and nutrition disorders	1 (10)	–	1 (10)	2 (7)
Decreased appetite	1 (10)	–	–	1 (3)
Hypoglycemia	–	–	1 (10)	1 (3)
Musculoskeletal and connective tissue disorders	1 (10)	–	–	1 (3)
Pain in extremity	1 (10)	–	–	1 (3)
Nervous system disorders	2 (20)	–	1 (10)	3 (10)
Dizziness	–	–	1 (10)	1 (3)
Headache	1 (10)	–	–	1 (3)
Sciatica	1 (10)	–	–	1 (3)
Psychiatric disorders	1 (10)	–	–	1 (3)
Insomnia	1 (10)	–	–	1 (3)
Respiratory, thoracic and mediastinal disorders	1 (10)	–	2 (20)	3 (10)
Nasal congestion	–	–	1 (10)	1 (3)
Oropharyngeal pain	1 (10)	–	1 (10)	2 (7)
Skin and subcutaneous tissue disorders	–	–	1 (10)	1 (3)
Dermatitis contact	–	–	1 (10)	1 (3)
Rash maculo-papular	–	–	1 (10)	1 (3)
Vascular disorders	–	–	1 (10)	1 (3)
Systolic hypertension	–	–	1 (10)	1 (3)

Abbreviation: AE = adverse event.

A participant was counted once per preferred term.

Source: Study 101 Day 119 CSR Table 32 (07 Oct 2020).

Table 35 Study 101: Unsolicited Adverse Events (All Participants ≥ 71 Years of Age)

System Organ Class Preferred Term	mRNA-1273 Dose Level 25 µg (N=10)	 50 µg (N=10)	 100 µg (N=10)	All Participants (N=30)
Number of unsolicited AEs	28	7	24	59
Participants with any unsolicited AE, n (%)	9 (90)	6 (60)	8 (80)	23 (77)
Cardiac disorders	1 (10)	–	1 (10)	2 (7)
Bradycardia	1 (10)	–	1 (10)	2 (7)
General disorders and administration site conditions	2 (20)	1 (10)	4 (40)	7 (23)
Energy increased	1 (10)	–	–	1 (3)
Fatigue	1 (10)	–	–	1 (3)

System Organ Class Preferred Term	mRNA-1273 Dose Level 25 µg (N=10)	 50 µg (N=10)	 100 µg (N=10)	All Participants (N=30)
Injection site bruising	1 (10)	1 (10)	1 (10)	3 (10)
Injection site erythema	–	–	1 (10)	1 (3)
Injection site pruritus	1 (10)	–	–	1 (3)
Vessel puncture site bruise	–	–	3 (30)	3(10)
Infections and infestations	1 (10)	–	1 (10)	2 (7)
Pustule	1 (10)	–	–	1 (3)
Urinary tract infection	–	–	1 (10)	1 (3)
Injury, poisoning and procedural complications	5 (50)	2 (10)	4 (40)	11 (37)
Arthropod bite	1 (10)	1 (10)	–	2 (7)
Contusion	–	–	2 (20)	2 (7)
Injury	–	2 (20)	–	2 (7)
Limb injury	1 (10)	–	–	1 (3)
Procedural pain	1 (10)	–	–	1 (3)
Skin abrasion	3 (30)	–	3 (30)	6 (20)
Sunburn	1 (10)	–	–	1 (3)
Thermal burn	1 (10)	–	–	1 (3)
Tooth fracture	–	–	1 (10)	1 (3)
Musculoskeletal and connective tissue disorders	4 (40)	–	1 (10)	5 (17)
Arthritis	1 (10)	–	–	1 (3)
Joint swelling	1 (10)	–	–	1 (3)
Muscle tightness	1 (10)	–	–	1 (3)
Musculoskeletal chest pain	1 (10)	–	–	1 (3)
Myalgia	–	–	1 (10)	1 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	–	–	1 (10)	1 (3)
Squamous cell carcinoma	–	–	1 (10)	1 (3)
Nervous system disorders	2 (20)	–	1 (10)	3 (10)
Dizziness	2 (20)	–	1 (10)	3 (10)
Visual field defect	1 (10)	–	–	1 (3)
Psychiatric disorders	2 (20)	–	–	2 (7)
Anxiety	1 (10)	–	–	1 (3)
Sleep disorder	1 (10)	–	–	1 (3)
Respiratory, thoracic and mediastinal disorders	–	1 (10)	–	1 (3)
Oropharyngeal pain	–	1 (10)	–	1 (3)
Skin and subcutaneous tissue disorders	3 (30)	–	4 (40)	7 (23)
Blister	–	–	1 (10)	1 (3)

System Organ Class Preferred Term	mRNA-1273 Dose Level 25 µg (N=10)	 50 µg (N=10)	 100 µg (N=10)	 All Participants (N=30)
Dermatitis	–	–	1 (10)	1 (3)
Dermatitis contact	–	–	1 (10)	1 (3)
Night sweats	1 (10)	–	1 (10)	2 (7)
Pruritus	1 (10)	–	–	1 (3)
Rash	–	–	1 (10)	1 (3)
Skin irritation	1 (10)	–	–	1 (3)
Vascular disorders	–	2 (20)	1 (10)	3 (10)
Hypertension	–	2 (20)	–	2 (7)
Systolic hypertension	–	–	1 (10)	1 (3)

Abbreviation: AE = adverse event.
A participant was counted once per preferred term.
Source: Study 101 Day 119 CSR Table 33 (07 Oct 2020).

2.7.4.2.4.2.3 Unsolicited Adverse Events by Maximum Intensity

Within each age group, the majority of unsolicited AEs were mild or moderate in intensity (Study 101 Day 119 CSR Section 7.2.3). There were 4 severe events reported by 3 participants, as follows:

Age Group: 18 to 55 Years

- One participant in the 250 µg vaccination group reported severe dizziness and syncope on Day 1 after the second injection. Both events resolved on the same day and were deemed related to mRNA-1273 by the investigator (Study 101 Day 119 CSR Listing 12).

Age Group: 56 to 70 Years

- One participant in the 50 µg vaccination group reported a severe AE of viral infection on Day 40 after the second injection. The event resolved after 27 days and was deemed not related to mRNA-1273 by the investigator (Study 101 Day 119 CSR Listing 12).

- One participant in the 100 µg vaccination group reported a severe AE of hypoglycemia on Day 8 after the first injection. The event resolved after 5 days and was deemed not related to mRNA-1273 by the investigator. The participant continued in the study and received the second dose per protocol (Study 101 Day 119 CSR Listing 12).

No severe AEs were reported in participants ≥ 71 years of age (Study 101 Day 119 CSR Table 36).

Among 18 to 55 year old participants, dose dependence was observed in the severity of unsolicited AEs, with fewer participants reporting mild AEs and more participants reporting moderate AEs as the dose of mRNA-1273 increased. No dose dependence trend was observed in the 2 older age groups (Study 101 Day 119 CSR Section 7.2.3).

Unsolicited AEs by severity are presented in the Study 101 Day 119 CSR for participants 18 to 55 years of age (Study 101 Day 119 CSR Table 34), 56 to 70 years of age (Study 101 Day 119 CSR Table 35), and ≥ 71 years of age (Study 101 Day 119 CSR Table 36).

2.7.4.2.4.2.4 Unsolicited Adverse Events by Relationship to Study Vaccine

Unsolicited AEs were deemed related to mRNA-1273 in 33%, 13%, and 23% of participants who were 18 to 55 years of age (Study 101 Day 119 CSR Table 37), 56 to 70 years of age (Study 101 Day 119 CSR Table 38), and ≥ 71 years of age (Study 101 Day 119 CSR Table 39), respectively.

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

2.7.4.2.4.3.1 Deaths

At the time of the data cutoff for the Study 101 Day 119 CSR, no deaths had occurred (Study 101 Day 119 CSR Section 7.3.1).

2.7.4.2.4.3.2 Other Serious Adverse Events

At the time of the data cutoff for the Study 101 Day 119 CSR, no SAEs had occurred (Study 101 Day 119 CSR Section 7.3.2).

2.7.4.2.4.3.3 Other Clinically Meaningful Unsolicited Adverse Events

2.7.4.2.4.3.3.1 Unsolicited Adverse Events Leading to Discontinuation from Vaccine or Study

Adverse events leading to treatment discontinuation were reported in 3 participants. Of these, 1 mild AE of urticaria (25 µg group, age group: 18 to 55 years) was considered related to mRNA-1273 (Study 101 Day 119 CSR Section 7.3.3.1). The other events (considered unrelated to treatment) that led to treatment discontinuation were mild oropharyngeal pain (250 µg group, age group: 18 to 55 years) and moderate rash maculo-papular (100 µg group, age group: 56 to 70 years) (Study 101 Day 119 CSR Listing 2).

2.7.4.2.4.3.3.2 Unsolicited Severe Adverse Events

Unsolicited AEs by maximum intensity are discussed in Section 2.7.4.2.4.2.3.

2.7.4.2.4.3.3.3 Medically Attended Adverse Events

As of the data cutoff for the Study 101 Day 119 CSR, 33 MAAEs had been reported in 24 participants (Study 101 Day 119 CSR Posttext Table 127). All MAAEs were deemed not related to mRNA-1273 except for moderate abdominal discomfort reported by 1 participant in the 250 µg treatment group (age group: 18 to 55 years) on Day 26 after the second injection. The event was deemed related to mRNA-1273 by the investigator and resolved within 10 days (Study 101 Day 119 CSR Listing 12).

2.7.4.2.4.4 Study 101 Data Collected Through Day 209

The Study 101 CSR Addendum 1 (Day 209) includes data through Day 209 to provide updated results including SAEs, MAAEs, and NOCMCs. No long-term safety concerns were apparent from the extended follow-up.

Some unsolicited AEs that occurred before the data cutoff date of the Study 101 Day 119 CSR (07 October 2020) that were not included in that CSR due to delays in data entry were considered as new unsolicited AEs in Study 101 CSR Addendum 1 (Day 209); there were 32 new AEs in 26 participants. One additional SAE of clear cell renal cell carcinoma occurred but was entered after the data cutoff for the Study 101 CSR Addendum 1 (Day 209); the event was not considered to be related to mRNA-1273 (Study 101 CSR Addendum 1 [Day 209] Posttext Table 79). A total of 29 new MAAEs were reported in 25 participants, of which most resolved or were resolving at the time of cutoff of this addendum; however, 6 events did not resolve (Study 101 CSR Addendum 1 [Day 209] Posttext Table 80). No deaths and no new TEAEs leading to discontinuation were reported in the study (Study 101 CSR Addendum 1 [Day 209] Section 7.3.1; Section 7.3.3.1).

2.7.4.2.5 Narratives

Individual participant narratives for deaths, other SAEs, and AEs resulting in treatment or study discontinuation are provided in the CSRs in Module 5 as follows:

- Study 301 Part A CSR Section 15
- Study 301 CSR Addendum 1 (Part B) Section 15

- Study 201 Primary Analysis CSR Section 15
- Study 201 CSR Addendum 1 (End of Part A) Section 15
- Study 101 Day 119 CSR Section 7.3.3.1
- Study 101 CSR Addendum 1 (Day 209) Section 7.3.2

2.7.4.3 CLINICAL LABORATORY EVALUATION

No effects of clinical concern on clinical laboratory evaluations after mRNA-1273 injection have been observed. Clinical laboratory assessments were not routinely performed per protocol in Study 301; any abnormalities of clinical concern in clinical laboratory results were captured as unsolicited AEs. Post-baseline safety clinical laboratory assessments in Study 201 (through Day 57) were performed for Cohort 2 only (ie, ≥ 55 years); no clinically relevant trends were observed in this cohort (Study 201 Primary Analysis CSR Table 14.3.2.1). Scheduled post-baseline safety laboratory assessments in Study 101, which included the highest evaluated mRNA-1273 dose of 250 µg, were performed at approximately Day 8, Day 29, and Day 36. No notable trends were observed in the hematology and chemistry laboratory test results for any group. No trends were observed between the dose levels and the presence or severity of laboratory test abnormalities. Most laboratory abnormalities had a maximum severity of mild (Study 101 Day 119 CSR Section 7.4).

2.7.4.4 VITAL SIGNS AND PHYSICAL EXAMINATIONS

Abnormalities of clinical concern in vital signs or physical examinations were captured as solicited ARs or unsolicited AEs. In Study 301, mean vital sign measurements (diastolic blood pressure, pulse rate, respiratory rate, systolic blood pressure, and temperature) observed after dosing and through Day 209 were consistent with those observed at baseline and no differences were apparent between groups (Study 301 Part A CSR Table 14.3.2.1 and Table 14.3.2.2). In Study 201 (through Day 57), mean vital sign measurements (diastolic blood pressure, pulse rate, respiratory rate, systolic blood pressure, and temperature) observed after dosing and through Day 57 were similar to those observed at baseline, with no notable trends or differences across groups (Study 201 Primary Analysis CSR Table 14.3.3.1). No notable trends were observed in vital sign results in Study 101 (Study 101 Day 119 CSR Listing 15).

2.7.4.5 SAFETY IN SPECIAL GROUPS AND SITUATIONS

2.7.4.5.1 Intrinsic Factors

Study 301 Part A data for solicited ARs and unsolicited AEs were summarized by subgroups including those based on age group, baseline SARS-CoV-2 status, race, ethnicity, sex, risk factors for severe COVID-19, and autoimmune disorders at baseline. In addition, deaths, SAEs, and other significant unsolicited AEs were summarized by subgroups based on age group and on baseline SARS-CoV-2 status. Subgroup summaries were not provided for Studies 201 or 101, but data presentations by age-based enrollment or randomization cohorts permit summaries by subgroups based on age group. Age group boundaries defined for each study were as follows:

- Study 301 age groups were ≥ 18 to < 65 years and ≥ 65 years; age subgroups were ≥ 18 to < 65 years, ≥ 65 to < 75 years, ≥ 75 to < 85 years, and ≥ 85 years.
- Study 201 age groups were ≥ 18 to < 55 years and ≥ 55 years.
- Study 101 age groups were 18 to 55 years, 56 to 70 years, and ≥ 71 years.

2.7.4.5.1.1 Age Group

2.7.4.5.1.1.1 Solicited Adverse Reactions

In Study 301, incidence of solicited local and systemic ARs after either injection in the mRNA-1273 group was lower among older adults (≥ 65 years) than among younger adults (≥ 18 to < 65 years) (Study 301 Part A CSR Table 14.3.1.1.2.1.1 and Table 14.3.1.1.2.1.2). No differences were apparent between the age subgroups for the most frequently reported ARs, AR severity, or duration of solicited local or systemic ARs after the first (Study 301 Part A CSR Table 14.3.1.4.2.1) or second (Study 301 Part A CSR Table 14.3.1.4.2.2) injections. Findings were similar in Study 201 (Study 201 Primary Analysis CSR Table 14.3.1.1.1, Table 14.3.1.1.2, and Table 14.3.1.1.3) and Study 101 (Section 2.7.4.2.4.1).

2.7.4.5.1.1.2 Unsolicited Adverse Events

In Study 301, analysis of unsolicited TEAEs by age group did not reveal any clinically relevant imbalances between the mRNA-1273 and placebo groups compared with the overall population. Age group cohorts were too small in Study 201 (Study 201 Primary Analysis CSR Table 14.3.1.7.2, Table 14.3.1.7.2, and Table 14.3.1.11.2) and Study 101 (Section 2.7.4.2.4.2) for

meaningful comparisons, but findings in these smaller studies were not inconsistent with those of Study 301.

In Study 301, incidence of unsolicited TEAEs was similar in both the younger (≥ 18 to < 65 years; 29.7% of 22,826 participants) and older (≥ 65 years; 30.6% of 7520 participants) age groups; this was also true for TEAEs assessed as treatment-related by the investigator (Study 301 Part A CSR Table 14.3.1.7.2.1.1). Incidence was also similar across the older age subgroups: 30.5% of 6122 participants aged ≥ 65 to < 75 years, 30.9% of 1308 participants aged ≥ 75 to < 85 years, and 34.4% of 90 participants aged ≥ 85 years (Study 301 Part A CSR Table 14.3.1.7.2.2.1).

In the ≥ 65 years age group, reported TEAE incidence was higher than in the younger age group in the following SOCs: musculoskeletal and connective tissue disorders (7.5% vs. 6.4%); vascular disorders (1.9% vs. 1.1%); metabolism and nutrition disorders (1.0% vs. 0.7%); cardiac disorders (0.9% vs. 0.4%); benign, malignant, and unspecified neoplasms (including cysts and polyps) (0.8% vs. 0.2%); eye disorders (0.7% vs. 0.4%); ear and labyrinth disorders (0.7% vs. 0.5%); and renal and urinary disorders (0.6% vs. 0.2%). These types of events are generally consistent with expected TEAEs in an older population. The most common unsolicited TEAEs were headache and fatigue in the younger age group and fatigue, headache, and arthralgia in the older age group, and findings were similar in the older age subgroups (Study 301 Part A CSR Table 14.3.1.8.2.1.1).

The overall incidence of severe unsolicited TEAEs was higher in the older age group (2.2%) compared with the younger age group (1.4%) (Study 301 Part A CSR Table 14.3.1.17.1.2). No difference was apparent between the age groups in the overall incidence of severe unsolicited TEAEs assessed by the investigator to be treatment-related (Study 301 Part A CSR Table 14.3.1.18.1.2).

The overall incidence of serious TEAEs in Part A was higher in older adults (≥ 65 years of age) compared to younger adults (18 to < 65 years of age) who received either mRNA-1273 (3.1% vs. 1.3%) or placebo (3.3% vs. 1.5%) (Study 301 Part A CSR Table 14.3.1.13.2.3). The overall incidence of serious treatment-related TEAEs in Part A was low and comparable at < 0.1% for younger adults (18 to < 65 years of age) and older adults (≥ 65 years of age) who received either mRNA-1273 or placebo (Study 301 Part A CSR Table 14.3.1.14.2.1).

2.7.4.5.1.2 Baseline SARS-CoV-2 Status

Solicited ARs and unsolicited AEs were summarized in Study 301 by baseline SARS-CoV-2 status determined by virologic and serologic evidence of SARS-CoV-2 infection on or before

Day 1. Baseline SARS-CoV-2 status was negative for most participants. In the Safety Set, 347 participants in the mRNA-1273 group and 337 participants in the placebo group had positive baseline SARS-CoV-2 status (Table 8). Results among participants with negative baseline status reflect those of the overall population. This subgroup was not assessed in Study 201 or Study 101.

2.7.4.5.1.2.1 Solicited Adverse Reactions

Among participants with baseline SARS-CoV-2 positive status in the mRNA-1273 group, the percentage of participants who reported a grade 3 solicited local or systemic AR after the first injection was 8.4% (29/346) (Study 301 Part A CSR Table 14.3.1.1.3.1) compared with 5.6% (849/15,166) (Table 11) in the overall population (regardless of status). This was largely driven by grade 3 solicited systemic ARs, which were reported for 6.6% (23/346) of participants among those in the mRNA-1273 group with positive baseline status (Study 301 Part A CSR Table 14.3.1.1.3.1) compared with 3.0% (449/15166) of participants (Table 11) for the overall mRNA-1273 group regardless of status.

No differences were apparent for this subgroup in duration of local or systemic ARs after the first (Study 301 Part A CSR Table 14.3.1.4.3.1) or second (Study 301 Part A CSR Table 14.3.1.4.3.2) injection or for ARs persisting beyond 7 days after the first (Study 301 Part A CSR Table 14.3.1.6.3.1) or second (Study 301 Part A CSR Table 14.3.1.6.3.2) injection.

2.7.4.5.1.2.2 Unsolicited Adverse Events

Among participants with positive baseline SARS-CoV-2 status, incidence of TEAEs was numerically lower in the mRNA-1273 group (22.2%) than in the placebo group (27.3%) (Study 301 Part A CSR Table 14.3.1.7.3.1) and compared with incidence in the overall mRNA-1273 population (31.3%) (Study 301 Part A CSR Table 14.3.1.7.1.1). Incidence was similarly lower in the mRNA-1273 group for severe TEAEs, SAEs, MAAEs, and TEAEs considered related to treatment. The comparison is limited by the small number of baseline positive participants. The most common TEAEs within 28 days after any injection were similar between participants with either a positive or negative baseline SARS-CoV-2 status (Study 301 Part A CSR Table 14.3.1.8.3.1).

The overall incidence of serious treatment-related TEAEs in Part A were low and comparable at < 0.1% for participants with a negative baseline SARS-CoV-2 status who received either mRNA-1273 or placebo (Study 301 Part A CSR Table 14.3.1.14.3.3).

2.7.4.5.1.3 Race and Ethnicity

In the Safety Set for Study 301, race was reported as White for 79.2% of participants overall, Black or African American for 10.2%, Asian for 4.6%, and multiracial for 2.1%; no other category was reported for > 2% of participants (Study 301 Part A CSR Table 14.1.3.2.2). Ethnicity was reported as Not Hispanic or Latino for 78.6% of participants overall. Results among participants who reported White race and those who reported Not Hispanic or Latino ethnicity reflect those of the overall population.

Race and ethnicity subgroup evaluations were not performed in Study 201 or Study 101.

2.7.4.5.1.3.1 Solicited Adverse Reactions

Compared with those who reported White race, participants who reported Black or African American race appeared to have lower incidence of solicited local ARs overall and for all reactions except axillary swelling or tenderness after the first injection, while incidence of systemic ARs appeared to be similar between the subgroups (Study 301 Part A CSR Table 14.3.1.1.4.1). After the second injection, participants who reported Black or African American race appeared to have lower incidence of local and systemic ARs compared with those who reported White race (Study 301 Part A CSR Table 14.3.1.1.4.2). Other subgroups by race were too small for meaningful comparison.

2.7.4.5.1.3.2 Unsolicited Adverse Events

In Study 301, the incidence of unsolicited TEAEs was similar across the race groups (Study 301 Part A CSR Table 14.3.1.7.4.1) and ethnic groups (Study 301 Part A CSR Table 14.3.1.7.5.1). Unsolicited TEAEs were not assessed by race or ethnicity subgroups in Study 201 or Study 101.

2.7.4.5.1.4 Sex

2.7.4.5.1.4.1 Solicited Adverse Reactions

In Study 301 after both the first (Study 301 Part A CSR Table 14.3.1.1.7.1) and second (Study 301 Part A CSR Table 14.3.1.1.7.2) injections, female participants appeared to have higher incidence of local and systemic ARs compared with male participants. Sex subgroup evaluations were not performed in Study 201 or Study 101.

2.7.4.5.1.4.2 Unsolicited Adverse Events

In Study 301, the observed incidence of unsolicited TEAEs during the 28-day follow-up was higher in females (35.5% of 7266 participants in the mRNA-1273 group) and lower in males (27.4% of 7918 participants in the mRNA-1273 group) (Study 301 Part A CSR Table 14.3.1.7.7.1). The difference between the mRNA-1273 and placebo groups, respectively, was larger for females (35.5% vs. 31.6%) than for males (27.4% vs. 26.0%). The reported TEAEs were similar for both sexes and the most common TEAEs were headache, fatigue, headache, myalgia, and arthralgia (Study 301 Part A CSR Table 14.3.1.8.7.1).

Unsolicited TEAEs were not assessed for sex subgroups in Study 201 or Study 101.

2.7.4.5.1.5 Risk Factors for Severe COVID-19 and Comorbidities

Assessment of unsolicited TEAEs was performed in Study 301 for subgroups based on risk factors for severe COVID-19 and on HIV status.

The incidence of unsolicited TEAEs up to 28 days after any IP administration in the mRNA-1273 group was 34.5% in the At Risk subgroup (3448 participants) and 30.4% in the Not At Risk subgroup (11,736 participants) (Study 301 Part A CSR Table 14.3.1.7.6.2.1). As expected based on their medical history and comorbidities, serious TEAEs were reported at a higher rate in the At Risk subgroup (1.0% in the mRNA-1273 group) compared with the Not At Risk subgroup (0.5% in the mRNA-1273 group). The overall incidence of unsolicited TEAEs was similar for the individual risk groups based on comorbidity description (Study 301 Part A CSR Table 14.3.1.7.6.3.1).

Among participants with HIV, the incidence of unsolicited TEAEs up to 28 days after any IP administration was generally similar between the mRNA-1273 group (35/94 [37.2%]) and the placebo group (38/91 [41.8%]; Study 301 Part A CSR Table 14.3.1.7.8.1). The incidence of unsolicited TEAEs that were considered treatment-related was also similar between the mRNA-1273 (11/94 [11.7%]) and placebo (10/91 [11.0%]) groups.

2.7.4.5.1.6 Participants with Autoimmune Disorders at Baseline

Assessment of unsolicited TEAEs was performed in Study 301 for participants who had an autoimmune disorder reported at baseline.

Among the 2296 participants for whom an autoimmune disorder was reported at baseline, the incidence of unsolicited TEAEs up to 28 days after any injection was 35.0% compared with 30.0% in the overall population. However, even in this large population of participants with at

least one autoimmune disorder at baseline, no difference in TEAE incidence was observed between the mRNA-1273 group (36.7% of 1152 participants) and the placebo group (33.2% of 1144 participants) (Study 301 Part A CSR Table 14.3.1.7.9.1). Events that were assessed as treatment-related were more commonly reported by participants who received mRNA-1273 (16.8%) than by those who received placebo (9.3%), as was observed in the overall study population. This is consistent with the observed higher incidence in the mRNA-1273 group of TEAEs that were associated with reactogenicity (ARs or similar to ARs), including fatigue, injection site conditions, and arthralgia (Study 301 Part A CSR Table 14.3.1.8.9.1). No cases of autoimmune disease exacerbations were explicitly reported.

2.7.4.5.2 Extrinsic Factors

Extrinsic factors are defined as those associated with the patient environment, including the effect of food. These were not evaluated for mRNA-1273.

2.7.4.5.3 Drug Interactions

Drug interactions were not evaluated for mRNA-1273. Concomitant medications that were excluded due to the potential impact on efficacy are described in Section 2.7.4.1.3.2.3.

2.7.4.5.4 Use in Pregnancy and Lactation

Use in pregnancy and lactation has not been formally evaluated for mRNA-1273, and available data on the vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy or the effects of the vaccine on the breastfed infant or on milk production or excretion. In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of nucleoside-modified mRNA (100 µg) and other ingredients found in a single human dose of mRNA-1273 was administered IM to female rats 4 times, 28 and 14 days before mating and on gestation days 1 and 13. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study (Section 2.4.4.3 [Nonclinical Overview]). An mRNA-1273 observational pregnancy outcome study and a clinical trial in pregnant women are ongoing to evaluate outcomes of pregnancies in females exposed to mRNA-1273 during pregnancy (details about these studies are provided in Section 2.5.1.4.2 [Clinical Overview]). Post-authorization experience with pregnancy and lactation is described in Section 2.7.4.6.4.5.1.

2.7.4.5.4.1 Study 301

Four participants in the mRNA-1273 group and 5 participants in the placebo group had a positive pregnancy test performed at the site during Part A as of the data cutoff for Study 301 Part A (Study 301 Part A CSR Listing 16.2.8). According to the safety database, 16 pregnancies were reported in the mRNA-1273 group and 11 pregnancies were reported in the placebo group during Part A (Table 36). Of the outcomes known as of 04 May 2021, 1 participant in the placebo group experienced a live birth. The participant was induced at 37 weeks due to polyhydramnios and gestational diabetes and the child was noted as having congenital anomalies of bilateral talipes equinovarus and hydronephrosis. Five participants (2 in the mRNA-1273 group and 3 in the placebo group) experienced spontaneous abortion/miscarriage. These events were reported as SAEs for 4 of the participants (2 participants in each group) and were considered not related to IP; for 1 participant in the placebo group, the event was considered nonserious and causality was not reported. Two participants (1 in each group) underwent elective termination of pregnancy; there were no reported pregnancy complications for either participant.

Nine participants in the placebo-mRNA-1273 group and 1 participant in the mRNA-1273 group had a positive pregnancy test performed at the site as of the data cutoff for Study 301 Part B (Study 301 CSR Addendum 1 [Part B] Listing 16.2.8.3). According to the safety database, pregnancy was reported for 18 participants who received mRNA-1273 in Part A and 19 participants who received placebo in Part A and mRNA-1273 in Part B (Table 37). Among few known outcomes, spontaneous abortion/miscarriage was reported for 1 participant in the mRNA-1273 group and 3 participants in the placebo–mRNA-1273 group; elective termination was reported for 1 participant in the placebo–mRNA-1273 group.

Table 36: Study 301: Incidence of Pregnancies Reported in Part A and Outcomes (Safety Set)

	Placebo (N=15162)	100 µg mRNA-1273 (N=15184)	Total (N=30346)
Number of pregnancies	11	16	27
Known pregnancy outcomes	5	3	8
Live born	1[a, b]	0	1
Spontaneous abortion/miscarriage	3	2	5
Elective termination	1	1	2[c]
Other maternal/gestational complications	1[a, b]	0	1
Outcome unknown/lost to follow-up	2[d, e]	1[d]	3

[a] Baby was born at 37 weeks with congenital anomalies of bilateral talipes equinovarus and hydronephrosis.

[b] The mother of the baby with talipes equinovarus and hydronephrosis had polyhydramnios and gestational diabetes.

[c] There were no reported pregnancy complications in either group.

[d] No response to follow-up requests in 1 subject in each group with expected dates of delivery prior to data cut off of 04 May 2021.

[e] One subject was categorized as study lost to follow-up.

Source: Data in the table was generated from the safety database and case narratives for the participants who experienced pregnancies are provided in Study 301 Part A CSR Section 15.

Table 37: Study 301 Open-Label Phase: Incidence of Pregnancies Reported in Part B and Outcomes (Safety Set, Participants Who Received Placebo in Part A and mRNA-1273 in Part B)

	Placebo (N=2514)	Placebo–100 µg mRNA-1273 (N=12648)	100 µg mRNA-1273 (N=15184)
Number of pregnancies	0	19	18
Known pregnancy outcomes	0	5	2
Spontaneous abortion/miscarriage	0	3	1
Elective termination	0	1[a]	0
Outcome unknown/lost to follow-up	0	1	1

[a] No complications reported with pregnancy.

Source: Data in the table was generated from the safety database and case narratives for the participants who experienced pregnancies are provided in Study 301 CSR Addendum 1 (Part B) Section 15.

2.7.4.5.4.2 Study 201

No pregnancies were reported in Study 201 through Day 57 (Study 201 Primary Analysis CSR Listing 16.2.8.5). Two pregnancies were reported in the Study 201 safety database through Day 209 (1 participant in the mRNA-1273 50 µg group and 1 participant in the mRNA-1273 100 µg group); both resulted in miscarriage/spontaneous abortion and were reported as SAEs

that were not considered related to the vaccine (Study 201 CSR Addendum 1 [End of Part A] Section 7.6).

2.7.4.5.4.3 Study 101

No pregnancies were reported in Study 101 (Study 101 Day 119 CSR Listing 18; Study 101 CSR Addendum 1 [Day 209] Section 7.6).

2.7.4.5.4.4 Post-authorization

A total of 2559 cases related to use in pregnancy have been reported in post-authorization monitoring (Section 2.7.4.6.4.5.1).

2.7.4.5.5 Overdose

Overdose is unlikely because mRNA-1273 is to be administered by a healthcare professional. The clinical consequence of mRNA-1273 overdose is unknown at this time. There is no specific antidote for an overdose with mRNA-1273.

No cases of overdose were reported in the 3 mRNA-1273 clinical studies. The highest single dose of mRNA-1273 administered in the clinical trials was 250 µg (given IM twice, 28 days apart) in Study 101 to participants in the 18 to 55 years of age cohort. At this highest dose level of exposure, 3 participants had severe solicited systemic ARs after the second injection. In addition, 1 participant who received mRNA-1273 250 µg experienced severe unsolicited AEs of dizziness and syncope on Day 1 after the second injection; these events were considered to be related to treatment (Study 101 Day 119 CSR Listing 12). Adverse reaction and AE data are presented for Study 101 in Section 2.7.4.2.4.

2.7.4.5.6 Drug Abuse

Not applicable.

2.7.4.5.7 Withdrawal and Rebound

Not applicable.

2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the effects of mRNA-1273 on the ability to drive or operate machinery or on impairment of mental ability have been performed.

2.7.4.6 POST-AUTHORIZATION DATA

Post-authorization safety data for mRNA-1273 (Moderna COVID-19 Vaccine [US], COVID-19 Moderna [all other countries]) included in this SCS include cumulative information received worldwide by the Sponsor from the International Birth Date (IBD) of 18 Dec 2020 (the first post-authorization use in the US) to the data lock point of 30 Jun 2021. In contrast to data obtained in clinical studies, the post-authorization safety data that have been collected for the mRNA-1273 vaccine rely on information that has been reported to regulatory authorities (69.6% of cases are from regulatory authorities including the Vaccine Adverse Event Reporting System [VAERS]), from spontaneous reports (30.0%; including HCPs and consumers), and from other sources including literature reports.

The scale of use of mRNA-1273 since emergency or conditional authorization is without precedent. As of 30 Jun 2021, according to Sponsor supply chain estimates, 301,035,380 doses had been distributed to 43 countries (Table 38).

As reported by US health authorities, the majority of mRNA-1273 administrations (73.4%) have occurred in the US, where (according to CDC estimates) approximately 134,076,668 doses of mRNA-1273 had been administered by this date (CDC 2021a). According to CDC estimates, as of 30 Jun 2021, 61,042,278 individuals are considered to be fully vaccinated after receiving 2 doses. More than 90% of all doses have been administered in the US and in the European Economic Area (EEA). Further information is provided in the Monthly Summary Safety Report (MSSR) #6 (Module 5.3.6).

Since 18 Dec 2020, the vast majority of case reports received by the Sponsor were from the US (80.3%), followed by the Netherlands (5.9%) and the United Kingdom (3.3%).

Table 38: mRNA-1273 Doses Distributed and Administered (Cumulative as of 30 Jun 2021)

	Doses Distributed[1]		Doses administered[2]	
	N	%	N	%
Total[3]	**301,035,380**	**100.0**	**182,716,703**	**100.0**
United States	(b) (4)		134,076,668	73.4
European Economic Area			32,964,580	18.0
Asia			2,996,423	1.6
Canada			4,483,925	2.5
Switzerland			4,573,159	2.5
Middle East			1,339,548	0.7
United Kingdom			2,220,000	1.2
Latin America			62,400	0.0

[1] Source: Moderna supply chain estimates
[2] Sources: CDC 2021a, ECDC 2021, Health Canada 2021, FOPH 2021, Our World in Data 2021.
[3] Refer to Monthly Summary Safety Report 6 Appendix 3 for a detailed list of doses distributed and administered by country within regions.

2.7.4.6.1 Determination/Identification of Events

The Sponsor has an established signal management process including signal detection, signal validation, and evaluation of spontaneous reports. During signal detection, data sources are screened for new safety information related to COVID-19 mRNA Vaccine and Moderna COVID-19 vaccine. Potential signal detection data sources include safety data from Moderna-sponsored clinical trials and clinical as well as non-interventional studies, spontaneous AE reports, published literature, and communications from external sources, including regulatory agencies, and (if applicable) business partners. Following initial review of the available data, a determination is made on the basis of the nature and the quality of the new information whether further investigation is warranted, at which point those topics referred for further investigation are considered "validated signals" (EMA 2017). Signaling for measures of disproportionality is also being conducted on a biweekly basis, with those signals exceeding the prespecified threshold being referred for signal validation. Information coming from the Sponsor's global safety database (as there is only one product) uses a threshold based in using the proportional fractional reporting ratio (PFRR), which compares (on a monthly basis) the monthly reporting rates to the cumulative data (prior to the reporting period [RP]) reporting rates. The threshold for flagging topics of interest for the PFRR is reporting ratio > 2, minimum 10 events in the RP and Not Classified as Standard Topic, Important Identified Risk, Important Potential Risk, Missing Information, or Adverse Event of Special Interest. For biweekly VAERS data disproportionality (mRNA-1273 compared with all vaccines in adults from VAERS): EB05 > 2 threshold (EB05 refers to the lower bound of the 90% CI for the empiric Bayes geometric mean). Routine

pharmacovigilance also includes a periodic review of the literature that involves targeted keyword searches in widely recognized biomedical literature databases (ie, MEDLINE, EMBASE).

Enhanced pharmacovigilance activities include targeted follow-up in individuals who have received Moderna COVID-19 mRNA vaccine via questionnaire to collect structured clinical details of any potential anaphylactic reactions, myocarditis and pericarditis, and COVID-19 disease (to provide insight into potential cases of vaccine lack of effect). These measures are in addition to routine pharmacovigilance activities, in which the Sponsor monitors the safety profile of mRNA-1273 continuously through routine surveillance of all AESIs and designated medical events (DMEs) and summarizes topics identified through signal management activities and from regulatory body requests; the most recent monthly report (MSSR #6 [Module 5.3.6]), which includes a list of DMEs, AESIs, and signals evaluated, is provided as an appendix and is referenced throughout this section. The company global safety database is queried for cases from clinical trials and spontaneous case reports received from HCPs, health authorities (HAs), consumers, and literature, reported worldwide for mRNA-1273. Additionally, since the IBD of the vaccine, the Sponsor has been conducting monthly reviews of the post-authorization safety data which are summarized and provided as MSSRs to HAs worldwide.

2.7.4.6.2 Overview of Events

Cumulatively, as of 30 Jun 2021, there have been 238,350 cases received by Moderna. These cases were associated with 916,192 events (a case may have more than one associated event). A total of 85,021 of these events were defined as serious. Of the 238,350 total reported cases, 35,011 cases were defined as serious; 2,842 cases had fatal outcomes. Out of the total reported cases, 159,557 cases were considered medically confirmed (a case is considered to be medically confirmed if it contains at least one event confirmed or reported by an HCP).

Most reports referred to individuals older than 40 years of age (157,796; 66.2%). The majority of cases were reported in females (171,826 [72.1%]) compared to males (56,526 [23.7%]); gender was not reported in 9,998 cases (4.2%). The preponderance of reports associated with females is consistent with studies in other therapeutic areas and vaccines, in which AE reporting disproportionately describes events occurring in females. Most of the cases reported had a time to onset (TTO) of < 7 days after any vaccination. Of the 513,320 events reported after the first dose, the majority of the events (56%) had a TTO of < 7 days, followed by 36.7% of the events reported with a TTO of > 7 days and < 14 days. This was consistent with events reported regardless of vaccine dose number where most of the events (65.9%) were reported within 7 days of vaccine administration (MSSR #6 Section 6.1).

Cumulatively, headache, pyrexia, and fatigue were the most frequently reported events (MSSR #6 Section 6.2). The top 3 MedDRA SOC, High Level Term (HLT), and PT for all events are presented in Table 39.

Table 39: Top 3 Most Frequently Reported Events by MedDRA[1] SOC, HLT, and PT (Cumulative)

SOC	**Total Events**	
	Total # Events	**% Total Events**
General disorders and administration site conditions	386,335	42.17
Nervous system disorders	120,231	13.12
Musculoskeletal and connective tissue disorders	93,252	10.18
HLT	**Total Events**	
	Total # Events	**% Total Events**
Injection site reactions	105,834	11.55
Asthenic conditions	63,816	6.97
Feelings and sensations NEC	51,041	5.57
PT	**Total Events**	
	Total # Events	**% Total Events**
Headache	47,861	5.22
Pyrexia	43,518	4.75
Fatigue	40,539	4.42

Abbreviations: HLT = higher level term; MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified; PT = preferred term; SOC = system organ class.
[1] MedDRA Version 24.0

2.7.4.6.3 Designated Medical Events

The European Medicines Agency (EMA) has developed the DME list to identify reports of suspected adverse drug reactions that deserve special attention. The list includes MedDRA PTs that identify serious medical concepts often causally associated with drugs across multiple pharmacological/therapeutic classes. It may not address product-specific issues, and conditions with high prevalence in the general population are excluded. The content of the DME list is not definitive and may change as further experience with its use is gathered.

Observed to expected analyses have been conducted for all DMEs and are included in (MSSR #6 Section 6.5). The observed number of cases has been generally been well below the expected based on cumulative data for DMEs.

2.7.4.6.4 Important Identified Risks Added Since Initial Authorization

Since initial authorization in the US and other countries, anaphylaxis, myocarditis, and pericarditis have been added as important identified risks to the risk management plan (RMP). The RMP version 1.0, dated 06 Jan 2021, was updated to include anaphylaxis as an important identified risk (after receipt of a case of anaphylaxis shortly after the IM administration of mRNA-1273, which was then classified as a Level 2 reaction according to Brighton Collaboration based on available information). The prescribing information for all countries in which mRNA-1273 was authorized was revised following the addition of anaphylaxis to the Company Core Data Sheet (CCDS) along with monitoring guidelines requiring close observation for 30 minutes for those individuals with a history of an immediate allergic reaction of any severity to another vaccine or injectable therapy and those with a history of anaphylaxis (due to any cause).

Case reports of myocarditis following vaccination with an mRNA vaccine (April 2021) led to increasing interest by several health authorities regarding the risk of myocarditis and/or pericarditis following mRNA-1273 vaccination. After a Vaccines and Related Biological Products Advisory Committee meeting held on 10 Jun 2021 in the US, the Sponsor updated the CCDS to include information describing very rare reports of myocarditis and pericarditis occurring after vaccination with mRNA-1273. Although causality has not been established, the majority of the cases have been reported in young males and shortly (between 2 to 3 days but up to 14 days) after the second dose of the vaccine. These are typically mild cases, and individuals tend to recover within a short time following standard treatment and rest.

Additional actions taken to address this risk included updating the RMP for inclusion of myocarditis and pericarditis as important identified risks, as well as creating and disseminating a joint Direct Healthcare Professional Communication (DHPC) between the EMA Pharmacovigilance Risk Assessment Committee (PRAC), Moderna, and Pfizer-BioNTech notifying HCPs that myocarditis and pericarditis events are being considered a class effect for the mRNA COVID-19 vaccines.

2.7.4.6.4.1 Anaphylaxis

Anaphylaxis is currently included in all mRNA-1273 vaccine package inserts under special warnings and precautions for use. Appropriate risk minimization strategies are included in the prescribing information providing a clear guidance for providers to understand the associated risk that may occur with the administration of mRNA-1273.

There was a total of 1214 cases within the narrow SMQ ‘anaphylactic reaction’ cumulative as of 30 Jun 2021. All cases were medically reviewed to determine Brighton Classification. These cases are presented in Table 40.

Cumulatively, there was a total of 421 cases that met Brighton Classification anaphylaxis case classification criteria Levels 1 through 3 (MSSR #6 Section 6.5.2) (Rüggeberg et al 2007).

Table 40: Number of Cases and Events Reported for Moderna COVID-19 mRNA Vaccine for Anaphylaxis According to the Brighton Collaboration Criteria

Brighton Classification	Total # of Cases Cumulative
Level 1	185
Level 2	204
Level 3	32
Total Confirmed Cases	421
Level 4	546
Level 5	247
Total	1214

Rüggeberg et al 2007.

2.7.4.6.4.2 Myocarditis and Pericarditis

Cumulatively, a total of 589 cases (a case may contain more than one event) of myocarditis and pericarditis have been reported to the company’s global safety database, of which 584 cases (99.2%) were considered serious. Out of the 589 cases reported to the global safety database, there were a total of 637 events of myocarditis and pericarditis included, of which 625 events were considered serious (98.1%). Most cases were in persons 18 to 49 years old (median: 31, range 14 to 94 years). Most cases (71.0%) were reported in males. The majority of the events (53.4%) were reported after the first 7 days after receiving any dose, with a higher proportion of events reported within the second dose of mRNA-1273.

There were 9 fatal case reports in 3 females and 6 males; there were 4 reports after the first dose, 4 after the second dose, and 1 after an unknown dose number. The median age for these 9 individuals was 59 years, and the median TTO was 5.5 days. In each of these reports, there were comorbidities that could reasonably have contributed to the fatality. Conditions reported in medical histories included hypertension, aortic stenosis, hyperthyroidism, rheumatoid arthritis, heart transplant, and previous history of pericarditis. Refer to MSSR #6 Appendix 11 for case narratives and additional information.

Myocarditis (with or without pericarditis) was observed in 362 cases cumulatively (reporting rate 3.45 cases per 100,000 person-years). The cumulative reporting rate was below estimates from the US (Kang 2021: 10 per 100,000 person-years, 1050.5 cases expected, rate ratio 0.34, 95% CI 0.31, 0.39 considering a 21-day risk window) (MSSR #6 Section 6.6.1.3.1). A recent systematic review of AE of special interest (AESI) rates published by the CDC (June 2021) also identified myopericarditis rates among active-duty military personnel of 0.24 to 2.07/100,000 vaccine recipients (recipients of any vaccine), which was comparable to the observed reporting rate of 0.36 per 100,000 Moderna COVID-19 mRNA vaccine recipients (Gubernot et al 2021). Variation in incidence estimates has been observed, however: estimates from the Center for Biologics Evaluation and Research (CBER) Biologics Effectiveness and Safety (BEST) initiative are between 4.5 and 122.28 cases per 100,000 person-years across subgroups of age and gender; and overall rates from the European ACCESS project estimates range from 0.67 to 23.68 cases per 100,000 person-years. This variation complicates interpretation of age, gender, and age-by-gender stratified incidence estimates. For example, the observed incidence of myocarditis following vaccination in men ages 18 to 29 years, 40.30 cases per 100,000 person-years, is comparable to estimates from Optum data (37.8 to 52.8 cases per 100,000 person-years among men ages 18 to 34 years) while exceeding estimates from some ACCESS sites (MSSR #6 Section 6.6.1.3.1) (Li et al 2021).

Pericarditis without myocarditis was observed in 227 cases cumulatively (reporting rate 2.16 per 100,000 person-years). This cumulative reporting rate was below estimates from the previously referenced CDC systematic review of AESI incidence, which described incidence of pericarditis hospitalization from 5.73 to 26 cases per 100,000 person-years (Gubernot et al 2021). Again, variation was seen in rates by age and gender, with the highest reporting rate observed for males ages 18 to 29 years (9.77 cases per 100,000 person-years).

2.7.4.6.4.3 Adverse Events of Special Interest

All routine and additional pharmacovigilance activities conducted by Moderna take into consideration the list of AESIs prepared by regulatory agencies and vaccine expert groups as follows:

- Brighton Collaboration (Safety Platform for Emergency vACcines; Law and Sturkenboom 2020)
- ACCESS protocol (Dodd and Willame 2020)
- US FDA CBER BEST Initiative Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring Draft Protocol (BEST 2020)

- US Center for Disease Control and Prevention (preliminary list of AESI for VAERS surveillance; Shimabukuro 2020)

- Medicines and Healthcare Regulatory Agency (unpublished guideline)

For AESIs, the Sponsor defines the observed reporting rate as the number of cases reported divided by the sum of accrued person-years. Person-time is calculated by assigning a 21-day risk window following each vaccine dose (excepting assessment of anaphylaxis, for which a 3-day window is used). All cases are included regardless of whether they occur during the specified window. The estimated reporting rate is then compared to background incidence rates from relevant published literature with a focus on population-based data from the US, where most vaccine administration and AE reports have occurred. Expected cases are estimated, and rate ratios and their 95% CIs calculated. Sensitivity analyses stratified by age, gender, and age-by-gender are conducted. Further, to account for potential under-reporting or data lags, rate ratios are re-calculated under the bias assumptions that (1) reported cases represent 50% of true vaccine-associated cases, and (2) reported cases represent 25% of true vaccine-associated cases.

Detailed analyses of AESIs are presented in MSSR #6 Section 6.6. As part of its ongoing safety surveillance program, the Sponsor continues to monitor post-marketing sources of information related to these AESIs.

Based on the analyses of cumulative safety data available as of 30 Jun 2021, the Sponsor considers the following AESIs to be temporally associated with the administration of mRNA-1273, but the post-authorization information provided does not presently support evidence of causality with regard to mRNA-1273 exposure:

- Acute disseminated encephalomyelitis (ADEM)

- Anosmia

- Bell’s palsy

- Erythema multiforme (males and females < 29 years old)

- General convulsions

- Myelitis transverse

- Single-organ cutaneous vasculitis (SOCV)

- Vaccine-associated enhanced disease (VAED)

2.7.4.6.4.4 Important Potential Risks

2.7.4.6.4.4.1 Vaccine-Associated Enhanced Disease

There is currently no widely accepted case definition for VAED; however, a recent publication by the Brighton Collaboration provides some guidance for assessment of potential VAED in COVID-19. Using their definition, a case of VAED requires not only that there be a breakthrough infection (ie, a vaccine failure, defined as exposure to and infection by SARS-CoV-2 in a fully immunized person), but also that the SARS-CoV-2 infection is significantly more severe than would be expected if the person had not been vaccinated (Munoz et al 2021). Therefore, the authors further suggest that the clinical presentation must be recognized as atypical or severe.

It should be noted that VAED has already been excluded in a placebo-controlled clinical efficacy trial that was actively and continuously monitored for VAED with prespecified criteria (Study 301). Not only was no VAED found, but also the vaccine showed overwhelming efficacy by all measures including severe disease and rare breakthrough cases in vaccinees had a lower viral load and tended to be milder.

There were 3056 COVID-19 cases of vaccine failure available for analysis included (cumulative as of 30 Jun 2021) with latency data (ie, known interval between date of vaccination and date of event) available. Of these, a total of 281 (9.2%) cases of COVID-19 had a latency of at least 14 days after the second vaccine dose. Review of these 281 cases of vaccine failure did not reveal cases of VAED fulfilling the proposed Brighton Collaboration case definitions.

In summary, the totality of post-authorization data, with more than 180 million doses of Moderna COVID-19 mRNA vaccine administered (as of 30 Jun 2021) has provided no evidence to identify any cases of VAED.

2.7.4.6.4.5 Missing Information

2.7.4.6.4.5.1 Use in Pregnancy and While Breastfeeding

Currently, pregnancy cases are pulled from the Sponsor’s global safety database according to the search criteria defined in the Sponsor’s Product Signaling Strategy Form (PSSF) version 5.1, using pregnancy related and congenital anomaly PT terms.

Monitoring use of Moderna COVID-19 mRNA vaccine in pregnant and breastfeeding women is important given that there are no prelicensure clinical trial safety and efficacy data in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or postnatal development. Based on these results and considering the potential risk of COVID-19 infection in pregnancy, many public health agencies recommended the vaccination of pregnant women.

USE IN PREGNANCY

Cumulatively, since the IBD, a total of 2559 cases related to use in pregnancy have been reported

When evaluating all events/all PTs associated with pregnancy-related cases, the 10 most frequently reported events within pregnancy cases by PT were exposure during pregnancy, fatigue, abortion spontaneous, pain in extremity, headache, pyrexia, chills, myalgia, nausea, and pain. Many pregnancy reports had limited information about past medical and obstetric history, gestational age at time of vaccination or onset of AE, diagnostics, treatment, and outcome. Noted confounding factors included advanced maternal age, in vitro fertilization, intrauterine insemination, concomitant medications, comorbidities (such as hypothyroidism), and previous relevant obstetric history.

For the serious cases, the 5 most common pregnancy-related PTs, aside from PTs describing exposure in pregnancy, were “abortion spontaneous” (242), fetal death (29, includes fetal deaths under 20 weeks gestational age), hemorrhage in pregnancy (12), premature labor (11), and induced labor (10). These and other reported serious complications of pregnancy were within the background expected rates of events (MSSR #6 Section 6.3.4).

Cumulatively, there are 9 fatal cases, of which 4 cases were misclassified as pregnancy-related and occurred in elderly persons. Of the 5 pregnancy-related cases coded as fatal, one described a 35-year-old female who, 8 days after vaccination, went into labor, during which she began “coughing,” lost consciousness, and died of cardio-respiratory arrest. An emergency Cesarean section was performed. The case had very limited information about past medical and obstetric history, gestational age at time of vaccination, diagnostics, treatment, and outcome, necessary to provide an accurate causality assessment. No autopsy was available. The 4 remaining cases coded as fatal were fetal deaths with limited information: 11 days after vaccination, 2 weeks after vaccination, termination of a pregnancy of 19-week gestational age fetus with microcephaly (vaccination given at 14 and 18 weeks gestational age), and 30-week gestational age fetus with cerebral hemorrhage and death occurring 3 days after the mother’s second dose (limited information, however, given TTO cannot exclude causality).

Overall, cases of adverse pregnancy-related complications and abortions reported are temporally related with the administration of the Moderna COVID-19 mRNA vaccine; however, the available information is inadequate to provide strong evidence of causality. The data reviewed do not represent any new safety issues of concern and do not identify a change to the benefit-risk profile for the pregnant or their neonates.

USE WHILE BREASTFEEDING

Cumulatively, there were 560 cases (of which 83 were serious, none were fatal) of use in lactating women/related to lactation, with a total of 579 (of which 37 were serious) cumulative lactation-related events.

The most common PTs reported in serious cases included: maternal exposure during breast feeding (52), exposure via breast milk (19), fatigue (19), pyrexia (14), mastitis (13), headache (12), and chills (9). Fifty-nine of these reports in breastfeeding women originate from a health authority and have been coded as “seriousness criterion medically significant” by the consumer. Additionally, there were 6 reports of breast pain, 6 reports of lymphadenopathy, 5 reports of breast swelling, 3 reports of suppressed lactation, and 2 reports of neonatal insufficient breast milk syndrome (MSSR #6 Section 6.3.4).

The serious lactation-related case events reported in neonates and children up to 23 months of age included 2 reports of seizures, and 1 of each of the following reports: abdominal pain, bowel movement irregularity, diarrhea neonatal, gastrointestinal sounds abnormal, hematochezia, hemorrhage, infantile vomiting, mucous stools, neonatal insufficient breast milk syndrome, pain, pyrexia, rash, and viral rash.

Upon review of the lactation-related reports, there were no unusual significant patterns that would change the benefit-risk profile of the use of vaccination while breastfeeding.

2.7.4.6.4.5.2 Use in Individuals With Autoimmune or Inflammatory Disease/Disorders

Cumulatively, there were 9944 (of which 2087 were serious and 125 were fatal) cases with 47,292 events (of which 6008 were serious) in individuals with a history of autoimmune or inflammatory disorders (AI/ID subpopulation). A breakdown of the 9944 cases reported by gender was 1457 males and 8422 females, and 65 unknown, with a mean age of 53.8 years (standard deviation [SD]: 15.6) and a median age of 54.0 years, with 162 cases missing age information.

Of the 125 fatal cases reported, 52 were males and 73 were females, with a mean age of 68.9 years (SD: 15) and a median age of 73 years. Ninety (72%) of the fatal cases occurred in those 65 years or older, and the majority had multiple comorbidities (MSSR #6 Section 6.4 provides a description of fatal cases for elderly and frail patients). Of the 125 fatal cases, 92 (73.6%) occurred in "frail" persons (MSSR #6 Section 6.3.3). Sixty-nine fatal events (55.2%) occurred within 7 days of the first vaccination, and while there are confounding factors and comorbidities described in the majority of cases, causality cannot be excluded given the temporal association. There were no identified clusters of unexpected causes of deaths in this subpopulation.

The most frequently reported non-AI/ID comorbidities/confounders in past medical history in the fatal cases included hypertension (46, 36.8%), chronic kidney disease (17, 13.6%), hyperlipidemia (16, 12.8%), chronic obstructive pulmonary disorders (15, 12.0%), atrial fibrillation (12, 9.6%), cardiac congestive failure (10, 8%), and coronary artery disease (7, 5.6%).

2.7.4.6.4.5.3 Use in Individuals With Immunosuppression

The general pattern of commonly reported AEs in those with a medical history of immunosuppression or with immunosuppressive concomitant medications (hereafter referred to as "the immunosuppressed subpopulation") cumulatively is comparable to the general population. The Sponsor did not identify specific findings or changes to the benefit-risk profile for this subpopulation from this cumulative review.

Cumulatively, there were 2668 cases (of which 714 were serious, and 65 were fatal) with 11,550 events (of which 2251 were serious) in the immunosuppressed subpopulation. Of the 2668 cases, 1901 cases were medically confirmed. Cumulatively, 1776 were females, 871 were in males, and 21 were missing gender information. The mean age was 58.9 (SD 15.4), and the median was 61 years, with 49 cases missing age information. Cumulatively, 74.1% of cases were from the US, and 20.8% were from the EEA.

Of the 65 fatal cases, 30 were in females and 35 were in males. Sixty cases were reported by HCPs. The mean age was 70.9 years (SD: 12.2), and the median age was 74 years (range: 35 to 97). Of the 65 fatal cases, 43 individuals were classified as "frail," representing that the majority of fatal cases had multiple comorbidities and older age (MSSR #6 Section 6.4). There were no clusters of unexpected causes of deaths identified with the available information in this subpopulation. Thirty-six of the fatal cases occurred within 1 week of vaccination, and thus given the TTO, causality cannot be excluded. While it is noted that multiple confounding conditions and comorbidities are reported, there is a limitation to the quality of spontaneous

reporting (including missing "cause of death"), which limits the analysis. Common comorbidities/confounders reported in the medical history of the fatal cases included hypertension (18, 27.7%), chronic obstructive pulmonary disease (10, 15.4%), atrial fibrillation (9, 13.8%), obesity (9, 13.8%), diabetes mellitus (8, 12.3%), chronic kidney disease (7, 10.8%), lymphoma (6, 9.2%), renal transplant (6, 9.2%), and HIV infection (5, 7.7%).

2.7.4.6.4.5.4 Interaction With Other Vaccines/Heterologous Vaccine

Several vaccines have demonstrated efficacy against SARS-CoV-2-mediated disease, yet there are limited data on the clinical efficacy/safety or immunogenicity of heterologous vaccine regimens (including those employing different vaccine platforms, eg, vectored vaccines) (Spencer et al 2021). There is no observed change to the current safety profile for drug-drug interactions in this review period.

A cumulative review of potential interaction with COVID-19 vaccines from other manufacturers was performed using the PT interchange of vaccine products. Cumulatively, a total of 1038 events were identified, of which 45 events were serious. There were 590 cases, with 538 medically confirmed. Out of the 590 cases, 18 cases were serious. Gender distribution was 245 males (41.5%), 305 females (51.7%), and 40 (6.8%) missing. There was 1 event with a fatal outcome, 546 events resolved, 52 did not recover, 8 were recovering, and outcome was unknown for 431 events. The fatal outcome was reported for a 91-year-old male who was in hospice care due to congestive heart failure and who died 13 days after receiving the second dose of the Moderna COVID-19 mRNA vaccine. The patient had received the Pfizer mRNA COVID-19 vaccine as his first vaccination dose. Very limited information regarding this patient was provided. However, the underlying medical condition in this advanced age remains an important confounder.

Pfizer-BioNTech COVID-19 Vaccine was reported as co-suspect in 132 cases, Johnson & Johnson's Janssen COVID-19 Vaccine in 6 cases, and AstraZeneca COVID-19 vaccine in 4 cases.

Table 41 summarizes the top 10 PTs reported with heterologous COVID-19 vaccine interchange.

Except for chest pain, the events are similar to the top 10 events reported generally after Moderna COVID-19 mRNA vaccine. For the 5 events (5 cases) of chest pain, information on both heterologous vaccines was only available in 3 of the 5 cases, and it is of note that all 3 were with AstraZeneca and Moderna vaccines. In 2 of the 3 cases, AstraZeneca vaccine was reported as the first dose and Moderna vaccine as second dose. In the third case, Moderna COVID-19 mRNA vaccine was reported as the first dose and AstraZeneca vaccine as second dose. Of the 5 cases, 4 were serious. One serious case described chest pain in a 17-year-old after the first dose

of Moderna COVID-19 mRNA vaccine and had no information on other heterologous vaccine. The other 3 serious cases are described in MSSR #6 Section 6.10.2.

Table 41: Top Ten Events Reported With Heterologous COVID-19 Vaccine Interchange

Preferred Term	# Events	% of Total Events
Pyrexia	16	1.50%
Fatigue	15	1.40%
Headache	14	1.30%
Chills	11	1.10%
Pain in extremity	10	1.00%
Nausea	9	0.90%
Injection site pain	8	0.80%
Myalgia	7	0.70%
Pain	7	0.70%
Chest pain	5	0.50%

2.7.4.6.4.6 Deaths

A total of 2842 deaths were reported cumulatively as of 30 Jun 2021 and included a total of 6066 events with a fatal outcome. Detailed information is provided in MSSR #6 Section 6.4.

A comparison of observed vs. expected deaths, stratified based on the age groups available for US COVID-19 vaccine administration data, was conducted (Table 42). Expected rates were obtained based on US data from the CDC (CDC 2021b). In both overall and age-stratified analyses, the observed reporting rate of death was substantially below the expected incidence (Table 42). Using data from US population-based studies to specify the expected rate suggests that the observed incidence overall and stratified by age is below the expected rate.

The events with a fatal outcome in individuals who received mRNA-1273 are similar in distribution to those reported by the CDC and represent the most frequent causes of death in the US (CDC 2021b). Most doses of mRNA-1273 have been administered in the US, providing support for the validity of this finding. The demographic characteristics and comorbid medical conditions in individuals who died following mRNA-1273 use are consistent with baseline populations at higher risk of death. Review of cumulative cases of sudden death and sudden cardiac death indicates that most of the events were reported in individuals with 1) other comorbid risk factors for death; or 2) had insufficient information provided to reliably assess the case. Fatal cardiac events in young adults are being reviewed by the Sponsor as part of the

ongoing surveillance for events of myocarditis and pericarditis. Overall, the review of deaths does not support a potential causal association between mRNA-1273 and death.

Table 42: Observed/Expected Analyses Stratified by Age and Gender, Death (All Cause), Expected Rates from the United States

	Person-Years	Observed		Expected		As Observed: Rate Ratio (95% CI)
		Cases	Rate	Cases	Rate[1]	
All	10,505,272	2,842	27.05	86805.1	826.30	0.03 (0.03, 0.03)
By age (years)						
<18	108,454	2	1.84	65.0	59.90	0.03 (0.01, 0.13)
18-29	865,795	27	3.12	794.8	91.80	0.03 (0.02, 0.05)
30-39	2,159,773	53	2.45	2319.6	107.40	0.02 (0.02, 0.03)
40-49	1,527,656	88	5.76	4618.1	302.30	0.02 (0.02, 0.02)
50-64	2,824,366	431	15.26	25167.9	891.10	0.02 (0.02, 0.02)
65-74	1,760,075	634	36.02	35219.1	2001.00	0.02 (0.02, 0.02)
75+	1,216,860	1,516	124.58	93516.9	7685.10	0.02 (0.02, 0.02)
By gender						
Male	4,947,983	1,588	32.09	43552.1	880.20	0.04 (0.03, 0.04)
Female	5,557,289	1,209	21.76	45530.9	819.30	0.03 (0.03, 0.03)

[1] Rates presented per 100,000 person-years. CDC 2021c.

2.7.4.6.4.7 Medication Errors

Cumulatively, there were 18,328 events (15,405 cases) identified using the medication error broad SMQ search. Of the 18,328 events, 751 involve reports of medication errors without an AE reported in conjunction with the medication errors.

Review of the data does not suggest any identifiable pattern or trend in these reports of medication error. The majority of the events associated with the medication error PTs reported above are consistent with the labeled events for mRNA-1273, including reactogenicity events described after receiving the vaccine (eg, injection site pain, pain in extremity, chills, headache, pyrexia, fatigue, nausea, and asthenia). There were 590 reports of interchange of vaccine products, including reports of individuals receiving the Pfizer/BioNTech COVID-19 vaccine or the other COVID-19 vaccines. No AEs were reported with these reports. For those events that were coded under product administered to patient of inappropriate age, if they refer to an individual younger than 18 years of age (21.0%), they are analyzed under the < 18 years subpopulation analysis in the MSSR #6 Section 6.3.1. No new safety signal was identified. The Sponsor will continue to monitor reports of medication error in patients receiving the Moderna COVID-19 mRNA vaccine. Detailed information is described in MSSR #6 Section 6.7.

2.7.4.6.4.8 Off-Label Use

Off-label use reports presented in this section relate to situations in which the vaccine was intentionally used off-label. Use in children < 18 years of age (summarized in Section 2.7.4.6.4.9) also constitutes off-label use but was not necessarily reported as such.

Off-label use was most commonly reported due to inappropriate age or dosing frequency. The majority of the events were nonserious, with most events reported as resolving. There was no pattern of off-label use observed that changes the safety profile of the Moderna COVID-19 mRNA vaccine.

Cumulatively, 402 cases (403 events) have been reported, of which 67 cases were serious. There were 119 males and 258 females, and gender information was missing for 25 case reports. There were 194 events reported as off-label use (48.1%), 139 events as intentional product use issue (34.5%), 67 events as intentional dose omission (16.6%), and 3 events as intentional product misuse (0.7%).

Out of the 194 events reporting PT of off-label use, 45 events occurred in children (< 18 years) and was described as use of the vaccine in an unapproved age. The 67 events reported as intentional dose omission described issues around second dose interval, heterologous vaccine administration, and dose administered beyond use date, off-label benefit, off-label unspecified, or unspecified contraindicated product administered. All 139 events in the PT of intentional product use issue were regarding intentional deviation from dose regimen, while the 3 events of intentional product misuse had no additional information.

Detailed information regarding the children < 18 subpopulation analysis is provided in MSSR #6 Section 6.3.1. Additional information on off-label use is included in MSSR #6 Section 6.11.2.

2.7.4.6.4.9 Use in Children (< 18 Years Old)

As noted in Section 2.7.4.6.4.8, use in children < 18 years old constitutes off-label use but was not necessarily reported as such; this section presents reports of vaccine administration to a child. Cumulatively, 4059 cases (5459 events) have been reported involving children under the age of 18 years old. Out of the 4059 cases, 61 cases (1.5%) were assessed as serious. There were 1611 males (39.7%), 2244 females (55.3%), and 203 (5.0%) where the gender information is missing. Mean age was 15.4 and median was 17 years (range: 1 month to 17 years of age). Reports in children < 2 years of age were in the context of exposure through the mother.

The majority of the reports (77.0%) are after the first dose of the vaccine, with 831 cases (16.6%) after the second dose, and 357 reports for which the dose information is missing (6.7%).

Most of the cases (3936 reports; 96.9%) were reported from the United States, followed by the United Kingdom with 25 cases (0.6%) and the Netherlands with 17 case reports (0.4%).

The top 3 PTs associated with a report for children < 18 years old by reported events were product administered to patient of inappropriate age (3772 events; 69.1%); no AE (475; 8.7%); and pain in extremity (109 events; 2.0%). The term “no AE” usually refers to an individual who was exposed to a product/vaccine but with no AEs to report.

For the 61 serious case reports, the most frequently reported PTs were syncope (10; 0.24%); seizure (7; 0.2%); pyrexia (4; 0.1%); and 3 reports (0.07%) each of anaphylactic reaction, chills, fatigue, headache, and paresthesia.

There were 2 deaths. A 15-year-old female experienced fatal cardiac arrest at an unknown time after the second dose of the Moderna COVID-19 mRNA vaccine. Her past medical history was significant for atrioventricular canal repair and concurrent medical history included binocular vision disorder, mixed conductive and sensorineural hearing loss, bronchopulmonary dysplasia, constipation chronic, autism, renal dysplasia, scoliosis, hypotonia, obstructive sleep apnea syndrome, asthma, hypothyroidism, trisomy 21, gastroesophageal reflux disease, cervical spinal instability, and feeding disorder. No additional information was provided surrounding death or on autopsy. The second death was reported for a 22-week old male, 11 days after being exposed to Moderna COVID-19 mRNA vaccine via mother during pregnancy. Cause of death was unknown.

Distribution of events in this age group (< 18 years) appears to be in line with the general population. No trends or patterns indicating a safety signal have been identified. These data represent off-label use in this age population, cumulative to 30 Jun 2021. The Moderna COVID-19 mRNA vaccine was not authorized in age groups < 18 years of age by 30 Jun 2021; thus the reports of AEs in individuals < 18 years of age reflect off-label use.

2.7.4.6.4.10 Conclusion

Examination of the post-authorization data contained within this summary supports the conclusion that the safety profile for the Moderna COVID-19 mRNA vaccine is comparable to that observed during the clinical studies for the vaccine.

2.7.4.7 REFERENCES

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