EU Risk Management Plan

For

mNEXSPIKE (COVID-19 mRNA Vaccine)

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Part V Risk minimisation measures	Not applicable
Part VI Summary of risk management plan	Not applicable
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[1] EU QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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LIST OF ABBREVIATIONS

Acronym	Definition
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ATC	anatomical therapeutic chemical
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	COVID-19 disease caused by the 2019 coronavirus
CSR	clinical study report
DCM	dilated cardiomyopathy
DMG	dimyristoyl glycerol
DP	drug product
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
e-RMR	electronic Reaction Monitoring Reports
ERVISS	European Respiratory Virus Surveillance System
EU	European Union
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
HIV	human immunodeficiency virus
HMA	Heads of Medicines Agencies
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Acronym	Definition
ICSR	individual case safety report
IgG	immunoglobulin G
IM	intramuscular
INN	international nonproprietary name
iPSP	initial Pediatric Study Plan
IV	intravenous
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MAA	marketing authorisation application
Max	maximum
MCM	major congenital malformation
MERS-CoV	Middle East respiratory syndrome coronavirus
Min	minimum
MIS	multisystem inflammatory syndrome
MMG	monomyristoyl glycerol
mRNA	messenger ribonucleic acid
NHP	nonhuman primate
NK	natural killer
NOAEL	no observed adverse effect level
NPI	nascent peptide imaging
NTD	N-terminal domain
PEG	polyethylene glycol
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PFS	pre-filled syringe
PIP	paediatric investigation plan
PL	package leaflet
PolyA	polyadenylated
PSUR	periodic safety update report
PV	pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
Q1	quartile 1
Q3	quartile 3

Acronym	Definition
RBD	receptor-binding domain
RMP	risk management plan
RNA	ribonucleic acid
rVE	relative vaccine efficacy
S	spike
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SD	standard deviation
SmPC	summary of product characteristics
SM-102	heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate
SPEAC	Safety Platform for Emergency vACcines
UK	United Kingdom
US	United States
UTR	untranslated region
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

Throughout the document, both mNEXSPIKE and mRNA-1283 including original (D614G) and variant formulations (mRNA-1283.211, mRNA-1283.529, mRNA-1283.222, and mRNA-1283.815) are used. The safety profile is applicable to all mRNA-1283 vaccines regardless of valency or variant.

PART I: PRODUCT OVERVIEW

Table Part I.1: Product Overview

Active substance (INN or common name)	COVID-19 mRNA vaccine
Pharmacotherapeutic groups (ATC Code)	Vaccines, COVID-19 vaccines (J07BN01)
Marketing Authorisation Applicant	MODERNA BIOTECH SPAIN, S.L. C/ Julián Camarillo nº 31 28037 Madrid Spain
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	mNEXSPIKE
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** The mRNA drug substance in mNEXSPIKE is chemically similar to naturally-occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N1-methylpseudouridine, a naturally-occurring pyrimidine base present in mammalian transfer RNAs (Rozenski et al 1999; Karikó et al 2005). This nucleoside is included in place of the normal uridine base to minimise the indiscriminate recognition of the mNEXSPIKE mRNA by pathogen-associated molecular pattern receptors (eg, toll-like receptors) (Desmet and Ishii 2012). The cap structure used in the mRNA is identical to the natural mammalian Cap 1 structure (Kozak 1991; Fechter and Brownlee 2005). **Structure of mRNA**  Abbreviations: mRNA = messenger RNA; PolyA = polyadenylated; UTR = untranslated region.
	Summary of mode of action: mNEXSPIKE is a nucleoside-modified mRNA-based vaccine, formulated in lipid particles, which encodes the membrane-bound, linked NTD and RBD of the spike (S) glycoprotein from SARS-CoV-2 strains. The vaccine elicits an immune response to the NTD and RBD of the S antigen, to generate neutralising antibodies, which contributes to protection against COVID-19.
	Important information about its composition: mNEXSPIKE is a nucleoside-modified mRNA encoding SARS-CoV-2, variant XBB.1.5, spike glycoprotein, NTD and RBD. mNEXSPIKE is a monovalent vaccine targeting Omicron XBB.1.5. One dose (0.2 mL) contains 10 micrograms of SARS-CoV-2 mRNA.

Hyperlink to the Product Information	mRNA-1283 Product Information (Module 1.3.1)
Indication in the EEA	**Current:** mNEXSPIKE is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The use of this vaccine should be in accordance with official recommendations.
	Proposed: Not applicable
Dosage in the EEA	**Current:** <u>Posology</u> The recommended dose of mNEXSPIKE is one single dose of 10 micrograms. If previously vaccinated with a COVID-19 vaccine, mNEXSPIKE should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Elderly* No dose adjustment is required in elderly individuals ≥65 years of age. *Paediatric population* The safety and efficacy of mNEXSPIKE in children less than 12 years of age have not yet been established. No data are available.
	Proposed: Not applicable
Pharmaceutical forms and strengths	**Current:** Dispersion for injection. White to off-white dispersion (pH: 7.1 – 7.8). One dose (0.2 mL) contains 10 micrograms of SARS-CoV-2 mRNA.
	Proposed: Not applicable
Vaccine Construct and the formulation	mNEXSPIKE is a nucleoside-modified mRNA encoding SARS-CoV-2, variant XBB.1.5, spike glycoprotein, NTD and RBD. mNEXSPIKE is a monovalent vaccine targeting Omicron XBB.1.5. The excipients are SM-102 (heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), trometamol, trometamol hydrochloride, sucrose, and water for injections.
Will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication: mNEXSPIKE is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

Coronaviruses are a large family of RNA viruses that cause illness ranging from the common cold (CoV species OC43, HKU1, NL63, and 229E) to more severe respiratory diseases (MERS-CoV, SARS-CoV, and SARS-CoV-2) (Jackson et al 2022). SARS-CoV-2 targets angiotensin converting enzyme 2 receptors that are expressed on epithelial cells of the lungs, nose, heart, intestine, and kidney (Jackson et al 2022; da Silva Torres et al 2022). The binding of the SARS-CoV-2 Spike protein to these receptors facilitates viral entry.

COVID-19 is caused by SARS-CoV-2 virus and contributes significantly to global morbidity and mortality. It is predominantly transmitted human-to-human via respiratory droplets from coughing or sneezing but can also persist in secretions on surfaces (ECDC 2022). Airborne transmission may be possible during certain medical procedures and in indoor, crowded, and poorly ventilated environments (WHO 2022).

Coronaviruses, including SARS-CoV-2, are prone to high levels of genetic mutations due to the presence of an error-prone RNA-dependent RNA polymerase and the unique ability of coronaviruses to recombine to generate novel viral variants (Gupta et al 2023; Su et al 2016; da Silva Torres et al 2022). Since the outbreak of the pandemic, multiple SARS-CoV-2 variants (eg, Delta, Omicron, and other recombinant variants) have emerged and have been able to evade immunity induced by vaccines targeting prior variants or by prior natural infection (Siddle et al 2022; Barouch 2022; Hastie et al 2021; Shrestha et al 2022), requiring COVID-19 vaccine updates.

Incidence

The first cases of SARS-CoV-2 were detected in Wuhan, Hubei Province, China in December 2019, and has since spread globally (WHO 2020a; WHO2020b). Widespread community transmission was subsequently reported in all WHO regions and the WHO declared COVID-19 a pandemic on 11 Mar 2020 (WHO 2020a; WHO 2020b). As of 11 Aug 2024, 775,917,102 COVID-19 cases and more than 7 million deaths had been reported globally (WHO 2024a; WHO 2024b). In Europe, as of 11 Aug 2024, 279,755,656 COVID-19 cases (36% of global cases) and 2,274,315 deaths had been reported (WHO 2024a; WHO 2024b). COVID-19 was the among the top 3 leading causes of death in Europe in 2021, the last year with available data (Europa 2024; WHO 2024c). In the US as of 03 Feb 2024, approximately 6.7 million COVID-19 related hospitalisations, and 1.1 million deaths had been reported (Panagiotakopoulos et al 2024). COVID-19 was related to 76,446 deaths in 2023 and remains the tenth leading cause of mortality in the US (Ahmad et al 2024a; Ahmad et al 2024b). The 2023 mortality data suggest that COVID-19 remains the leading cause of potentially vaccine-preventable deaths in the US (Ahmad et al 2024a; Ahmad et al 2024b).

The seasonality pattern is yet to be established for COVID-19, but global and regional (US and Europe) infection and hospitalisation rates during the 2023/2024 season suggest a bimodal distribution with peaks observed in both late summer-to-autumn and winter months. Globally in

2023, COVID-19 cases peaked in August (702,000 new cases the week of 06 Aug 2024) with another peak in December (382,000 new cases the week of 17 Dec 2024). COVID-19 cases rose again in the summer of 2024, with 57,300 new weekly cases detected in late July 2024 (WHO 2024a). In Europe in 2023, COVID-19 cases reached a peak in September, followed by a second peak in December, and started to rise again in summer 2024 (ERVISS 2024a). In the US, during the 2023/2024 season, COVID-19 associated hospitalisations peaked in the autumn (4.6 per 100,000 population per week in September 2023) and winter (7.8 per 100,000 population per week in December 2023) and are projected to peak again in late summer-autumn 2024, with the most recent hospitalisations reported at 4.4 per 100,000 population for the week ending 03 Aug 2024 (CDC 2024a).

Risk Factors for Severe COVID-19 Outcomes

Age has been identified as a key risk factor for severe COVID-19 outcomes, and adults ≥50 years of age are more likely than younger people to have hospitalisations or deaths due to SARS CoV-2 infection (Garg et al 2020; Kim et al 2021). Adults ≥65 years of age are at highest risk of COVID-19 and severe COVID-19 outcomes, including death (Kim et al 2021). This increased risk for older adults is most apparent during periods of higher SARS CoV-2 transmission. Across EU/ EEA countries in Week 50 2023 (December 2023), the cumulative rate of nonsentinel laboratory-confirmed SARS-CoV-2 hospital admissions was 9 per 100,000 among individuals ≥65 years of age as compared with 3 per 100,000 among those 15-64 years of age (ERVISS 2024b). In the US in December 2023, the rate of hospitalisation due to COVID-19 was 34.4 per 100,000 among individuals ≥65 years of age, 5.8 per 100,000 among individuals 50 to 64 years of age, and 2.1 per 100,000 among individuals 18 to 49 years of age (CDC COVID-NET 2024). Among 8996 adults hospitalised for COVID-19 between 01 Oct 2022 and 31 Jan 2023, the 30-day death rate from COVID-19 was 6.42 (95% CI 5.85, 6.98) among those >65 years of age vs 1.29 (95% CI 0.77, 1.82) among those ≤65 years of age (Xie et al 2023). Additionally, individuals who are immunocompromised as well as those with chronic kidney, heart and lung diseases, diabetes mellitus, and/or obesity are at increased risk for severe COVID-19 outcomes including hospitalisation and death (CDC 2024b).

The Main Existing Treatment Options

Intervention for SARS-CoV-2 infection includes prophylactic vaccination, supportive care for symptomatic infection, and treatments for the viral infection, including antivirals, immune modulators, and monoclonal antibodies.

Currently authorised vaccines in the EU and US include mRNA vaccines and protein subunit vaccines. As of 23 Jun 2025, five vaccines are currently authorised for COVID-19 prevention in the EU including originally authorised and adapted vaccines (EMA 2025).

The following medicinal products are currently authorised in the EU: Kineret (anakinra), an immunosuppressive medicine; Paxlovid (nirmatrelvir/ritonavir), a protease inhibitor; RoActemra (tocilizumab), interleukin-6 inhibitor; Ronapreve (casirivimab/imdevimab), combination of two monoclonal antibodies; Veklury (remdesivir), an antiviral medication; Xevudy (sotrovimab), human neutralising monoclonal antibody; Evusheld (tixagevimab/ cilgavimab), combination of two recombinant human IgG1 monoclonal antibodies; Kavigale (sipavibart), a monoclonal antibody for pre-exposure prophylaxis of immunocompromised individuals; and Gohibic (vilobelimab), a human complement C5a inhibitor (EMA 2025).

Natural History of COVID-19 in the Unvaccinated Population and Co-morbidities

Common symptoms of SARS-CoV-2 infections include fever and cough, and other symptoms can include shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. The spectrum of illness from SARS-CoV-2 infections can range from asymptomatic infection to severe pneumonia, acute respiratory distress syndrome, respiratory failure, and death (Hu et al 2021). While COVID-19 is primarily a pulmonary disease, it can also lead to cardiac, dermatologic, haematologic, hepatic, neurologic, renal, and other complications, including thromboembolic events and peri- and myocarditis (Gavriatopoulou et al 2020; Kamath et al 2023; Boehmer et al 2021; Buckley et al 2021; Wang et al 2022; Priyadarshni et al 2022). Lastly, after COVID-19 illness long-term sequelae have been observed, characterised by a range of persistent symptoms such as fatigue, dyspnoea, chest pain, cognitive impairment, and sleeping disturbances that can last for weeks, months, or even years after the initial illness episode. This constellation of symptoms is termed post-acute sequelae of COVID-19 or Long COVID (Davis et al 2023; Soriano et al 2022; Thaweethai et al 2023; Alkodaymi et al 2022; Nasserie et al 2021).

Long COVID has been recognised as a significant and serious consequence of symptomatic SARS-CoV-2 infection affecting multiple organ systems (Davis et al 2023). Across all age groups, an estimated 50% to 70% of hospitalised individuals, 10% to 30% of nonhospitalised individuals have experienced Long COVID (Davis et al 2023). A population-based study conducted in the US between June and July 2022 estimated the overall prevalence of Long COVID among 3042 adults surveyed to be 7.3% overall (and 8.3% among adults 55 to 64 years), corresponding to potentially 18 million cases of Long COVID in the US adult population (3.4 million among adults 55 to 64 years) (Robertson et al 2023). Similarly, a population-based study of 10,615 adults ≥18 years of age conducted in France between August and November 2022 estimated the prevalence of WHO-defined post-COVID conditions to be 4.0% overall and 8.0% among individuals with confirmed or probable SARS-CoV-2 infection in the prior 3 months (Coste et al 2024). Furthermore, among those in the study who had prior SARS-CoV-2 infection, the prevalence of Long COVID was highest among those who had been hospitalised for COVID-19 (18.6%) and those who were 45 to 54 years of age (10%). Long COVID therefore represents a long-term outcome that can result in significant impact to health.

Most children and adolescents appear to have asymptomatic or nonsevere symptomatic SARS-CoV-2 infections (Viner et al 2021; Forrest et al 2022). SARS-CoV-2-related death in children and adolescents is rare (Smith et al 2022). However, COVID-19 can lead to severe outcomes in children and adolescents (Marks et al 2022; Shi et al 2022; Preston et al 2021). Most common chronic conditions associated with hospitalised paediatric patients are diabetes, gastrointestinal, neurological, cardiac, and pulmonary diseases, specifically asthma and obesity, but some of these conditions may not be necessarily causally associated with COVID-19 (Forrest et al 2022; Bailey et al 2021). MIS is a rare but serious condition associated with COVID-19 in which different body parts become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs. It can affect people who are younger than 21 years old (MIS-C) and adults 21 years and older (MIS-A) (CDC 2023). The usual duration between acute infection and onset of MIS-C symptoms is two to 12 weeks (Dufort et al 2020; Ahmad et al 2021). In contrast to acute SARS-CoV-2 infection in children, MIS-C has higher severity with 68% of cases requiring critical care support (Radia et al 2021). MIS shares features

with other paediatric inflammatory syndromes such as Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Moderna has developed mRNA-1283, an LNP-encapsulated mRNA-based vaccine against SARS-CoV-2, which has demonstrated relative noninferior vaccine efficacy and immunogenicity at a lower dose compared with the authorised SARS-CoV-2 vaccine (SPIKEVAX™; mRNA-1273).

Table SII.1 summarises the key nonclinical findings and their relevance to safety in humans. In summary, the nonclinical package, which consisted of both studies performed with mRNA-1283 and with mRNA vaccines formulated in the same SM-102 LNP vaccine matrix to support mRNA-1283 use in humans, identified no safety concerns.

Table SII.1: Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Findings	Relevance to Human Use
Safety pharmacology		
Consistent with the WHO regulatory guidelines on the nonclinical evaluation of vaccines (WHO 2005), no safety pharmacology studies have been performed with mRNA-1283 because primary effects of the vaccines were related to the immune system/inflammatory response. Effects on vital organ function were assessed using clinical observations and/or histopathological evaluations in the GLP and non-GLP repeat-dose toxicity studies conducted with mRNA-1283.222 or other mRNA vaccines formulated in SM-102-containing LNPs. No findings of concern on vital functions or organs, such as the cardiovascular, respiratory, or central nervous system were observed in any study.		Nonclinical findings do not suggest a specific risk to cardiovascular, respiratory, or central nervous systems.
Pharmacokinetics and drug metabolism		
Single and repeat dose intramuscular (IM) tissue distribution studies	To support the development of mRNA-1283, 3 biodistribution studies were conducted using mRNA-LNP DPs comprised of the same 4 lipids (ie, SM-102, cholesterol, DSPC, and PEG2000 DMG) and generally similar lipid:mRNA ratios as mRNA-1283. The biodistribution and kinetics of SM-102 lipid, mRNA, and/or expressed protein(s) following a single IM administration were evaluated using NPI-Luc mRNA encapsulated in SM-102/PEG2000 DMG-containing LNPs and mRNA-1647. In a study with mRNA-1273, the biodistribution and kinetics of SM-102 lipid, mRNA, and SARS-CoV-2 S protein were evaluated following a single or 2-dose IM administration to assess potential accumulation and effect of an immune response following repeat dosing. Results from the biodistribution studies demonstrated that there are general similarities in exposure tissue rank order and kinetics across mRNA LNP DPs (highest concentrations of mRNA and SM-102 lipid were observed at the injection site, spleen, and lymph nodes), substantiating that mRNA cargo and the presence or absence of an immune response do not alter tissue distribution of mRNA LNP DPs. Additionally, tissue distribution of mRNA and SM-102 lipid is similar following 1 or 2 administration(s) of mRNA-1273, demonstrating that there is low to no risk of accumulation and no differences in distribution of DP components with repeat dosing.	The biodistribution of mRNA-based vaccines formulated in LNPs is consistent with administration of IM drug products and distribution via the lymphatics. Results from the rat biodistribution studies are corroborated by a published report by Hassett et al (2023) where a single IM dose of an mRNA-LNP DP formulated in the same 4 lipids was administered to NHPs, and mRNA concentrations were measurable in plasma and spleen over 168 hours. In that report, mRNA was not detected in the injection site, lymph nodes, and liver beyond 24 hours. Overall, the data derived from the rat biodistribution studies confirm similarities in tissue distribution and kinetics, consistent with distribution via the lymphatic system, and indicate cross species similarities.

Study Type	Important Nonclinical Findings	Relevance to Human Use
Metabolite profile and identification of SM-102 in rat plasma, urine, and bile	Metabolism occurred primarily by hydrolysis of the ester groups and subsequent β-oxidation of the resulting aliphatic acidic linkers. In addition to SM-102, low abundances of eight metabolites appeared in plasma from 2 to 6 hours. SM-102 is extensively metabolised through multiple high-capacity systems leading to almost complete clearance of SM-102 within 24 hours. Intact SM-102 was not detected in urine above the LLOQ (0.2 ng/mL) at any time tested (2 to 24 hours post dose). No human specific metabolites were detected.	SM-102 is unlikely to accumulate on repeat IM dosing or be a risk for elimination in patients with hepatic or renal insufficiency.
Identification and profiling of metabolites of SM-102 in rat, monkey, and human hepatocytes	SM-102 and 5 metabolites (Metabolite IDs: M1, M3, M4, M6 and M7) were detected in human and NHP hepatocytes. Metabolites (Metabolite IDs: M1, M4, M6 and M7) were detected in rat hepatocytes. SM-102 metabolites were formed by ester hydrolysis, ester hydrolysis with beta-oxidation chain shortening or N-dealkylation followed by ester hydrolysis.	The similarities in formation of SM-102 metabolites between animals and humans suggest low risk for human-specific metabolites.
Identification and profiling of metabolites of PEG2000-DMG in rat, monkey, and human serum	Following spiking PEG2000-DMG in serum, identical metabolites were formed in all species, namely PEG-glycerol and PEG-MMG isomers, through ester hydrolysis. This expected outcome was due to the presence of an ester bond in the PEG2000-DMG molecule and is consistent with known PEG metabolic pathways (Webster et al 2007). The increase in the PEG glycerol metabolite was consistent among species, while the metabolism of PEG-MMG isomers was faster and more extensive in rats due to higher esterase activity. No human specific metabolites were found.	No human specific metabolites were formed.
Repeat-dose toxicity studies		
GLP toxicity study of mRNA-1283.222 in male and female Sprague Dawley rats (administered IM two times at 0, 2, 5, and 10 µg/dose once every 4 weeks followed by a 2-week recovery period)	The GLP toxicity study utilised a DP encoding antigens for the circulating 2022/2023 variants (mRNA-1283.222), which included the Omicron BA.4/BA.5 variant circulating at the time of the initiation of the study and is the same DP used in the pivotal clinical study mRNA-1283-P301. There were no test article related clinical signs, injection site observations, or mortalities when administered IM followed by a 2-week recovery period. At main study terminal necropsy, microscopic findings were observed at the injection sites and draining iliac lymph nodes. The primary finding was mixed-cell inflammation in the second site that was injected (ie, 24 hours prior to necropsy). The inflammation was minimal to moderate with secondary infiltration of neutrophils in the iliac (draining) lymph node of a few animals. The injection site findings correlated with clinical pathology changes consistent with an inflammatory and/or acute phase response, including increases in neutrophil counts and/or fibrinogen concentrations. All microscopic and clinical pathology findings were partially or completely reversed by the end of the 2-week recovery period. The NOAEL for mRNA-1283.222 was 10 µg/dose, the highest dose tested.	Using the NOAEL (10 µg/dose) and assuming a rat body weight estimate of 0.3 kg, there is a 195-fold safety margin compared to the human dose (10 µg/dose and assuming a conservative human body weight estimate of 60 kg or 0.17 µg/kg). Potential for treatment-related effects at the injection site and systemic inflammatory responses and/or immune response related to administration to the LNP and/or induction of an immune response to the expressed antigen(s). Data suggest potential for other clinical findings such as increased body temperature, injection site pain, or other inflammation related findings.
Platform GLP toxicity studies evaluating mRNA vaccines formulated in the same SM-102 LNP vaccine matrix as mRNA-1283 in male and female Sprague Dawley rats (administered IM at doses ranging from 9 to 150 µg/dose once	Clinical observations included generally dose-dependent erythema and oedema at the injection site and transient increases in body temperature at 6 hours post-vaccination returning to baseline 24 hours post-vaccination were observed at ≥9 µg/dose. These observations resolved or were considered resolving within 72 hrs. There were clinical chemistry and haematology changes consistent with inflammatory responses (ie, increases in white blood cells, neutrophils, eosinophils, and decreased lymphocytes); minimal coagulation changes consisting of a slightly increased activated partial thromboplastin time and an	Same potential for treatment-related effects at the injection site and systemic inflammatory responses and/or immune responses and/or immune response related to administration of the LNP and/or induction of an immune response to the expressed antigen(s).

Study Type	Important Nonclinical Findings	Relevance to Human Use
every 2 weeks for up to 6 weeks with a 2-week recovery period)	associated increase in fibrinogen were observed. Clinical chemistry results indicated a decrease in albumin, increase in globulin, and a corresponding decrease in albumin/globulin ratio. Consistent with other indicators of systemic inflammation in response to vaccine administration, transient cytokine increases were observed at ≥9 µg/dose at 6 hours post-vaccination including interferon gamma, monocyte chemoattractant protein-1, and macrophage inflammatory protein 1alpha. Macroscopic and microscopic changes were observed and included skin thickening at the injection site and enlarged lymph nodes. These observations were correlated with microscopic changes that included mixed cell inflammation at the injection site; increased cellularity and mixed cell inflammation in the lymph nodes. Additionally, decreased cellularity in the splenic periarteriolar lymphoid sheath; increased myeloid cellularity in the bone marrow; and hepatocyte vacuolation and Kupffer cell hypertrophy was occasionally observed in the liver. All findings were fully or partially resolved by the end of the 2-week recovery period. The NOAEL was always the highest dose tested (ranging from 89 to 150 µg/dose).	
Other nonclinical toxicology studies		
GLP perinatal/ postnatal developmental and reproductive toxicity with 80 µg/dose mRNA-1283 (administered via IM twice prior to mating and twice during gestation)	No adverse effects on maternal mating and fertility, ovarian/uterine examinations, natural delivery or litter assessments. Further, there were no foetal and/or pup effects on in-life parameters, gross pathology, foetal sex, external or visceral assessments, or skeletal malformations. Robust IgG antibody responses to the SARS-CoV-2 NTD and RBD proteins were present in the maternal serum samples after dosing, and continued into the gestation and lactation periods. Antibodies were also present in maternal milk samples, and in foetal and pup serum during gestation and the postnatal period, respectively, demonstrating effective placental and lactation transfer of anti-SARS-CoV-2 antibodies to offspring when females were immunised prior to and after mating.	Regarding the NOAEL for female reproduction and peri/post-natal development in rats (80 µg/dose, or 266.7 µg/kg based on a 0.3 kg rat), the safety margin is nearly 1600-fold compared to the human dose (10 µg/dose and assuming a conservative human body weight estimate of 60 kg or 0.17 µg/kg). The risk for adverse pregnancy outcomes after exposure is unknown in humans, but nonclinical findings do not suggest a specific risk. Exposure during pregnancy was limited in the clinical studies through the inclusion criteria that required a negative pregnancy test and use of adequate contraception for female participants of childbearing potential (Module SVII.1.2). Use of mRNA-1283 in pregnancy will be further characterised through routine pharmacovigilance activities (Part III).
Genotoxicity studies with SM-102, the ionisable lipid, and PEG2000-DMG as individual agents (in vitro) or as formulated LNPs containing mRNA (in vivo)	In vitro GLP studies (bacterial reverse mutation [Ames] tests in Salmonella typhimurium and Escherichia coli and in vitro micronucleus tests in human peripheral blood lymphocytes) were negative for both SM-102 and PEG2000-DMG. To support the use of SM-102 lipid and PEG2000-DMG in formulated mRNA-based drug products, 2 in vivo micronucleus studies were completed in rats (1 GLP-compliant study and a mechanistic follow-up non-GLP-compliant study).	When considering the conservative, lowest dose level where a positive result was observed in the GLP study with mRNA-1706 (1.3 mg/kg based on mRNA dose, albeit only in males and using IV administration, which would results in greater systemic exposure than IM administration),

Study Type	Important Nonclinical Findings	Relevance to Human Use
	These studies used the IV route of administration (as opposed to IM, the clinical route for mRNA-1283) to maximise systemic exposure using representative mRNA drug products formulated in SM-102 LNPs. There were weakly positive results from the GLP in vivo micronucleus study with mRNA-1706; however, these lacked dose dependence (observed at low and high, but not intermediate, dose) and were inconsistent across sexes and timepoints, suggesting that the results were variable and/or equivocal. Data from the mechanistic non-GLP in vivo micronucleus study with NPI-Luc mRNA were negative for inducing micronucleated erythrocytes at SM-102 doses that were within the range of doses in the GLP study but confirmed increases in body temperature and cytokines under the same experimental conditions. Transient hyperthermia in vivo, for as little as 30 minutes, has been shown to increase micronucleated erythrocytes in the bone marrow of rodents for agents that are not genotoxic, which has been attributed to the disturbance of the mitotic apparatus. Additionally, circulating cytokines are known endogenous pyrogens. Collectively, based on the weight of evidence, transient increases in body temperature and cytokines are considered a contributing factor to the weakly positive but inconsistent, results in the GLP in vivo micronucleus study.	there is an approximate 7000-fold safety margin when compared to the proposed marketed dose of mRNA-1283 (10 µg/dose or 0.17 µg/kg based on a conservative body weight estimate of 60 kg). The genotoxic risk to humans is considered to be low for SM-102-containing mRNA vaccines due to minimal systemic exposure following IM administration, limited duration of exposure, negative in vitro, and equivocal in vivo results, the latter of which are considered the result of the transient hyperthermia produced by the systemic inflammatory response.

There are no safety concerns for mRNA-1283 based on nonclinical data.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The safety and tolerability of the mRNA-1283 vaccine has been assessed using an overall safety database of over 6200 participants who have received at least 1 injection of mRNA-1283 (including the original D614G and variant formulations: mRNA-1283.211, mRNA-1283.529, mRNA-1283.222, or mRNA-1283.815) at any dose.

The mRNA-1283 clinical development programme includes a Phase 1 Study (mRNA-1283-P101), a Phase 2a Study (mRNA-1283-P201), a Phase 3 Study (mRNA-1283-P301 Part 1, which evaluated a bivalent formulation in Part 1 (mRNA-1283.222, targeting Original and Omicron BA.4/5), and a country-specific study part conducted in Japan [mRNA-1283-P301-Japan] which evaluated a monovalent formulation of mRNA-1283 (mRNA-1283.815, targeting Omicron XBB.1.5). A summary of the mRNA-1283 clinical development program is provided in Table SIII.1.

The mRNA-1283 study vaccines in the nonclinical and clinical development programmes evolved with the variant landscape and strain recommendations made by regulatory and public health bodies. Both monovalent and bivalent vaccines have been evaluated in the clinic and include the original SARS-CoV-2, Beta, Omicron BA.1, Omicron BA.4/5, and Omicron XBB.1.5.

Table SIII.1: Clinical Studies Supporting the Safety of mRNA-1283

Study Number (Country)	Study Design	Study Population(s)	Regimen	Number of Participants Exposed	Safety Objectives
mRNA-1283-P301 Part 1[a] (US, Canada and the UK)	Phase 3 randomised, observer-blind, active-controlled study to investigate the safety, immunogenicity, and relative vaccine efficacy of a single dose of mRNA-1283 compared to mRNA-1273	Previously vaccinated, medically stable individuals 12 years and older	Single IM injection: mRNA-1283.222[b] (10 µg) or mRNA-1273.222[b] (50 µg)	mRNA-1283.222 10 µg: n=5706 mRNA-1273.222 50 µg: n=5711	Primary Safety Objective: • To evaluate the safety and reactogenicity of mRNA-1283.222 10 µg dose after the study injection.
mRNA-1283-P301 (country-specific amendment, Japan)	Phase 3 randomised, observer-blind, active-controlled study to investigate the safety, immunogenicity, of a single-dose of mRNA-1283 compared to mRNA-1273.	Previously vaccinated Japanese participants 12 years and older	mRNA-1283.815[c] (10 µg) mRNA-1273.815[c] (50 µg)	mRNA-1283.815 10 µg: n=343 mRNA-1273.815 50 µg: n=346	Primary Safety Objective: • To evaluate the safety and reactogenicity of mRNA-1283.815 10 µg dose after the study injection.

Study Number (Country)	Study Design	Study Population(s)	Regimen	Number of Participants Exposed	Safety Objectives
mRNA-1283-P201 (US)	Phase 2a observer-blind, dose-ranging, single-dose study which consisted of 2 parts: Part A was a randomised, observer-blinded study that evaluated the immunogenicity, reactogenicity, and safety of a single injection of mRNA-1283 or the active comparator mRNA-1273. Part B was an open-label study that evaluated the immunogenicity, reactogenicity, and safety of a single injection of mRNA-1283.529 with no comparator group.	Previously vaccinated, healthy adults 18 years of age and older	Single IM injection: **Part A:** mRNA-1283[d]: 2.5, 5, 10 µg mRNA-1283.211[e] 5 µg and 10 µg mRNA-1273 50 µg **Part B:** mRNA-1283.529[f] 5 µg and 10 µg	**Part A:** mRNA-1283[c] 2.5 µg: n=57 5 µg: n=63 10 µg: n=56 mRNA-1283.211 5 µg: n=53 10 µg: n=54 mRNA-1273 50 µg: n=57 **Part B:** mRNA-1283.529 5 µg: n=103 10 µg: n=97	Part A Primary Safety Objective: • To assess the safety and reactogenicity of the study vaccine candidates. Part B Primary Safety Objective: • To assess the safety and reactogenicity of the mRNA-1283.529 booster vaccine candidate.
mRNA-1283-P101 (US)	A Phase 1, randomised, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1283 and mRNA-1273.	Unvaccinated adults aged 18-55 years	Three dose levels (10, 30, and 100 µg) of mRNA-1283 (Arms 1 through 3) and 1 dose level (100 µg) of mRNA-1273 (Arm 5) were evaluated in a 2-dose regimen, with the doses administered 28 days apart. One dose level (100 µg) of mRNA-1283 was evaluated in a single dose regimen (Arm 4).	104 participants: Arm 1: mRNA-1283 10 µg: n=21 Arm 2: mRNA-1283 30 µg: n=22 Arm 3: mRNA-1283 100 µg: n=21 Arm 4: Placebo + mRNA-1283 100 µg: n=18 Arm 5: mRNA-1273 100 µg: n=22	Primary Safety Objective: • To evaluate the safety and reactogenicity of 3 dose levels of mRNA-1283 and 1 dose level of mRNA-1273, each administered as 2 doses, 28 days apart, and 1 high-dose level of mRNA-1283 administered as a single dose.

Abbreviations: COVID-19 = coronavirus disease 2019; CSR = clinical study report; DSMB = Data Safety Monitoring Board; IM = intramuscular; mRNA = messenger ribonucleic acid; NTD = N-terminal domain; RBD = receptor binding domain; rVE = relative vaccine efficacy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; UK = United Kingdom; US = United States.

[a] Based on the adaptive study design, the study's independent DSMB reviewed rVE information (Study mRNA-1283-P301 Part 1) and recommended to the Applicant that the primary rVE objective had been met. As a result, there was no enrolment in Study mRNA-1283-P301 Part 2 and the Applicant proceeded with an rVE, immunogenicity, and safety analysis in May 2024.

[b] mRNA-1283.222 and mRNA-1273.222 are bivalent vaccines targeting Omicron BA.4/5 and original SARS-CoV-2
[c] mRNA-1283.815 and mRNA-1273.815 are monovalent vaccines targeting Omicron XBB.1.5.
[d] mRNA-1283 is a monovalent mRNA-1283 vaccine candidate encoding the linked RBD-NTD of the Spike protein of the original SARS-CoV-2.
[e] mRNA-1283.211 is a bivalent vaccine candidate composed of equal amounts of 2 mRNAs; one encoding the linked NTD-RBD of the Spike protein of the original SARS-CoV-2 and the other mRNA encodes for the Spike protein of the B.1.351 (Beta).
[f] mRNA-1283.529 is a monovalent mRNA-1283 vaccine candidate encoding the linked RBD-NTD of the Spike protein of Omicron B.1.1.529.
Source: Module 2.5, Section 2.5.1.4, Table 1.

Clinical trial exposure data are presented below for Phase 3 Study mRNA-1283-P301 Part 1, Phase 2a Study mRNA-1283-P201, and Phase 1 Study mRNA-1283-P101.

Study mRNA-1283-P301

Ongoing pivotal Study mRNA-1283-P301 is a Phase 3, randomised, observer-blind, active-controlled, multicentre study to evaluate the safety, immunogenicity, and rVE of mRNA-1283 10 µg compared to mRNA-1273 50 µg when given as a single dose in participants aged 12 years and older. To qualify for the study, participants were to have previously received a primary series of an authorised/approved COVID-19 vaccine and those ≥18 years of age were to have also received at least 1 booster dose, but no more than 5 vaccine doses. Participants 12 to <18 years of age had no booster dose requirement prior to study entry. The study allowed for the inclusion of participants with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 2 months before enrolment, as well as participants with stable HIV infection.

In Part 1 of the study, Omicron BA.4/BA.5 formulations, mRNA-1283.222 and mRNA-1273.222 were used during enrolment (March-August 2023) as these formulations reflected the vaccine strain update at the time of enrolment. A total of 11,454 participants were 1:1 randomly assigned to study treatment and at the time of the data cutoff (23 Feb 2024), a total of 5706 participants received the mRNA-1283.222 10 µg vaccine and 5711 participants received the mRNA-1273.222 50 µg vaccine (mRNA-1283-P301 CSR, Table 14.1.2.1). Clinical trial exposure data for Part 1 of Study mRNA 1283 P301 are presented by duration of exposure, age and sex, race and ethnicity up to the data cutoff (23 Feb 2024) in Table SIII.2 to Table SIII.5.

A potential Part 2 of Study mRNA-1283-P301 was designed and linked to Part 1 as part of the adaptive study design. Part 2 would only be conducted if a sample size increase was needed to support the rVE objective from Part 1. A prespecified DSMB review of interim data from Part 1 met criteria such that Part 2 was not conducted.

Part 3 is an ongoing independent study part designed to generate additional clinical experience in adolescent, COVID-19 vaccine naive, and adult populations. Part 3 enrolled up to 2100 additional participants (approximately 1000 adolescent participants, 500 adult participants, and 600 previously unvaccinated participants) randomised 1:1 to receive a single 10 µg dose of mRNA-1283.815 or a single 50 µg dose of mRNA-1273.815. The primary objective in Part 3 is to evaluate the safety and reactogenicity of 10 µg mRNA-1283.815.

Table SIII.2: Summary of Study Duration for mRNA-1283-P301 (Safety Set)

Duration of exposure	mRNA-1283.222 10 µg (N=5706)	mRNA-1273.222 50 µg (N=5711)	Total (N=11417)
Number of participants, n (%)			
≥28 days since injection	5695 (99.8)	5703 (99.9)	11398 (99.8)
≥3 months since injection	5629 (98.7)	5654 (99.0)	11283 (98.8)
≥6 months since injection	5540 (97.1)	5574 (97.6)	11114 (97.3)
≥8 months since injection	3908 (68.5)	3954 (69.2)	7862 (68.9)
≥10 months since injection	878 (15.4)	896 (15.7)	1774 (15.5)
Time on study (months)[1]			
n	5706	5711	11417
Mean (SD)	8.505 (1.5200)	8.546 (1.4589)	8.526 (1.4899)
Median	8.772	8.772	8.772
Q1, Q3	7.688, 9.528	7.721, 9.528	7.688, 9.528
Min, Max	0.07, 10.68	0.23, 11.01	0.07, 11.01
Person-years from injection[2]	4044.12	4067.29	8111.41
Person-months from injection[2]	48529.41	48807.49	97336.90

Abbreviations: max = maximum; min = minimum; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.
Participants are included in the treatment group that they actually received.
Percentages are based on the number of participants in Safety Set.
[1] Time on study in months is defined as [end of study date for discontinued participants or data cutoff date for ongoing study subjects – study drug injection date +1]/30.4375.
[2] Person-years (months) is defined as the total years (months) of participants' time on study. One year =365.25 days
Source: Study mRNA-1283-P301 CSR, Table 14.1.1.5
Data from ongoing trial as of 23 Feb 2024.

Table SIII.3: Participant Age and Sex in Study mRNA-1283-P301 (Safety Set)

Characteristic	mRNA-1283.222 10 µg (N=5706)	mRNA-1273.222 50 µg (N=5711)	Total (N=11417)
Actual age group, n (%)			
≥12 to <18 years	497 (8.7)	495 (8.7)	992 (8.7)
≥18 years	5209 (91.3)	5216 (91.3)	10425 (91.3)
≥18 to <65 years	3575 (62.7)	3576 (62.6)	7151 (62.6)
≥65 years	1634 (28.6)	1640 (28.7)	3274 (28.7)
≥75 years	322 (5.6)	269 (4.7)	591 (5.2)
Age (years)			
n	5706	5711	11417
Mean (SD)	51.1 (18.58)	51.2 (18.32)	51.2 (18.45)
Median	56.0	55.0	56.0
Q1, Q3	38.0, 66.0	39.0, 66.0	38.0, 66.0
Min, Max	12, 96	12, 90	12, 96

Characteristic	mRNA-1283.222 10 µg (N=5706)	mRNA-1273.222 50 µg (N=5711)	Total (N=11417)
Sex, n (%)			
Male	2586 (45.3)	2631 (46.1)	5217 (45.7)
Female	3120 (54.7)	3080 (53.9)	6200 (54.3)

Abbreviations: max = maximum; min = minimum; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.
Participants are included in the treatment group that they actually received.
Percentages are based on the number of participants in Safety Set.
Source: Study mRNA-1283-P301 CSR, Table 14.1.3.1
Data from ongoing trial as of 23 Feb 2024.

Table SIII.4: Participant Race in Study mRNA-1283-P301 (Safety Set)

Race, n (%)	mRNA-1283.222 10 µg (N=5706)	mRNA-1273.222 50 µg (N=5711)	Total (N=11417)
White	4670 (81.8)	4711 (82.5)	9381 (82.2)
Black or African American	640 (11.2)	635 (11.1)	1275 (11.2)
Asian	225 (3.9)	183 (3.2)	408 (3.6)
American Indian or Alaska Native	20 (0.4)	26 (0.5)	46 (0.4)
Native Hawaiian or Other Pacific Islander	9 (0.2)	6 (0.1)	15 (0.1)
Multiple	81 (1.4)	94 (1.6)	175 (1.5)
Other	20 (0.4)	20 (0.4)	40 (0.4)
Not reported	36 (0.6)	26 (0.5)	62 (0.5)
Unknown	5 (0.09)	10 (0.2)	15 (0.1)

Participants are included in the treatment group that they actually received.
Percentages are based on the number of participants in Safety Set.
Source: Study mRNA-1283-P301 CSR, Table 14.1.3.1
Data from ongoing trial as of 23 Feb 2024.

Table SIII.5: Participant Ethnicity in Study mRNA-1283-P301 (Safety Set)

Ethnicity, n (%)	mRNA-1283.222 10 µg (N=5706)	mRNA-1273.222 50 µg (N=5711)	Total (N=11417)
Hispanic or Latino	769 (13.5)	741 (13.0)	1510 (13.2)
Not Hispanic or Latino	4860 (85.2)	4864 (85.2)	9724 (85.2)
Not reported	59 (1.0)	87 (1.5)	146 (1.3)
Unknown	18 (0.3)	19 (0.3)	37 (0.3)

Participants are included in the treatment group that they actually received.
Percentages are based on the number of participants in Safety Set.
Source: Study mRNA-1283-P301 CSR, Table 14.1.3.1
Data from ongoing trial as of 23 Feb 2024.

Study mRNA-1283-P301-Japan was added to evaluate mRNA-1283 in Japanese participants 12 years and older. The primary objectives of the Japan study included noninferior immunogenicity of mRNA-1283.815 vs mRNA-1273.815, and evaluation of the safety and reactogenicity of mRNA-1283.815 10 µg. A total of 689 participants were dosed, of which 343 received mRNA-1283.815 10 µg and 346 received mRNA-1273.815 50 µg. All participants

had previously received at least 1 dose of a COVID-19 vaccine prior to their enrolment with a median time of 16.7 months since the last dose. The study allowed for the inclusion of participants with stable pre-existing medical conditions, defined as no significant change in therapy or hospitalisation for worsening disease during the 2 months before enrolment, as well as participants with stable HIV infection. The Japan cohort enrolled similar age groups as the global study population (12 to <18, 18 to <65, and ≥65 years).

Study mRNA-1283-P201

Completed Study mRNA-1283-P201 was a Phase 2a observer-blind, dose-ranging, single-dose, 2-part study. Part A was a randomised, observer-blinded study that evaluated the immunogenicity, reactogenicity, and safety of mRNA-1283 (original SARS-CoV-2, 2.5, 5, or 10 µg) and mRNA-1283.211 (bivalent, original SARS-CoV-2, and Beta variant; 5 µg or 10 µg), versus the active comparator, mRNA-1273 (original SARS-CoV-2) 50 µg.

Part B was an open-label study initiated after the emergence of the Omicron BA.1 variant that evaluated the immunogenicity, reactogenicity, and safety of the monovalent Omicron BA.1 vaccine (mRNA-1283.529, 5 µg or 10 µg).

In this study of previously vaccinated healthy adult participants, 483 participants received mRNA-1283 across various dose groups (2.5, 5, and 10 µg; 5 and 10 µg of mRNA-1283.211; and 5 and 10 µg of mRNA-1283.529), and 57 participants in a control group received 50 µg mRNA-1273. Study mRNA-1283-P201 was conducted in the US between 06 Dec 2021 to 23 Mar 2023.

Clinical trial exposure data for Part A of Study mRNA-1283-P201 are presented by duration of exposure, age and sex, race and ethnicity in Table SIII.6 to Table SIII.9.

Table SIII.6: Summary of Study Duration for mRNA-1283-P201 Part A (Safety Set)

Duration of exposure	mRNA-1283			mRNA-1283.211		mRNA-1273
	2.5 µg (N=57)	5 µg (N=64)	10 µg (N=56)	5 µg (N=52)	10 µg (N=54)	50 µg (N=57)
Study duration from Randomisation (Days)						
n	57	64	56	52	54	57
Mean (SD)	358.7 (36.69)	345.5 (69.01)	355.9 (48.83)	355.1 (55.15)	342.4 (69.75)	335.9 (85.27)
Median	360.0	361.5	363.5	365.0	359.5	358.0
Min, Max	170, 421	29, 408	29, 403	14, 434	31, 402	16, 419
Study duration from Injection (Days)						
n	57	64	56	52	54	57
Mean (SD)	358.7 (36.69)	345.5 (69.01)	355.9 (48.83)	355.1 (55.15)	342.3 (69.73)	336.5 (85.46)
Median	360.0	361.5	363.5	365.0	359.5	359.0
Min, Max	170, 421	29, 408	29, 403	14, 434	31, 402	16, 419

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation.
Note: Numbers were based on actual vaccine group and percentages were based on the number of participants in Safety Set.
Source: Study mRNA-1283-P201 CSR, Table 14.1.6.1
Final analysis database lock date: 06 Jun 2023.

Table SIII.7: Participant Age and Sex in Study mRNA-1283-P201 Part A (Safety Set)

Characteristic	mRNA-1283			mRNA-1283.211		mRNA-1273
	2.5 µg (N=57)	5 µg (N=64)	10 µg (N=56)	5 µg (N=52)	10 µg (N=54)	50 µg (N=57)
Age subgroup, n (%)						
≥18 to <56 years	40 (70.2)	46 (71.9)	42 (75.0)	37 (71.2)	40 (74.1)	42 (73.7)
≥56 years	17 (29.8)	18 (28.1)	14 (25.0)	15 (28.8)	14 (25.9)	15 (26.3)
Age (years)						
n	57	64	56	52	54	57
Mean (SD)	44.6 (15.12)	45.4 (14.87)	44.5 (14.20)	46.2 (15.74)	47.1 (12.55)	44.2 (13.84)
Median	42.0	45.0	44.0	47.0	46.0	41.0
Min, Max	19, 79	19, 74	21, 79	19, 87	19, 79	23, 75
Sex, n (%)						
Male	26 (45.6)	21 (32.8)	24 (42.9)	18 (34.6)	15 (27.8)	25 (43.9)
Female	31 (54.4)	43 (67.2)	32 (57.1)	34 (65.4)	39 (72.2)	32 (56.1)

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation.
Note: Numbers were based on actual vaccine group and percentages were based on the number of participants in Safety Set.
Source: Study mRNA-1283-P201 CSR, Table 14.1.3.2.1
Final analysis database lock date: 06 Jun 2023.

Table SIII.8: Participant Race in Study mRNA-1283-P201 Part A (Safety Set)

Race, n (%)	mRNA-1283			mRNA-1283.211		mRNA-1273
	2.5 µg (N=57)	5 µg (N=64)	10 µg (N=56)	5 µg (N=52)	10 µg (N=54)	50 µg (N=57)
White	41 (71.9)	48 (75.0)	41 (73.2)	38 (73.1)	37 (68.5)	47 (82.5)
Black or African American	11 (19.3)	11 (17.2)	9 (16.1)	9 (17.3)	10 (18.5)	6 (10.5)
Asian	5 (8.8)	1 (1.6)	3 (5.4)	3 (5.8)	3 (5.6)	3 (5.3)
American Indian or Alaska Native	0	0	0	0	2 (3.7)	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Multiracial	0	2 (3.1)	1 (1.8)	1 (1.9)	1 (1.9)	1 (1.8)
Other	0	0	0	0	1 (1.9)	0
Not reported	0	2 (3.1)	2 (3.6)	1 (1.9)	0	0
Unknown	0	0	0	0	0	0

Note: Numbers were based on actual vaccine group and percentages were based on the number of participants in Safety Set.
Source: Study mRNA-1283-P201 CSR, Table 14.1.3.2.1
Final analysis database lock date: 06 Jun 2023.

Table SIII.9: Participant Ethnicity in Study mRNA-1283-P201 Part A (Safety Set)

Ethnicity, n (%)	mRNA-1283			mRNA-1283.211		mRNA-1273
	2.5 µg (N=57)	5 µg (N=64)	10 µg (N=56)	5 µg (N=52)	10 µg (N=54)	50 µg (N=57)
Hispanic or Latino	10 (17.5)	14 (21.9)	8 (14.3)	9 (17.3)	8 (14.8)	11 (19.3)
Not Hispanic or Latino	47 (82.5)	50 (78.1)	47 (83.9)	43 (82.7)	43 (79.6)	45 (78.9)
Not reported	0	0	1 (1.8)	0	3 (5.6)	1 (1.8)
Unknown	0	0	0	0	0	0

Note: Numbers were based on actual vaccine group and percentages were based on the number of participants in Safety Set.
Source: Study mRNA-1283-P201 CSR, Table 14.1.3.2.1
Final analysis database lock date: 06 Jun 2023.

Clinical trial exposure data for Part B of Study mRNA-1283-P201 are presented by duration of exposure, age and sex, race and ethnicity in Table SIII.10 to Table SIII.13.

Table SIII.10: Summary of Study Duration for mRNA-1283-P201 Part B (Safety Set)

Duration of exposure	mRNA-1283.529	
	5 µg (N=103)	10 µg (N=97)
Study Duration from Enrolment (Days)		
n	103	97
Mean (SD)	354.0 (39.27)	344.5 (62.29)
Median	360.0	359.0
Min, Max	48, 377	84, 378
Study Duration from Injection (Days)		
n	103	97
Mean (SD)	354.0 (39.27)	344.5 (62.29)
Median	360.0	359.0
Min, Max	48, 377	84, 378

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation.
Note: Numbers were based on actual vaccine group and percentages were based on the number of participants in Safety Set.
Source: Study mRNA-1283-P201 CSR, Table 14.1.6.2
Final analysis database lock date: 06 Jun 2023.

Table SIII.11: Participant Age and Sex in Study mRNA-1283-P201 Part B (Safety Set)

Characteristic	mRNA-1283.529	
	5 µg (N=103)	10 µg (N=97)
Age subgroup, n (%)		
≥18 to <56 years	44 (42.7)	59 (60.8)
≥56 years	59 (57.3)	38 (39.2)
Age (years)		
n	103	97
Mean (SD)	57.3 (14.25)	52.1 (14.15)
Median	59.0	50.0

Characteristic	mRNA-1283.529	
	5 µg (N=103)	10 µg (N=97)
Min, Max	21, 93	19, 85
Sex, n (%)		
Male	33 (32.0)	35 (36.1)
Female	70 (68.0)	62 (63.9)

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation.
Note: Numbers were based on actual vaccine group and percentages were based on the number of participants in Safety Set.
Source: Study mRNA-1283-P201 CSR, Table 14.1.3.2.2
Final analysis database lock date: 06 Jun 2023.

Table SIII.12: Participant Race in Study mRNA-1283-P201 Part B (Safety Set)

Race, n (%)	mRNA-1283.529	
	5 µg (N=103)	10 µg (N=97)
White	94 (91.3)	88 (90.7)
Black or African American	7 (6.8)	7 (7.2)
Asian	0	2 (2.1)
American Indian or Alaska Native	1 (1.0)	0
Native Hawaiian or Other Pacific Islander	1 (1.0)	0
Multiracial	0	0
Other	0	0
Not reported	0	0
Unknown	0	0

Note: Numbers were based on actual vaccine group and percentages were based on the number of participants in Safety Set.
Source: Study mRNA-1283-P201 CSR, Table 14.1.3.2.2
Final analysis database lock date: 06 Jun 2023.

Table SIII.13: Participant Ethnicity in Study mRNA-1283-P201 Part B (Safety Set)

Ethnicity, n (%)	mRNA-1283.529	
	5 µg (N=103)	10 µg (N=97)
Hispanic or Latino	2 (1.9)	4 (4.1)
Not Hispanic or Latino	100 (97.1)	93 (95.9)
Not reported	1 (1.0)	0
Unknown	0	0

Note: Numbers were based on actual vaccine group and percentages were based on the number of participants in Safety Set.
Source: Study mRNA-1283-P201 CSR, Table 14.1.3.2.2
Final analysis database lock date: 06 Jun 2023.

Study mRNA-1283-P101

Completed Study mRNA-1283-P101 was a Phase 1, randomised, observer-blind, dose-ranging study that evaluated the safety, reactogenicity and immunogenicity of mRNA-1283 and mRNA-1273 (both encoding for the original SARS-CoV-2 strain Spike protein) in adults 18 to 55 years of age administered as a primary series (2-doses). A total of 79 participants received mRNA-1283 across 4 dose groups (2 doses at 10 µg, 30 µg, and 100 µg or a single dose at 100 µg) and 22 participants in a control group received 100 µg of mRNA-1273.

Clinical trial exposure data for Study mRNA-1283-P101 are presented by duration of exposure, age and sex, race and ethnicity in Table SIII.14 to Table SIII.17.

Table SIII.14: Summary of Study Duration for mRNA-1283-P101 (Safety Set)

Duration of exposure	mRNA-1283					mRNA-1273 100 µg (N=22)
	mRNA-1283 10 µg (N=21)	mRNA-1283 30 µg (N=22)	mRNA-1283 100 µg (N=21)	Placebo+ 100 µg (N=18)	Total mRNA-1283 (N=82)	
Number of participants, n (%)						
Received first injection	21 (100)	22 (100)	21 (100)	18 (100)	82 (100)	22 (100)
Received second injection	19 (90.5)	20 (90.9)	21 (100)	15 (83.3)	75 (91.5)	20 (90.9)
≥56 days since first injection	20 (95.2)	21 (95.5)	21 (100)	16 (88.9)	78 (95.1)	20 (90.9)
<28 days since second injection	0	0	0	0	0	1 (4.5)
≥28 days since second injection	19 (90.5)	20 (90.9)	21 (100)	15 (83.3)	75 (91.5)	19 (86.4)
≥28 and <56 days since second injection	0	1 (4.5)	1 (4.8)	1 (5.6)	3 (3.7)	0
≥56 days since second injection	19 (90.5)	19 (86.4)	20 (95.2)	14 (77.8)	72 (87.8)	19 (86.4)
Study duration from first injection (days)						
Mean (SD)	490.3 (237.34)	570.8 (239.59)	615.3 (201.15)	266.7 (142.02)	494.8 (244.77)	561.4 (257.61)
Median	402.0	738.0	736.0	297.0	397.0	735.5
Q1, Q3	386.0, 736.0	385.0, 754.0	410.0, 754.0	129.0, 383.0	379.0, 750.0	392.0, 755.0
Min, Max	8, 761	9, 763	57, 768	8, 395	8, 768	29, 763
Study duration from second injection (days)[a]						
Mean (SD)	428.0 (247.79)	528.5 (262.09)	586.7 (200.43)	237.5 (142.99)	453.8 (252.67)	507.6 (281.58)
Median	365.0	710.5	707.0	269.0	367.0	707.0
Q1, Q3	355.0, 705.0	360.0, 726.0	384.0, 726.0	101.0, 354.0	339.0, 720.0	351.0, 728.0
Min, Max	0, 733	0, 740	29, 741	0, 367	0, 741	0, 736
Study duration from second injection in participants who received second injection (days)						
n	19	20	21	15	75	20
Mean (SD)	473.1 (213.82)	581.4 (208.75)	586.7 (200.43)	285.0 (101.60)	496.2 (220.41)	558.4 (240.41)
Median	374.0	713.5	707.0	339.0	374.0	711.5
Q1, Q3	356.0, 707.0	366.0, 727.0	384.0, 726.0	246.0, 361.0	355.0, 721.0	365.0, 729.0
Min, Max	87, 733	56, 740	29, 741	30, 367	29, 741	24, 736

Abbreviations: Max=maximum; Min=minimum; Q1 = first quartile; Q3 = third quartile; SD=standard deviation.
Note: Percentages were based on the number of participants in Safety Set.
[a] Study duration from second injection is 0 day for participants who did not receive second injection.
Source: Study mRNA-1283-P101 CSR, Table 7
Final analysis database lock date: 07 Sep 2023.

Table SIII.15: Participant Age and Sex in Study mRNA-1283-P101 (Full Analysis Set)

Characteristic	mRNA-1283				mRNA-1273
	10 µg (N=21)	30 µg (N=22)	100 µg (N=21)	Placebo+ 100 µg (N=18)	100 µg (N=22)
Age (years)					
n	21	22	21	18	22
Median	41.0	30.5	36.0	30.5	43.0
Q1, Q3	28.0, 45.0	26.0, 42.0	27.0, 47.0	25.0, 43.0	35.0, 52.0
Min, Max	23, 51	21, 54	19, 51	19, 49	22, 55
Sex, n (%)					
Male	9 (42.9)	13 (59.1)	12 (57.1)	12 (66.7)	14 (63.6)
Female	12 (57.1)	9 (40.9)	9 (42.9)	6 (33.3)	8 (36.4)

Abbreviations: Max=maximum; Min=minimum; Q1 = first quartile; Q3 = third quartile.
Note: Percentages were based on the number of participants in Full Analysis Set.
The Full Analysis Set is the same as the Safety Set (Study mRNA-1283-P101 CSR, Table 5)
Source: Study mRNA-1283-P101 CSR, Table 6
Final analysis database lock date: 07 Sep 2023.

Table SIII.16: Participant Race in Study mRNA-1283-P101 (Full Analysis Set)

Race, n (%)	mRNA-1283				mRNA-1273
	10 µg (N=21)	30 µg (N=22)	100 µg (N=21)	Placebo+ 100 µg (N=18)	100 µg (N=22)
White	15 (71.4)	16 (72.7)	16 (76.2)	10 (55.6)	16 (72.7)
Black	1 (4.8)	2 (9.1)	1 (4.8)	0	1 (4.5)
Asian	0	1 (4.5)	2 (9.5)	1 (5.6)	1 (4.5)
American Indian or Alaska Native	0	0	0	1 (5.6)	0
Native Hawaiian or Other Pacific Islander	0	0	0	1 (5.6)	0
Multiracial	1 (4.8)	0	0	2 (11.1)	0
Other	0	0	0	0	0
Not reported	4 (19.0)	3 (13.6)	2 (9.5)	3 (16.7)	4 (18.2)
Unknown	0	0	0	0	0

Note: Percentages were based on the number of participants in Full Analysis Set.
The Full Analysis Set is the same as the Safety Set (Study mRNA-1283-P101 CSR, Table 5)
Source: Study mRNA-1283-P101 CSR, Table 6
Final analysis database lock date: 07 Sep 2023.

Table SIII.17: Participant Ethnicity in Study mRNA-1283-P101 (Full Analysis Set)

Ethnicity, n (%)	mRNA-1283				mRNA-1273
	10 µg (N=21)	30 µg (N=22)	100 µg (N=21)	Placebo+ 100 µg (N=18)	100 µg (N=22)
Hispanic or Latino	7 (33.3)	7 (31.8)	5 (23.8)	4 (22.2)	7 (31.8)
Not Hispanic or Latino	14 (66.7)	15 (68.2)	16 (76.2)	13 (72.2)	14 (63.6)
Not reported	0	0	0	1 (5.6)	1 (4.5)
Unknown	0	0	0	0	0

Note: Percentages were based on the number of participants in Full Analysis Set.
The Full Analysis Set is the same as the Safety Set (Study mRNA-1283-P101 CSR, Table 5)
Source: Study mRNA-1283-P101 CSR, Table 6
Final analysis database lock date: 07 Sep 2023.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Participants were excluded from the pivotal Phase 3 Study mRNA-1283-P301 according to the general criteria listed below (Table SIV.1). Detailed descriptions of all exclusion criteria are provided in the individual protocols.

Table SIV.1: Important Exclusion Criteria in the Pivotal Study

Criterion	Reason for Exclusion	Included as Missing Information? (Yes/No)	Rationale (if not included as missing information)
Paediatric participants (aged less than 12 years old).	Clinical development programmes generally investigate first the benefit-risk in adults. In adults, the risk of symptomatic and severe COVID-19 disease is higher.	No	mNEXSPIKE is not indicated for use in paediatric participants less than 12 years of age. A PIP was agreed upon by EMA. The FDA approved an iPSP in the US.
Pregnant women.	Clinical development generally first demonstrates safety and efficacy in non-pregnant women.	Yes	Not applicable.
Acutely ill/febrile (temperature >38°C/100.4°F) 72 hours prior to or at screening visit or Day 1	Allowance of these conditions would confound assessment of safety and these febrile participants might already be infected with SARS-CoV-2.	No	It is common medical practice to not administer vaccines in febrile participants. Febrile participants with minor illnesses could be enrolled at the discretion of the investigator. mNEXSPIKE SmPC advises healthcare professionals that vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.
Known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients.	Participants with medical history significant for allergic reactions following the vaccine or its excipients are at increased risk for hypersensitivity reactions when	No	It is common medical practice to not administer a new vaccine in participants who have history of significant allergic reactions to the vaccine or its excipients. mNEXSPIKE SmPC contraindicates administration of mNEXSPIKE in individuals with known hypersensitivity to the active substance or to any of the excipients.

Criterion	Reason for Exclusion	Included as Missing Information? (Yes/No)	Rationale (if not included as missing information)
	receiving another vaccine.		Furthermore, appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. The SmPC advises close observation for at least 15 minutes following vaccination and no further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of the vaccine.
Bleeding disorder that is considered a contraindication to IM injection or phlebotomy.	Participants have a potential risk of haematoma due to the puncture of the deep tissues. Allowance of these conditions would confound assessment of safety.	No	It is common medical practice to not administer a product by the IM route in participants with coagulopathy or bleeding disorders although the use of a needle of a proper gauge can decrease the risk. mNEXSPIKE SmPC advises that as with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.
Has tested positive for SARS-CoV-2 using an authorised/approved lateral flow/rapid antigen or PCR test within 90 days of Screening.	Allowance of this condition would confound assessment of safety and efficacy.	No	At baseline, most participants had a positive prior SARS-CoV-2 infection, specifically, 4211/5706 (73.8%) participants in the mRNA-1283.222 group (Study mRNA-1283-P301 CSR, Table 14.1.3.1).
Has received or plans to receive any licensed vaccine ≤60 days prior to the study injection (Day 1) or plans to receive a licensed vaccine within 60 days after the study injection.	Allowance of these vaccinations would confound assessment of safety and efficacy.	No	The study included participants with different number of prior vaccination doses after a COVID-19 primary series immunisation. Specifically in the mRNA-1283.222 group, 218/5706 (3.8%) participants had no prior booster doses, 2131/5706 (37.3%) participants had 1 prior booster dose, 1889/5706 (33.1%) participants had 2 prior booster doses, and 1451/5711 (25.4%) participants had 3 or more prior booster doses (Study mRNA-1283-P301 CSR, Table 14.1.3.1). mNEXSPIKE SmPC advises that if previously vaccinated with a COVID-19 vaccine, mNEXSPIKE should be administered at least 3 months after the

Criterion	Reason for Exclusion	Included as Missing Information? (Yes/No)	Rationale (if not included as missing information)
			most recent dose of a COVID-19 vaccine. Concomitant administration of mNEXSPIKE with other vaccines has not been studied.
Has received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 181 days prior to Screening (for corticosteroids ≥10 mg/day of prednisone equivalent) or is anticipating the need for immunosuppressive treatment at any time during participation in the study.	Allowance of these conditions would confound assessment of efficacy.	No	No significant safety concerns have been identified in the literature to date for vaccination of immunocompromised patients with a COVID-19 vaccine. Countries have amended/approved an additional primary series dose in immunocompromised patients to achieve an adequate, more robust immune response. mNEXSPIKE SmPC states that safety and immunogenicity data on mNEXSPIKE are not available for immunocompromised individuals and that individuals receiving immunosuppressant therapy or patients with immunodeficiency may have a diminished immune response to this vaccine.
Has received systemic immunoglobulins or blood products within 3 months prior to the day of screening.	Allowance of these conditions would confound assessment of efficacy.	No	No significant safety concerns have been identified in the literature to date for vaccination of immunocompromised patients with a COVID-19 vaccine. Countries have amended/approved an additional primary series dose in immunocompromised patients to achieve an adequate, more robust immune response. mNEXSPIKE SmPC states that safety and immunogenicity data on mNEXSPIKE are not available for immunocompromised individuals and that individuals receiving immunosuppressant therapy or patients with immunodeficiency may have a diminished immune response to this vaccine.
Has donated ≥450 mL of blood products within 28 days prior to Screening or plans to donate blood products during the study.	Allowance of these conditions would confound assessment of safety.	No	It is common practice to not give blood prior to entry in a clinical trial. There is no suspected biological reason to expect the safety or efficacy of mNEXSPIKE in these participants would be different from the rest of the population receiving mNEXSPIKE.
Has history of myocarditis, pericarditis, or myopericarditis that has	Including this population could have impacted the	No	Myocarditis and pericarditis are important potential risks (Module SVII.1.2).

Criterion	Reason for Exclusion	Included as Missing Information? (Yes/No)	Rationale (if not included as missing information)
not fully resolved within 3 months prior to Screening.	safety outcome of the study.		
Dermatologic conditions that could affect local solicited AR assessments (eg, psoriasis patches affecting skin over the deltoid areas).	Including this population could have impacted the safety outcome of the study.	No	Local solicited adverse reactions were expected during the study. Consistently in the clinical studies, the local reactogenicity is lower with mNEXSPIKE than Spikevax. In Study mRNA-1283-P301, solicited local ARs were less frequent in the mRNA-1283.222 group (4007/5701 [70.3%] participants) compared to the mRNA-1273.222 group (4473/5705 [78.4%] participants) (mRNA-1283-P301 CSR, Section 7.1.1.1). There is no suspected reason to expect the safety or efficacy of mNEXSPIKE in these individuals would be different from the rest of the population receiving mNEXSPIKE.
Diagnosis of malignancy within the previous 5 years (excluding nonmelanoma skin cancer).	Including this population could have impacted the safety outcome of the study.	No	There is no suspected reason to expect the safety or efficacy of mNEXSPIKE in these individuals would be different from the rest of the population receiving mRNA-1283. However, if the individual is immunocompromised the efficacy of mNEXSPIKE could be impacted. mNEXSPIKE SmPC states that safety and immunogenicity data on mNEXSPIKE are not available for immunocompromised individuals and that individuals receiving immunosuppressant therapy or patients with immunodeficiency may have a diminished immune response to this vaccine.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The current studies supporting the authorisation of mRNA-1283 in the clinical development programme are unlikely to detect certain types of adverse reactions such as rare (<1/1000) adverse reactions or adverse reactions with a long latency. There is no prolonged exposure to mRNA-1283.

The safety profile is based on the ongoing, randomised, observer-blind, active-controlled Phase 3 Study mRNA-1283-P301, in which 5,706 participants aged ≥12 years received one injection of 10 µg mRNA-1283; and 5,540 of these participants (97.1%) had at least 6 months of follow-up

after injection. At the time of data cutoff of 23 Feb 2024, the median study duration from injection in the mRNA-1283 group was 8.77 months (Table SIII.2, Module SIII).

In Study mRNA-1283-P301-Japan, the median duration of follow-up after study vaccination was 35.0 days in both groups (mRNA-1283-P301-Japan CSR Addendum, Section 5.5).

The safety profile of mRNA-1283 is further supported by data from Phase 2a Study mRNA-1283-P201 in which participants aged ≥18 years were followed up for 12 months post vaccination in both Part A (283 participants received mRNA-1283 including 177 participants who received 2.5 µg, 5 µg or 10 µg mRNA-1283 and 106 participants who received 5 µg or 10 µg mRNA-1283.211) (mRNA-1283-P201 CSR, Section 5.1.4) and Part B (200 participants received 5 µg or 10 µg mRNA-1283.529) (mRNA-1283-P201 CSR, Section 5.2.4) of the study. In Part A, the median duration of follow-up ranged from 359.0 to 365.0 days (range: 14 to 434 days) across vaccination groups (Table SIII.6, Module SIII). In Part B, the median duration of follow-up was 360.0 days in the mRNA-1283.529 5 µg group and 359.0 days in the 10 µg group (range: 48 to 378 days) (Table SIII.10, Module SIII).

In Study mRNA-1283-P101, the median duration of follow-up for the 82 participants who received mRNA-1283 was 397 days (Table SIII.14, Module SIII).

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table SIV.2: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Paediatric participants	Paediatrics <12 years of age were not included in the clinical development programme to support the indication in individuals ≥12 years.
Pregnant women	Not included in the clinical development programme to support the indication in individuals ≥12 years, although a small number of pregnancies were reported in the mRNA-1283 clinical programme. In Study mRNA-1283-P301 10 participants had reported pregnancies: 3 participants in the mRNA-1283.222 group and 7 participants in the mRNA-1273.222 group (Module 2.7.4, Section 2.7.4.6.4). At the time of the data cutoff date (23 Feb 2024), in the mRNA-1283.222 group all 3 pregnancies were pending the final outcome. Of the 7 pregnancies in the mRNA-1273.222 group, 3 pregnancies resulted in term births without complications, 1participant had an induced abortion on Day 37, and the final outcomes for the 3 remaining pregnancies had not yet been reported.
Breastfeeding women	Not included in the clinical development programme to support the indication in individuals ≥12 years.
Participants with relevant comorbidities	
Participants with hepatic impairment	Hepatic impairment at baseline was not evaluated in the clinical development programme.
Participants with renal impairment	Renal impairment at baseline was not evaluated in the clinical development programme.
Participants with cardiovascular impairment	In Study mRNA-1283-P301, participants had a medical history of cardiac disorders (6.7% and 6.1%) in the mRNA-1283.222 and mRNA-1273.222 groups, respectively (mRNA-1283-P301 CSR, Table 14.1.4). Atrial fibrillation (1.9% and 1.7%), coronary artery disease (1.1% and 0.9%), myocardial infarction (0.8% and 0.8%), cardiac failure congestive (0.4% and 0.4%), and myocardial ischaemia (0.3% and 0.4%) were the most frequently reported cardiac disorders in the mRNA-1283.222 and mRNA-1273.222 groups, respectively (mRNA-1283-P301 CSR, Table 14.1.4).

Type of Special Population	Exposure
Immunocompromised participants	Not included in the clinical development programme.
Participants with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	Participant exposure by race and ethnicity in Study mRNA-1283-P301 are presented in Table SIII.4 and Table SIII.5 (Module SIII), respectively. In this study, the majority of participants in the mRNA-1283.222 and mRNA-1273.222 groups were White (81.8% and 82.5%), followed by Black or African American (11.2% and 11.1%), Asian (3.9% and 3.2%), multiple (1.4% and 1.6%), other (0.4% and 0.4%), American Indian or Alaska Native (0.4% and 0.5%), Native Hawaiian or Other Pacific Islander (0.2% and 0.1%); in 0.6% and 0.5% of participants the race was not reported and in 0.1% and 0.2% of participants the race was unknown, respectively (mRNA-1283-P301 CSR, Table 14.1.3.1). In terms of ethnicity, the majority of participants in the mRNA-1283.222 and mRNA-1273.222 groups in mRNA-1283-P301 were Not Hispanic or Latino (both 85.2%), followed by Hispanic or Latino (13.5% and 13.0%); in 1.0% and 1.5% of participants ethnicity was not reported and ethnicity was not known in 0.3% of participants in both groups, respectively (mRNA-1283-P301 CSR, Table 14.1.3.1).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Others	
Participants ≥75 years of age	Participant exposure by age in Study mRNA-1283-P301 is presented in Table SIII.3 (Module SIII). In this study, 5.6% and 4.7% of participants were ≥75 years of age in the mRNA-1283.222 and mRNA-1273.222 groups, respectively (mRNA-1283-P301 CSR, Table 14.1.3.1).
Diabetes (Type 1, Type 2)	In Study mRNA-1283-P301, participants had a medical history of Type 1 diabetes mellitus (0.4% and 0.4%), Type 2 diabetes mellitus (9.5% and 10.1%), and diabetes mellitus (0.5% and 0.5%) in the mRNA-1283.222 and mRNA-1273.222 groups, respectively (mRNA-1283-P301 CSR, Table 14.1.4).
Chronic lung disease	In Study mRNA-1283-P301, participants had a medical history of asthma (9.0% and 9.2%), COPD (1.7% and 1.9%), emphysema (0.1% and 0.1%), bronchitis chronic (0.1% and 0.1%), asthma-chronic obstructive pulmonary disease overlap syndrome (0 and 0.02%), and chronic respiratory failure (0 and 0.02%) in the mRNA-1283.222 and mRNA-1273.222 groups, respectively (mRNA-1283-P301 CSR, Table 14.1.4).
Severe obesity (BMI ≥40 kg/m^2)	In Study mRNA-1283-P301, 451 (7.9%) participants in the mRNA-1283.222 group and 489 (8.6%) participants in the mRNA-1273.222 group had a BMI of ≥40 kg/m^2 (mRNA-1283-P301 CSR, Table 14.1.3.1).
HIV infection	No participants had a medical history of HIV infection in Study mRNA-1283-P301 (mRNA-1283-P301 CSR, Table 14.1.4).

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Experience

Not applicable.

SV.1.1 Method Used to Calculate Exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for Misuse for Illegal Purposes

Not applicable.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Important identified risks	None
Important potential risks	Myocarditis Pericarditis
Missing information	Use in pregnancy

In line with the EMA guidance document 'Consideration on core requirements for RMPs of COVID-19 vaccines' (CoreRMP19 guidance v3.1), the following items are presented for consideration for the generation of the safety specification but are determined not to be important identified risks or important potential risks.

Vaccine construct and formulation

Moderna has developed a proprietary vaccine platform based on an mRNA delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently.

Moderna used its mRNA-based platform to develop a LNP encapsulated mRNA-based vaccine for active immunisation to prevent COVID-19 caused by SARS-CoV-2 (SPIKEVAX™). The vaccine is updated seasonally to provide immunity to circulating variants. Myocarditis and pericarditis are important identified risks for currently approved COVID-19 vaccines. A leading hypothesis for the mechanism of myocarditis and/or pericarditis after SARS-CoV-2 vaccination is that these events are mediated by circulating Spike-S1 protein (Khan et al 2021; Stewart-Jones et al 2023; Yonker et al 2023). Currently approved COVID-19 mRNA vaccines encode the membrane-anchored, full-length spike protein of SARS-CoV-2, modified with 2 proline mutations to increase prefusion stabilisation. This spike protein includes a native furin cleavage site which can allow a portion of the S1 head domain of the translated Spike protein to cleave from the cell membrane on cells expressing the protein and enter circulation (Ogata et al 2021).

Myocarditis and pericarditis are considered important potential risks of mNEXSPIKE (Module SVII.1.2). However, it is anticipated that the improved mRNA design will decrease the risk of myocarditis and pericarditis. Indeed, mNEXSPIKE encodes the NTD and RBD subdomains of the spike protein, and as the furin cleavage site is not in these domains, little, if

any, of the mNEXSPIKE immunogen is expected to be released into systemic blood stream. Therefore, it is hypothesised that this limited quantity of circulating spike protein that can interact with heart tissue could mitigate the risk of myocarditis and/or pericarditis.

Degradation

The mRNA degradation products are not expected to represent functionally active mRNA molecules, are naturally metabolised, and are considered pharmacologically inactive.

Adjuvant statement

mNEXSPIKE vaccine does not contain an adjuvant.

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Adverse drug reactions are considered identified risks for mNEXSPIKE, but they do not qualify as important to be included in the list of safety concerns for the purpose of risk management planning.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Reactogenicity

  The safety profiles of mRNA-1283 and mRNA-1273 were generally similar across clinical studies. A single dose of mRNA-1283 10 µg was well tolerated. The overall safety profile across age groups (adolescents 12 to <18 years of age, adults 18 to 64 years of age, and adults ≥65 years of age) was consistent and no safety concerns were identified.

  The incidence of solicited local ARs with mRNA-1283 administered in a 0.2 mL volume was lower than mRNA-1273 (0.5mL) and the incidence of solicited systemic ARs was similar to mRNA-1273. The most frequently reported solicited local AR included injection site pain which was often mild (median duration 2 days); the most frequently reported solicited systemic ARs were headache and fatigue, which were also mild or moderate and resolved within 2 days (median). Systematic medical review of Investigator-reported (AESIs) and programmed SMQs/CMQ for AESI considered of relevance to COVID-19 vaccine studies did not identify any specific vaccine-associated risks for mRNA-1283. No deaths or discontinuations of vaccination were reported as related to mRNA-1283.

  The following reactogenicity events are identified risks not considered as important: lymphadenopathy, headache, nausea/vomiting, myalgia, arthralgia, injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site erythema, injection site pruritus, injections site bruising.

  Other risks not considered important: hypersensitivity reactions, hypoaesthesia, diarrhoea, rash.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each country where the product is authorised):

- Anaphylaxis

  Anaphylaxis is not an important risk of mNEXSPIKE.

  Any individual receiving a vaccine is at risk of anaphylaxis, with individuals with a known history of hypersensitivity to any component of the vaccine at increased risk of anaphylaxis. While anaphylaxis is a clinically important and potentially life-threatening reaction, anaphylaxis is not considered an important risk of mNEXSPIKE as it is adequately managed by healthcare professionals and has become fully integrated into standard clinical practice, such as inclusion into treatment protocols and clinical guidelines. Furthermore, anaphylaxis is considered to be fully characterised and the risk is not considered to have an impact on the benefit-risk balance of the vaccine. The SmPC advises close observation for at least 15 minutes following vaccination and no further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of the vaccine.

  Anaphylactic reactions are very rare. The observed reporting rate of anaphylaxis following administration of SPIKEVAX was 2.5 cases/million doses in the US VAERS (Shimabukuro et al 2021). In the EU, the reporting rate of anaphylaxis following SPIKEVAX was approximately 20 cases/million doses in the European EudraVigilance from week 52/2020 through week 31/2021 (Maltezou et al 2022).

  Anaphylaxis is an AESI in pivotal Study mRNA-1283-P301 and supportive Study mRNA-1283-P201 as it is a recognised immediate systemic allergic reaction that can occur after any injectable vaccine.

  In Study mRNA-1283-P301, up to 28 days after injection, 1 (0.02%) participant in the mRNA-1283.222 group had an event reported as anaphylactic reaction; no participants in the mRNA-1273.222 group experienced anaphylaxis (mRNA-1283-P301 CSR, Table 14.3.1.6.1.1). The Investigator considered this a possible case of delayed anaphylaxis due to symptoms involving 2 organ systems and meeting seriousness criteria of a medically important event and assessed the event as related to the study vaccine (mRNA-1283-P301 CSR, Section 7.3.2). Moderna assessed the reported events as “not a case of Anaphylaxis”, according to the Brighton Collaboration case definition for Anaphylaxis (Level 5 – not a case of Anaphylaxis) (Module 2.7.4, Section 2.7.4.3.1.6.4.1).

  Up to the data cutoff (23 Feb 2024), there were no other cases of anaphylaxis reported in either vaccine group (mRNA-1283-P301 CSR, Section 7.3.4.1.2).

  In Study mRNA-1283-P301-Japan, no cases of anaphylaxis were reported in either the mRNA-1283.815 or mRNA-1273.815 vaccine groups up to the data cutoff (02 May 2024) (mRNA 1283-P301-Japan CSR Addendum, Section 7.4).

In Study mRNA-1283-P201, no events of anaphylaxis were reported throughout the study (mRNA-1283-P201 CSR, Section 7.1.3.3; Section 7.2.3.5).

Likewise in Study mRNA-1283-P101, no events of anaphylaxis were reported throughout the study (mRNA-1283-P101 CSR, Section 7.3.5).

Anaphylaxis can be managed post-authorisation with the guidance as presented in the product information which contraindicates administration of mNEXSPIKE in individuals with known hypersensitivity to the active substance or to any of the excipients and through the availability of appropriate medical treatment and supervision to manage possible anaphylactic reactions following administration of the vaccine as recommended in the mNEXSPIKE SmPC. The SmPC advises close observation for at least 15 minutes following vaccination and no further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of the vaccine.

Anaphylaxis will continue to be monitored through routine pharmacovigilance activities (Part III.1).

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None

Known risks that do not impact the risk-benefit profile

None

Other reasons for considering the risks not important:

None

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Potential Risk 1: Myocarditis

Myocarditis is an important potential risk of mNEXSPIKE.

Analyses of postmarketing data from use of authorised or approved mRNA COVID-19 vaccines, have demonstrated increased risks of myocarditis and pericarditis, with onset of symptoms typically in the first week following vaccination. The observed risk has been highest in males 12 years through 24 years of age.

In Study mRNA-1283-P301 Part 1, there were no myocarditis events in either the mRNA-1283.222 or mRNA-1273.222 groups within 28 days post injection (mRNA-1283-P301 CSR, Table 14.3.1.6.1.1) or up to the data cutoff (23 Feb 2024) (mRNA-1283-P301 CSR, Table 14.3.1.6.1.2).

In Study mRNA-1283-P301-Japan, no events of myocarditis were reported in either the mRNA-1283.815 or mRNA-1273.815 vaccine groups up to the data cutoff (02 May 2024) (mRNA-1283-P301-Japan CSR Addendum, Section 7.4).

In Study mRNA-1283-P201 Part A, no events of myocarditis were observed throughout the study (mRNA-1283-P201 CSR, Section 7.1.3.5; Section 7.2.3.5).

Likewise in Study mRNA-1283-P101, no events of myocarditis were reported throughout the study (mRNA-1283-P101 CSR, Section 7.3.5).

A leading hypothesis for the mechanism of myocarditis and/or pericarditis after SARS-CoV-2 vaccination is that these events are mediated by circulating Spike-S1 protein (Khan et al 2021; Stewart-Jones et al 2023; Yonker et al 2023). Approved mRNA vaccines currently encode the membrane-anchored, full-length spike protein of SARS-CoV-2, modified with 2 proline mutations to increase prefusion stabilisation. This spike protein includes a native furin cleavage site which can allow a portion of the S1 head domain of the translated Spike protein to cleave from the cell membrane on cells expressing the protein and enter circulation (Ogata et al 2021). mNEXSPIKE mRNA encodes the NTD and RBD subdomains of the spike protein, and as the furin cleavage site is not in these domains, little, if any, of the mNEXSPIKE immunogen is expected to go into systemic circulation. Therefore, it is hypothesised that the limited quantity of circulating S1 spike protein that can interact with heart tissue could decrease the risk of myocarditis with mNEXSPIKE.

Based on the current available safety information, there is insufficient evidence at this time to confirm a temporal or causal association between myocarditis and mNEXSPIKE vaccination and therefore myocarditis is considered an important potential risk.

Risk-benefit impact:

Myocarditis is an under-diagnosed cardiac disease resulting from any one of a broad range of infectious, immune, and toxic causes. Most cases of myocarditis are caused by infectious agents, toxic substances, drugs or autoimmune disorders. Hence, it is increasingly recognised that myocarditis is an inflammatory condition of the myocardium triggered by various factors rather than a distinct cardiovascular disease. Infectious causes include viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa. Noninfectious triggers have been identified such as toxins, auto immunes disease and hypersensitive reactions. Numerous medications like antipsychotics (eg, clozapine), antibiotics (penicillin, ampicillin, sulfonamides, tetracyclines), and antiphlogistic (eg, mesalamine) can induce hypersensitivity eosinophilic myocarditis. Myocarditis has been reported following many different vaccines including flu vaccine, however the smallpox vaccine has the strongest association.

Myocarditis related to SARS-CoV-2 infection has been reported since the beginning of the pandemic.

Myocarditis and pericarditis are serious conditions that may occur concomitantly and that may range in clinical importance from mild to life-threatening.

The relative risk (RR) of myocarditis is over 7 times higher in individuals with SARS-CoV-2 infection (RR: 15.0; 95% CI: 11.09–19.81) compared to those who received mRNA COVID-19 vaccines (RR: 2.0; 95% CI: 1.44–2.65). The prevalence of cardiac complications in adults after being diagnosed with COVID-19, included heart failure (23%–33.3%), myocardial injury/myocarditis (8%–27.8%), arrhythmia (16.7%), and thromboembolism (31%–40%), which are substantially more severe than with COVID-19 vaccine associated myocarditis (Woo et al 2022). Post-marketing data with authorised or approved mRNA COVID-19 vaccines, have

demonstrated increased risks of myocarditis and pericarditis as a very rare event (frequency <1 event per 10,000 doses administered), with onset of symptoms typically in the first week following vaccination, especially after a second dose of the vaccine. The observed risk is higher in males 12 years through 24 years of age, with an estimated unadjusted incidence of myocarditis and/or pericarditis during the period of 1 through 7 days of approximately 25 cases per million doses in this age group. These events are generally mild, and often self-limiting, with resolution of symptoms within a few days with conservative management. However, underlying pathogenesis and risk factors for myocarditis and pericarditis are not well understood (Bularga et al 2023).

While an increased risk of myocarditis has been observed following vaccination with some other COVID-19 vaccines, no events of myocarditis have been observed in the clinical studies to date with mNEXSPIKE. The benefit of mNEXSPIKE as a preventive vaccine for COVID-19 caused by SARS-CoV-2 is considered to outweigh the important potential risk of myocarditis, that has yet to be confirmed in individuals vaccinated with mNEXSPIKE.

mNEXSPIKE SmPC advises healthcare professionals of the increased risk of myocarditis and pericarditis following vaccination with some other COVID-19 vaccines and states that these conditions can develop within a few days, primarily occur within 14 days, and have been observed more often in younger males. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccine recipients (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.

Myocarditis will be further characterised through 3 planned post-authorisation safety studies, mRNA-1283-P901, mRNA-1283-P904, and mRNA-1283-P906, as well as routine pharmacovigilance activities (Part III).

Important Potential Risk 2: Pericarditis

Pericarditis is an important potential risk of mNEXSPIKE.

The occurrence of pericarditis following COVID-19 mRNA vaccines is very rare (Ling et al 2022), with higher incidence rates in young males and within a short risk window (7 days) after the second dose (Yasuhara et al 2023; Knudsen and Prasad 2022).

In Study mRNA-1283-P301 Part 1, there were no pericarditis events in either the mRNA-1283.222 or mRNA-1273.222 groups within 28 days post injection (mRNA-1283-P301 CSR, Table 14.3.1.6.1.1). Up to the data cutoff (23 February 2024), 1 event of suspected pericarditis was reported in the mRNA-1273.222 group that occurred on Day 136; the case was adjudicated as “not a Charter-defined event” (not pericarditis) by the independent CEAC and assessed as not related to study injection by the Investigator and Moderna (Module 2.7.4, Section 2.7.4.3.1.6.6.1.1). No pericarditis events were observed in the mRNA-1283.222 group (mRNA-1283-P301 CSR, Table 14.3.1.6.1.2).

In Study mRNA-1283-P301-Japan, no events of pericarditis were reported in either the mRNA-1283.815 or mRNA-1273.815 vaccine groups up to the data cutoff (02 May 2024) (mRNA-1283-P301-Japan CSR Addendum, Section 7.4).

In Study mRNA-1283-P201, no events of pericarditis were observed throughout the study (mRNA-1283-P201 CSR, Section 7.1.3.5; Section 7.2.3.5).

Likewise in Study mRNA-1283-P101, no events of pericarditis were reported throughout the study (mRNA-1283-P101 CSR, Section 7.3.5).

A leading hypothesis for the mechanism of myocarditis and/or pericarditis after SARS-CoV-2 vaccination is that these events are mediated by circulating Spike-S1 protein (Khan et al 2021; Stewart-Jones et al 2023; Yonker et al 2023). Approved mRNA vaccines currently encode the membrane-anchored, full-length spike protein of SARS-CoV-2, modified with 2 proline mutations to increase prefusion stabilisation. This spike protein includes a native furin cleavage site which can allow a portion of the S1 head domain of the translated Spike protein to cleave from the cell membrane on cells expressing the protein and enter circulation (Ogata et al 2021). mNEXSPIKE mRNA encodes the NTD and RBD subdomains of the spike protein, and as the furin cleavage site is not in these domains, little, if any, of the mNEXSPIKE immunogen is expected to go into systemic circulation. Therefore, it is hypothesised that the limited quantity of circulating S1 spike protein that can interact with heart tissue could decrease the risk of pericarditis with mNEXSPIKE.

Based on the current data there is insufficient evidence at this time to confirm a temporal or causal association between pericarditis and mNEXSPIKE vaccination and therefore pericarditis is considered an important potential risk.

Risk-benefit impact:

Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterised by chest pain, pericardial friction rub, changes in the ECG and occasionally, a pericardial effusion. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases and other common causes include infection, renal failure, myocardial infarction, post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women and it more commonly affects adults aged 50 years and older than the younger population.

Myocarditis and pericarditis are serious conditions that may occur concomitantly and that may range in clinical importance from mild to life-threatening.

While an increased risk of pericarditis has been observed following vaccination with some other COVID-19 vaccines, no events of pericarditis have been observed in the clinical studies to date with mNEXSPIKE. The benefit of mNEXSPIKE as a preventive vaccine for COVID-19 caused by SARS-CoV-2 is considered to outweigh the important potential risk of pericarditis, that has yet to be confirmed in individuals vaccinated with mNEXSPIKE.

mNEXSPIKE SmPC advises healthcare professionals of the increased risk of myocarditis and pericarditis following vaccination with some other COVID-19 vaccines and states that these conditions can develop within a few days, primarily occur within 14 days, and have been observed more often in younger males. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccine recipients (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.

Pericarditis will be further characterised through 2 planned post-authorisation safety studies, mRNA-1283-P901 and mRNA-1283-P906, and routine pharmacovigilance activities (Part III).

Missing information 1: Use in pregnancy

The intended target population for mNEXSPIKE covers women of childbearing potential. However, the clinical development programme has not evaluated mNEXSPIKE exposure during pregnancy.

In Study mRNA-1283-P301, female participants of childbearing potential were required to practice adequate contraception for ≥28 days prior to baseline visit, have a negative pregnancy test prior to vaccination, and were to continue contraception for 90 days following vaccine administration (mRNA 1283-P301 CSR, Section 3.3.1).

In this study, up to the data cutoff (23 Feb 2024), 10 participants had reported pregnancies, 3 participants in the mRNA-1283.222 vaccine group and 7 participants in the mRNA-1273.222 vaccine group (Module 2.7.4, Section 2.7.4.6.4). In the mRNA-1283.222 vaccine group all 3 pregnancies were pending the final outcome. Of the 7 pregnancies in the mRNA-1273.222 vaccine group, 3 resulted in term births without complications, 1 participant had an induced abortion on Day 37, and the final outcomes for the 3 remaining pregnancies had not yet been reported.

In Study mRNA-1283-P301-Japan, no participants had reported pregnancies in either the mRNA-1283.815 or mRNA-1273.815 vaccine groups up to the data cutoff (02 May 2024) (mRNA-1283-P301-Japan CSR Addendum, Section 7.6.2).

Similar inclusion criteria applied for female participants of childbearing potential in Study mRNA-1283-P201 (mRNA-1283-P201 CSR, Section 3.3.1). No pregnancies were reported throughout the study in Part A (mRNA-1283-P201 CSR, Section 7.1.4.1). In Part B, 2 pregnancies occurred after 10 µg mRNA-1283.529 exposure (beyond 28 days after mRNA-1283 vaccination; Day 113 and Day 233) with 1 pregnancy reporting a full-term birth without complications for the mother and the child, and small for gestational age; the outcome of the other pregnancy is not yet known (Module 2.7.4, Section 2.7.4.6.4).

In Study mRNA-1283-P101, no pregnancies were reported during the study (mRNA-1283-P101 CSR, Section 7.4.1).

A GLP reproduction and peri/post-natal developmental study in rats administered mRNA-1283 did not suggest a specific risk (Module SII). Regarding the NOAEL for female reproduction and peri/post-natal development in rats (80 µg/dose, or 266.7 µg/kg based on a 0.3 kg rat), the safety margin is nearly 1600-fold compared to the human dose (10 µg/dose and assuming a conservative human body weight estimate of 60 kg or 0.17 µg/kg).

As exposure to mNEXSPIKE during pregnancy is limited and as use in this population is anticipated since COVID-19 vaccines have been recommended and included in the corresponding product information, use in pregnancy is proposed as missing information.

Risk-benefit impact:

Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during pregnancy to prevent severe COVID-19 disease and related complications in

this population (WHO 2021, Berman 2022). The benefit of mNEXSPIKE as a preventive vaccine for COVID-19 caused by SARS-CoV-2 is considered to outweigh any risks associated with use during pregnancy, an area of missing information that has yet to be characterised in humans.

mNEXSPIKE SmPC advises healthcare professionals that there are no or limited data (less than 300 pregnancy outcomes) from the use of mNEXSPIKE in pregnant women and that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. The SmPC advises, as a precautionary measure, it is preferable to avoid the use of mNEXSPIKE during pregnancy.

Use in pregnancy is considered missing information and will be further characterised through planned post-authorisation safety study mRNA-1283-P902 and routine pharmacovigilance activities (Part III.1).

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table SVII.3.1: Presentation of Important Potential Risks

Important Potential Risk	**Myocarditis**
Potential mechanism	Myocarditis is an inflammatory condition of the myocardium triggered by various factors including infectious agents, toxic substances, drugs or autoimmune disorders rather than a distinct cardiovascular disease. The most common aetiology of myocarditis is viral infections, accounting for 50-70% of all cases (Baral et al 2020). Myocarditis has previously been reported following vaccines including smallpox vaccine (Halsell et al 2003). The occurrence of myocarditis/pericarditis following COVID-19 mRNA vaccines was very rare (Ling et al 2022), with higher incidence rates in young males and within a short risk window (7 days) after the second dose (Yasuhara et al 2023; Knudsen and Prasad 2022). A leading hypothesis for the mechanism of myocarditis and/or pericarditis after SARS-CoV-2 vaccination is that these events are mediated by circulating Spike-S1 protein (Khan et al 2021; Stewart-Jones et al 2023; Yonker et al 2023). Approved COVID-19 mRNA vaccines currently encode the membrane-anchored, full-length spike protein of SARS-CoV-2, modified with 2 proline mutations to increase prefusion stabilisation. This spike protein includes a native furin cleavage site which can allow a portion of the S1 head domain of the translated Spike protein to cleave from the cell membrane on cells expressing the protein and enter circulation (Ogata et al 2021). mNEXSPIKE mRNA encodes the NTD and RBD subdomains of the spike protein, and as the furin cleavage site is not in these domains, little, if any, of the mNEXSPIKE immunogen is expected to go into systemic circulation. Therefore, it is hypothesised that the limited quantity of circulating spike protein that can interact with heart tissue could decrease the risk of myocarditis with mNEXSPIKE.

Important Potential Risk	**Myocarditis**
Evidence source and strength of evidence	Myocarditis can be caused by a variety of factors; the most common aetiology is viral infection. Myocarditis has not been causally associated with mNEXSPIKE and the risk is anticipated to be lower than approved COVID-19 vaccines as it does not include the furin cleavage site, potentially eliminating circulating spike protein antigen that may interact with heart tissue. In Study mRNA-1283-P301, there were no myocarditis events in either mRNA-1283 or mRNA-1273 vaccinated participants up to the data cutoff (23 Feb 2024). In Study mRNA-1283-P301-Japan, no events of myocarditis were reported in either vaccine group up to the data cutoff (02 May 2024). Likewise in studies mRNA-1283-P201 and mRNA-1283-P101, no events of myocarditis were observed throughout the studies.
Characterisation of risk	In Study mRNA-1283-P301, there were no myocarditis events in either the mRNA-1283.222 (N=5706) or mRNA-1273.222 (N=5711) groups within 28 days post injection (mRNA-1283-P301 CSR, Table 14.3.1.6.1.1) or up to the data cutoff (23 Feb 2024) (mRNA-1283-P301 CSR, Table 14.3.1.6.1.2). In Study mRNA-1283-P301-Japan, no events of myocarditis were reported in either the mRNA-1283.815 or mRNA-1273.815 vaccine groups up to the data cutoff (02 May 2024) (mRNA-1283-P301-Japan CSR Addendum, Section 7.4). In Study mRNA-1283-P201 Part A, no events of myocarditis were observed in any of the mRNA-1283, mRNA-1283.211, or mRNA-1273 groups throughout the study (mRNA-1283-P201 CSR, Section 7.1.3.5). Likewise in Part B of the study, there were no myocarditis events in either the 5 µg or 10 µg mRNA-1283.529 groups throughout the study (mRNA 1283-P201 CSR, Section 7.2.3.5). In Study mRNA-1283-P101, no events of myocarditis were reported throughout the study (mRNA-1283-P101 CSR, Section 7.3.5).
Risk factors and risk groups	Acute myocarditis is overall more common in men than in women (Kytö et al 2013). The incidence rate occurs with 2 peaks: the highest in those under one year old with both genders combined (Vasudeva et al 2021) and young males aged 16 to <40 years old (Vasudeva et al 2021; Kytö et al 2013).
Preventability	Myocarditis presents with a spectrum of symptoms ranging from mild dyspnoea or chest pain that spontaneously resolves without treatment to cardiogenic shock and sudden death. The major long-term consequence is DCM with chronic heart failure. Common viral infections are the most frequent cause of myocarditis, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated (Blauwet and Cooper 2010). Myocarditis has not been causally associated with mNEXSPIKE. mNEXSPIKE SmPC advises healthcare professionals that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines. Typically, these conditions develop in the first week following vaccination, especially after a second dose of the vaccine. The observed risk is highest in males 12 years through 24 years of age, with an estimated unadjusted incidence of myocarditis and/or pericarditis during the period of 1 through 7 days of approximately 25 cases per million doses in this age group. These events are generally mild, and often self-limiting, with resolution of symptoms within a few days with conservative management; however, underlying pathogenesis and risk factors for myocarditis and pericarditis are not well understood (Bularga et al 2023). Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccine recipients (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis. No cases of vaccine-related myocarditis or pericarditis have been reported in clinical studies of mNEXSPIKE.
Impact on the benefit-risk balance of the product	The benefit of mNEXSPIKE (prevention of COVID-19 disease and associated hospitalisations, ICU admissions, and deaths) as a preventive vaccine for COVID-19 caused by SARS-CoV-2 outweigh the risk of myocarditis, a risk for which a causal association with mNEXSPIKE has not been established.
Public health impact	The potential impact on public health is expected to be low since myocarditis is a very rare reaction that has yet to be confirmed as causally associated with mNEXSPIKE. Although the potential clinical consequence of myocarditis is serious, this adverse effect, should it occur, can be managed with supportive treatment.

Important Potential Risk	**Pericarditis**
Potential mechanism	Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterised by chest pain, pericardial friction rub, changes in the ECG and occasionally, a pericardial effusion. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases and other common causes include infection, renal failure, myocardial infarction, post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women and it more commonly affects adults aged 50 years and older than the younger population. The occurrence of myocarditis/pericarditis following COVID-19 mRNA vaccines was very rare (Ling et al 2022), with higher incidence rates in young males and within a short risk window (7 days) after the second dose (Yasuhara et al 2023; Knudsen and Prasad 2022). A leading hypothesis for the mechanism of myocarditis and/or pericarditis after SARS-CoV-2 vaccination is that these events are mediated by circulating Spike-S1 protein (Khan et al 2021; Stewart-Jones et al 2023; Yonker et al 2023). Approved COVID-19 mRNA vaccines currently encode the membrane-anchored, full-length spike protein of SARS-CoV-2, modified with 2 proline mutations to increase prefusion stabilisation. This spike protein includes a native furin cleavage site which can allow a portion of the S1 head domain of the translated Spike protein to cleave from the cell membrane on cells expressing the protein and enter circulation (Ogata et al 2021). mNEXSPIKE mRNA encodes the NTD and RBD subdomains of the spike protein, and as the furin cleavage site is not in these domains, little, if any, of the mNEXSPIKE immunogen is expected to go into systemic circulation. Therefore, it is hypothesised that the limited quantity of circulating spike protein that can interact with heart tissue could decrease the risk of pericarditis with mNEXSPIKE.
Evidence source and strength of evidence	Pericarditis can be caused by a variety of factors; the most common aetiology is viral infection. Pericarditis has not been causally associated with mNEXSPIKE and the risk is anticipated to be lower than approved COVID-19 vaccines as it does not include the furin cleavage site, potentially eliminating circulating spike protein antigen that may interact with heart tissue. In Study mRNA-1283-P301, there were no pericarditis events in either mRNA-1283 or mRNA-1273 vaccinated participants within 28 days post injection. Up to the data cutoff (23 Feb 2024), 1 event of suspected pericarditis was reported in the mRNA-1273 group that was assessed as not related to study injection; no pericarditis events were observed in the mRNA-1283 group. In Study mRNA-1283-P301-Japan, no events of pericarditis were reported in either vaccine group up to the data cutoff (02 May 2024). In studies mRNA-1283-P201 and mRNA-1283-P101, no events of pericarditis were observed throughout the studies.
Characterisation of risk	In Study mRNA-1283-P301, there were no pericarditis events in either the mRNA-1283.222 (N=5706) or mRNA-1273.222 (N=5711) groups within 28 days post injection (mRNA-1283-P301 CSR, Table 14.3.1.6.1.1). Up to the data cutoff (23 Feb 2024), 1 event of suspected pericarditis was reported in the mRNA-1273.222 group that occurred on Day 136; the case was adjudicated as "not a Charter-defined event" (not pericarditis) by the independent CEAC and assessed as not related to study injection by the Investigator and Moderna (Module 2.7.4, Section 2.7.4.3.1.6.6.1.1). No pericarditis events were observed in the mRNA-1283.222 group up to the data cutoff (23 Feb 2024) (mRNA-1283-P301 CSR, Table 14.3.1.6.1.2). In Study mRNA-1283-P301-Japan, no events of pericarditis were reported in either the mRNA-1283.815 or mRNA-1273.815 vaccine groups up to the data cutoff (02 May 2024) (mRNA-1283-P301-Japan CSR Addendum, Section 7.4). In Study mRNA-1283-P201, no events of pericarditis were reported in any of the mRNA-1283, mRNA-1283.211, or mRNA-1273 groups throughout the study in Part A (mRNA-1283-P201 CSR, Section 7.1.3.5). Likewise in Part B of the study, no pericarditis events were reported in either the 5 µg or 10 µg mRNA-1283.529 groups throughout the study (mRNA-1283-P201 CSR, Section 7.2.3.5). In Study mRNA-1283-P101, no events of pericarditis were reported throughout the study (mRNA-1283-P101 CSR, Section 7.3.5).
Risk factors and risk groups	Acute pericarditis is overall more common in men than in women. However, the gender difference is reduced with advancing age and became nominal in persons aged >65 years (Kytö et al 2014). In males, the incidence rate of acute pericarditis declines between 16 to 45 years followed by an increase in older individuals aged >50 years (Kytö et al 2014). In females, the incidence rate of acute pericarditis gradually increases with age, with a peak in the population aged 65 to 74 years (Kytö et al 2014; Kumar et al 2016).

Important Potential Risk	**Pericarditis**
Preventability	Pericarditis may be caused by many disorders (eg, infection, myocardial infarction, trauma, tumours, metabolic disorders) but is often idiopathic. Symptoms include chest pain or tightness, often worsened by deep breathing. Cardiac output may be greatly reduced if cardiac tamponade or constrictive pericarditis develops. Diagnosis is based on symptoms, a friction rub, electrocardiographic changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram (Hoit 2022). Pericarditis may result in one of two serious complications: cardiac tamponade and chronic constrictive pericarditis. Cardiac tamponade is considered a medical emergency and, if left untreated, can quickly become fatal. Pericarditis has not been causally associated with mNEXSPIKE but can be managed in clinical practice with supportive treatment should it occur. mNEXSPIKE SmPC advises healthcare professionals that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines. Typically, these conditions develop in the first week following vaccination, especially after a second dose of the vaccine. The observed risk is highest in males 12 years through 24 years of age, with an estimated unadjusted incidence of myocarditis and/or pericarditis during the period of 1 through 7 days of approximately 25 cases per million doses in this age group. These events are generally mild, and often self-limiting, with resolution of symptoms within a few days with conservative management; however, underlying pathogenesis and risk factors for myocarditis and pericarditis are not well understood (Bularga et al 2023). Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccine recipients (including patients or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis. No cases of vaccine-related myocarditis or pericarditis have been reported in clinical studies of mNEXSPIKE.
Impact on the benefit-risk balance of the product	The benefit of mNEXSPIKE (prevention of COVID-19 disease and associated hospitalisations, ICU admissions, and deaths) as a preventive vaccine for COVID-19 caused by SARS-CoV-2 is considered to outweigh the risk of pericarditis, a risk for which a causal association with mNEXSPIKE has not been established.
Public health impact	The potential impact on public health is expected to be low since pericarditis is a very rare reaction that has yet to be confirmed as causally associated with mNEXSPIKE. Although the potential clinical consequence of pericarditis is serious, this adverse effect, should it occur, can be managed with supportive treatment.

SVII.3.2 Presentation of the Missing Information

Table SVII.3.2: Presentation of Missing Information

Missing Information	Use in pregnancy
Evidence source	Exposure data in pregnancy are limited. In Study mRNA-1283-P301, female participants of childbearing potential female participants of childbearing potential were required to practice adequate contraception for ≥28 days prior to baseline visit, have a negative pregnancy test prior to vaccination, and were to continue contraception for 90 days following vaccine administration (mRNA-1283-P301 CSR, Section 3.3.1). In this study, up to the data cutoff (23 Feb 2024), 10 participants had reported pregnancies, 3 participants in the mRNA-1283.222 vaccine group and 7 participants in the mRNA-1273.222 vaccine group (Module 2.7.4, Section 2.7.4.6.4). In the mRNA-1283.222 vaccine group all 3 pregnancies were pending the final outcome. Of the 7 pregnancies in the mRNA-1273.222 vaccine group, 3 resulted in term births without complications, 1 participant had an induced abortion on Day 37, and the final outcomes for the 3 remaining pregnancies had not yet been reported. In Study mRNA-1283-P301-Japan, no participants had reported pregnancies in either the mRNA-1283.815 or mRNA-1273.815 vaccine groups up to the data cutoff (02 May 2024) (mRNA-1283-P301-Japan CSR Addendum, Section 7.6.2). Similar inclusion criteria applied for female participants of childbearing potential in Study mRNA-1283-P201 (mRNA-1283-P201 CSR, Section 3.3.1). No pregnancies were reported throughout the study in Part A (mRNA-1283-P201 CSR, Section 7.1.4.1). In Part B, 2 pregnancies occurred after 10 µg mRNA-1283.529 exposure (beyond 28 days after mRNA-1283 vaccination; Day 113 and Day 233) with 1 pregnancy reporting a full-term birth without complications for the mother and the child, and small for gestational age; the outcome of the other pregnancy is not yet known (Module 2.7.4, Section 2.7.4.6.4). In Study mRNA-1283-P101, no pregnancies were reported during the study (mRNA-1283-P101 CSR, Section 7.4.1). A GLP reproduction and peri/post-natal developmental study in rats administered mRNA-1283 did not suggest a specific risk (Module SII). Regarding the NOAEL for female reproduction and peri/post-natal development in rats (80 µg/dose, or 266.7 µg/kg based on a 0.3 kg rat), the safety margin is nearly 1600-fold compared to the human dose (10 µg/dose and assuming a conservative human body weight estimate of 60 kg or 0.17 µg/kg).
Anticipated risk/consequence of the missing information	Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during pregnancy to prevent severe COVID-19 disease and related complications (WHO 2021, Berman 2022). It is not expected that the safety profile of mNEXSPIKE to be different regarding its use in pregnant women than the observed safety profile for all COVID-19 vaccines, including approved mRNA COVID-19 vaccines. Overall, exposure of mNEXSPIKE during pregnancy is not expected to cause maternal or foetal harm. An in vivo study found no adverse effects on reproduction or peri/post-natal development in pups following IM injection of 80 µg/dose mRNA-1283 to female rats (Module SII). mNEXSPIKE SmPC advises healthcare professionals that there are no or limited amount of data (less than 300 pregnancy outcomes) from the use of mNEXSPIKE in pregnant women and that animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of mNEXSPIKE during pregnancy.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Myocarditis Pericarditis
Missing information	Use in pregnancy

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Moderna has an established signal management process including signal detection, validation and evaluation of spontaneous reports from all sources, which follows the principle of the Guideline on Good Pharmacovigilance Practices (GVP) Module IX for Signal Management (GVP Module IX – Signal Management (Rev.1)). During signal detection, data sources will be screened for new safety information related to mNEXSPIKE. Following initial review of the available data, a determination will be 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". Potential signals may be identified from any data source including, but not limited to, safety data from Moderna-sponsored clinical trials and noninterventional studies, spontaneous AE reports, published literature, regulatory safety surveillance databases (eg, Eudravigilance, VAERS) and communications from external sources, including regulatory agencies, and (if applicable) business partners. As part of the Moderna's routine pharmacovigilance activities, Moderna performs periodic signal detection analyses, in line with the product's Signaling Strategy Plan. These analyses include but not limited to safety concerns, Adverse Events of Special Interest (AESIs), and missing information. The following data sources are routinely reviewed: Moderna global PV database (Argus platform) using a defined signal detection methodology (both qualitative and quantitative aggregated analyses), signals of disproportionate reporting from regulatory databases (eg, Eudravigilance, VAERS), published literature that involves targeted keyword searches in widely recognised databases (ie, MEDLINE, EMBASE), health authority websites screening, review of publicly available competitors' labels, as well as social media.

Moderna employs routine pharmacovigilance consistent with that described in the ICH E2F Pharmacovigilance Planning Guideline. Moderna's standard processes and systems for collecting and recording information about all events potentially related to drug/ product safety, and for expedited and periodic reporting are in compliance with current local regulations and defined in globally applied Moderna Standard Operating Procedures.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires

None.

AESIs

For pharmacovigilance activities and to further characterise the safety of mNEXSPIKE, Moderna will search the Global Safety Database and clinical studies for AESIs prepared by the following regulatory agencies and vaccine expert groups:

- Brighton Collaboration (SPEAC 2024)
- ACCESS protocol (Willame et al 2021)
- CBER Surveillance Program - List of Adverse Events of Special Interest (CBER 2021)

Standard case definitions from the Brighton Collaboration are used to classify AESIs by level of diagnostic certainty. The data sources, type and frequency of the signal detection analyses are summarised in Table Part III.1.

Table Part III.1: Signal Data Sources and Frequency of Evaluations

Data Source	Frequency of Safety Evaluations
Company global safety database	Ongoing monitoring of ICSRs from all sources, safety concerns, and AESI. Weekly aggregated review of ICSRs for trend analyses. Review of disproportionate reporting of preferred terms during a time interval as compared to all data prior to the reporting period for mNEXSPIKE. Review of endpoints of interest (ie, case counts, demographics, country of origin, time to onset, seriousness, batch numbers, fatalities, AEs from the product surveillance list of safety topics and based on MedDRA system organ class and high-level term, and identification of potential clusters of ICSRs).
Literature	Weekly literature review. Any literature abstract or article signal detection run will be reviewed.
EudraVigilance	Continuous monitoring. Biweekly critical review of the EudraVigilance data analysis system using available reports (ie, Electronic Reaction Monitoring Reports and active substance groupings, ICSR line listings and ICSR forms).
VAERS	Frequency of review will depend on public availability of redacted VAERS extracts. Current estimates based on public communication as well as processing time indicate this frequency will range between every two to four weeks. Generation of disproportionality scores using Empirical Bayesian Geometrical Mean and its 90% confidence intervals after new uploads of Vaccine Adverse Event Reporting System extracts in Empirica Signal.
Health Authorities websites	Ongoing review of data published on the Safety Web Portals of selected major regulatory agencies to identify required actions regarding the product and similar products.

Product surveillance to identify safety signals will occur for any reported AEs including reactogenicity. Safety surveillance prioritisation is for the safety concerns of the RMP, AESIs, or those AEs that may be serious or known to be often vaccine related.

If any cluster of events is detected which points towards an unexpected event/syndrome, Moderna will perform appropriate signal evaluation and will provide this information to the appropriate regulatory agencies.

Table Part III.2: Product Surveillance List of Signalling Strategy by Category

Category	Safety Topics (Updates may be Needed if New Adverse Events Emerge)
Safety concerns	Myocarditis Pericarditis Use in pregnancy
Adverse events of special interest (AESI)	List of AESIs (AESIs will be updated as new information arises): Brighton Collaboration (Safety Platform for Emergency vACcines) ACCESS protocol US Centers for Disease Control and Prevention (preliminary list of AESI for VAERS surveillance)
Standard safety topics	Off-label Use Overdose

Category	Safety Topics (Updates may be Needed if New Adverse Events Emerge)
	Vaccination Administration Errors Product Quality Issues Drug-Drug Interactions Death Paediatric Use Geriatric Use Designated Medical Events (EMA/326038/2020)

Other forms of routine pharmacovigilance activities

Observed-To-Expected Analyses

Using background rates from the scientific literature and/or other sources (Willame et al 2021), observed rates of AEs, when relevant, will be compared with expected rates in order to support signal validation and/or signal evaluation analysis.

Reporting to EMA

Valid ICSRs that fulfil the local regulatory requirements for submission to the EudraVigilance database will be submitted within the 15- or 90-day time frame. This includes any COVID-19 cases requiring hospitalisation, vaccination administration errors, and MIS that may have been reported to occur in vaccinees.

Potential medication errors

Potential medication errors are very limited and mitigated through the guidance in the mNEXSPIKE SmPC.

Traceability

mNEXSPIKE SmPC includes instructions for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability.

A Datamatrix will be printed on the carton of the vaccine. Per country guideline, it is encoding specific Application Identifiers (for example AI(01) GTIN, AI(21) Serial Number, AI (10) for Lot and AI(17) for Expiry Date). In addition, Moderna provides single or double peel-off stickers on the PFS in the countries where this is required.

III.2 Additional Pharmacovigilance Activities

Table Part III.3: Additional Pharmacovigilance Activities

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population	Milestones
mRNA-1283-P901 US	Post-marketing safety of the mRNA-1283 vaccine in the United States Planned	Primary Objectives: • Estimate the incidence of myocarditis and pericarditis among recipients of mRNA1283 and among individuals who have not received the prior seasonal formulation of COVID-19 vaccine within the past 90 days or the same seasonal formulation previously • Compare the risk of myocarditis and pericarditis among the recipients of mRNA-1283 with the risk among individuals who have not received the prior seasonal formulation of COVID-19 vaccine within the past 90 days or the same seasonal formulation previously	A retrospective US cohort study to actively monitor safety outcomes following administration of mRNA-1283 among individuals enrolled in commercial and Medicare claims databases. The study will descriptively monitor the utilisation of mRNA-1283 and inferentially assess the risk of myocarditis, pericarditis and other safety topics of interest in recipients of these vaccines.	Exposed persons are defined as those who receive mRNA-1283 in routine clinical practice. The comparator cohort will consist of both inactive and active comparators, which will be selected based on vaccine coadministration status and the specific vaccine(s) that are co-administered with mRNA-1283.	Protocol submission: 31 Mar 2026 Final report: 30 Sep 2029

Study Number **Country(ies)**	**Study Title** **Study Type** **Study Status**	**Rationale and Study Objectives**	**Study Design**	**Study Population**	**Milestones**
mRNA-1283-P902 US	An observational cohort study to assess maternal and infant outcomes following exposure to mRNA-1283 during pregnancy Planned	Primary Objectives: • Describe the utilisation of the mRNA-1283 vaccine in routine clinical practice and estimate incidence rates of pregnancy complications (gestational hypertensive disorders and gestational diabetes), adverse pregnancy outcomes (medically attended spontaneous abortion, stillbirth, and preterm birth), and infant major congenital malformations among mRNA-1283 vaccine recipients using large-scale administrative claims data in the US. • Upon accrual of a sufficient number of exposed pregnancies: o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of pregnancy complications. o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of adverse pregnancy outcomes. o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased prevalence of infant MCM.	This is a staged observational cohort study to assess mRNA-1283 exposure, pregnancy complications, adverse pregnancy outcomes, and infant outcomes, utilising a large US administrative database.	This study will include pregnancies among women aged 12-50 years without receipt of COVID-19 vaccine(s) in the 90 days before pregnancy until cohort entry. Mothers and infants will be linked via a common identifier and date of birth event.	Final report: 15 Dec 2032

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population	Milestones
mRNA-1283-P904 US	Long-term outcomes of myocarditis following administration of the mRNA-1283 vaccine Planned	Primary Objectives: • Characterise the presentation and clinical course of vaccine-associated myocarditis • Characterise potential long-term outcomes following vaccine-associated myocarditis	This retrospective observational cohort study will follow patients with myocarditis for at least 5 years to assess long-term outcomes of mRNA-1283-associated myocarditis versus non-vaccine-associated myocarditis	Individuals with myocarditis within 30 days after a mRNA-1283 vaccine administration will comprise the exposed cohort. The primary comparison group will consist of contemporaneous age and sex matched patients with myocarditis who have not received a COVID-19 vaccination within 30 days prior to the event.	Final report: 31 Mar 2034
mRNA-1283-P906 EU	Post-marketing safety of the mRNA-1283 vaccine in Europe Planned	Primary Objectives: • Monitor the distribution of mRNA-1283 in Europe. • Describe the uptake of mRNA-1283, characterise vaccine recipients, and estimate the incidence of myocarditis and pericarditis among them. • Compare the risk of myocarditis and pericarditis among the recipients of mRNA-1283 with the risk among individuals who have not received a COVID-19 vaccine within the past 90 days.	This is a staged retrospective cohort study to actively monitor safety outcomes following the administration of mRNA-1283 using real-world healthcare data in Europe.	Exposed cohort will consist of individuals who receive mRNA-1283 in routine clinical practice, and the index date will be the date of vaccination. Comparator cohort will consist of both inactive and active comparators, which will be selected based on vaccine coadministration status and the specific vaccine(s) co-administered.	Final report: 30 Sep 2030

Abbreviations: COVID-19 = coronavirus disease 2019; MCM = major congenital malformation; mRNA = messenger ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; EU = European Union; US = United States.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.4: Ongoing and Planned Additional Pharmacovigilance Activities

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
mRNA-1283-P901 Post-marketing safety of the mRNA-1283 vaccine in the United States (Planned)	Primary Objectives: • Estimate the incidence of myocarditis and pericarditis among recipients of mRNA-1283 and among individuals who have not received the prior seasonal formulation of COVID-19 vaccine within the past 90 days or the same seasonal formulation previously • Compare the risk of myocarditis and pericarditis among the recipients of mRNA-1283 with the risk among individuals who have not received the prior seasonal formulation of COVID-19 vaccine within the past 90 days or the same seasonal formulation previously	Myocarditis Pericarditis	Protocol submission: Final report:	31 Mar 2026 30 Sep 2029

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
mRNA-1283-P902 An observational cohort study to assess maternal and infant outcomes following exposure to mRNA-1283 during pregnancy (Planned)	Primary Objectives: • Describe the utilisation of the mRNA-1283 vaccine in routine clinical practice and estimate incidence rates of pregnancy complications (gestational hypertensive disorders and gestational diabetes), adverse pregnancy outcomes (medically attended spontaneous abortion, stillbirth, and preterm birth), and infant major congenital malformations among mRNA-1283 vaccine recipients using large-scale administrative claims data in the US. • Upon accrual of a sufficient number of exposed pregnancies: o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of pregnancy complications. o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of adverse pregnancy outcomes. o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased prevalence of infant MCM.	Use in pregnancy	Final report:	15 Dec 2032

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
mRNA-1283-P904 Long-term outcomes of myocarditis following administration of the mRNA-1283 vaccine (Planned)	Primary Objectives: • Characterise the presentation and clinical course of vaccine-associated myocarditis • Characterise potential long-term outcomes following vaccine-associated myocarditis	Myocarditis	Final report:	31 Mar 2034
mRNA-1283-P906 Post-marketing safety of the mRNA-1283 vaccine in Europe (Planned)	Primary Objectives: • Monitor the distribution of mRNA-1283 in Europe. • Describe the uptake of mRNA-1283, characterise vaccine recipients, and estimate the incidence of myocarditis and pericarditis among them. • Compare the risk of myocarditis and pericarditis among the recipients of mRNA-1283 with the risk among individuals who have not received a COVID-19 vaccine within the past 90 days.	Myocarditis Pericarditis	Final report:	30 Sep 2030

Abbreviations: COVID-19 = coronavirus disease 2019; MCM = major congenital malformation; mRNA = messenger ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; US = United States.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Myocarditis	Routine risk communication: • SmPC Section 4.4 Special warnings and precautions for use • PL Section 2 What you need to know before you are given mNEXSPIKE Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning for healthcare professionals to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines and to be alert to the signs and symptoms of myocarditis and pericarditis (SmPC Section 4.4) • Warning for healthcare professionals to instruct vaccine recipients (including parents or caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis (SmPC Section 4.4) • Warning for users to be aware that cases of myocarditis and pericarditis (inflammation of the heart muscle or the membrane around the heart) have been reported for other authorised COVID-19 vaccines (PL Section 2) • Warning for users to be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, following vaccination and to seek immediate medical attention should these occur (PL Section 2) Other routine risk minimisation measures beyond the Product Information: • None
Pericarditis	Routine risk communication: • SmPC Section 4.4 Special warnings and precautions for use • PL Section 2 What you need to know before you are given mNEXSPIKE Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning for healthcare professionals to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines and to be alert to the signs and symptoms of myocarditis and pericarditis (SmPC Section 4.4) • Warning for healthcare professionals to instruct vaccine recipients (including parents or caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis (SmPC Section 4.4) • Warning for users to be aware that cases of myocarditis and pericarditis (inflammation of the heart muscle or the membrane around the heart) have been reported for other authorised COVID-19 vaccines (PL Section 2) • Warning for users to be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, following vaccination and to seek immediate medical attention should these occur (PL Section 2) Other routine risk minimisation measures beyond the Product Information: • None

Safety Concern	Routine Risk Minimisation Activities
Use in pregnancy	Routine risk communication: • SmPC Section 4.6 Fertility, pregnancy and lactation and Section 5.3 Preclinical safety data • PL Section 2 What you need to know before you are given mNEXSPIKE Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning for healthcare professionals that, as a precautionary measure, it is preferable to avoid the use of mNEXSPIKE during pregnancy (SmPC section 4.6) • Guidance for the user to tell their doctor, nurse or pharmacist if they are pregnant or think they may be pregnant before they receive this vaccine (PL Section 2) Other routine risk minimisation measures beyond the Product Information: • None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety of mRNA-1283.

V.3 Summary of Risk Minimisation Measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis (Important potential risk)	Routine risk minimisation measures: • *Warning for healthcare professionals to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines and to be alert to the signs and symptoms of myocarditis and pericarditis in SmPC Section 4.4* • *Warning for healthcare professionals to instruct vaccine recipients (including parents or caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis in SmPC Section 4.4* • *Warning for users to be aware that cases of myocarditis and pericarditis (inflammation of the heart muscle or the membrane around the heart) have been reported for other authorised COVID-19 vaccines in PL Section 2* • *Warning for users to be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, following vaccination and to seek immediate medical attention should these occur in PL Section 2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1283-P901* • *mRNA-1283-P904* • *mRNA-1283-P906*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pericarditis (Important potential risk)	Routine risk minimisation measures: • *Warning for healthcare professionals to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines and to be alert to the signs and symptoms of myocarditis and pericarditis in SmPC Section 4.4* • *Warning for healthcare professionals to instruct vaccine recipients (including parents or caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis in SmPC Section 4.4* • *Warning for users to be aware that cases of myocarditis and pericarditis (inflammation of the heart muscle or the membrane around the heart) have been reported for other authorised COVID-19 vaccines in PL Section 2* • *Warning for users to be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, following vaccination and to seek immediate medical attention should these occur in PL Section 2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1283-P901* • *mRNA-1283-P906*
Use in pregnancy (Missing information)	Routine risk minimisation measures: • *SmPC Section 4.6* • *SmPC Section 5.3* • *Precautionary guidance to avoid the use of mNEXSPIKE during pregnancy in SmPC Section 4.6* • *Guidance for the user to tell their doctor, nurse or pharmacist if they are pregnant or think they may be pregnant before they receive this vaccine in PL Section 2* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1283-P902*

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for mNEXSPIKE dispersion for injection in pre-filled syringe (COVID-19 mRNA Vaccine)

This is a summary of the risk management plan (RMP) for mNEXSPIKE. The RMP details important risks of mNEXSPIKE, how these risks can be minimised, and how more information will be obtained about mNEXSPIKE's risks and uncertainties (missing information).

mNEXSPIKE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how mNEXSPIKE should be used.

This summary of the RMP for mNEXSPIKE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of mNEXSPIKE's RMP.

I. The Medicine and What it is Used for

mNEXSPIKE is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The active substance is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 circulating variant.

Further information about the evaluation of mNEXSPIKE's benefits can be found in mNEXSPIKE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise These Risks

Important risks of mNEXSPIKE, together with measures to minimise such risks and the proposed studies for learning more about mNEXSPIKE's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of mNEXSPIKE is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of mNEXSPIKE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of mNEXSPIKE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part VI.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important Identified Risks	None
Important Potential Risks	Myocarditis Pericarditis
Missing Information	Use in pregnancy

II.B Summary of Important Risks

Table Part VI.2: Important Potential Risk: Myocarditis

Important Potential Risk: Myocarditis	
Evidence for linking the risk to the medicine	Myocarditis can be caused by a variety of factors; the most common aetiology is viral infection. Myocarditis has not been causally associated with mNEXSPIKE and the risk is anticipated to be lower than approved COVID-19 vaccines as it does not include the furin cleavage site, potentially eliminating circulating spike protein antigen that may interact with heart tissue. In Study mRNA-1283-P301, there were no myocarditis events in either mRNA-1283 or mRNA-1273 vaccinated participants up to the data cutoff (23 Feb 2024). In Study mRNA-1283-P301-Japan, no events of myocarditis were reported in either vaccine group up to the data cutoff (02 May 2024). Likewise in studies mRNA-1283-P201 and mRNA-1283-P101, no events of myocarditis were observed throughout the studies.
Risk factors and risk groups	Acute myocarditis is overall more common in men than in women (Kytö et al 2013). The incidence rate occurs with 2 peaks: the highest in those under one year old with both genders combined (Vasudeva et al 2021) and young males aged 16 to <40 years old (Vasudeva et al 2021; Kytö et al 2013).

Important Potential Risk: Myocarditis	
Risk minimisation measures	Routine risk minimisation measures: Warning for healthcare professionals to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines and to be alert to the signs and symptoms of myocarditis and pericarditis in SmPC Section 4.4 Warning for healthcare professionals to instruct vaccine recipients (including parents or caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis in SmPC Section 4.4 Warning for users to be aware that cases of myocarditis and pericarditis (inflammation of the heart muscle or the membrane around the heart) have been reported for other authorised COVID-19 vaccines in PL Section 2 Warning for users to be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, following vaccination and to seek immediate medical attention should these occur in PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1283-P901 mRNA-1283-P904 mRNA-1283-P906 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table Part VI.3: Important Potential Risk: Pericarditis

Important Potential Risk: Pericarditis	
Evidence for linking the risk to the medicine	Pericarditis can be caused by a variety of factors; the most common aetiology is viral infection. Pericarditis has not been causally associated with mNEXSPIKE and the risk is anticipated to be lower than approved COVID-19 vaccines as it does not include the furin cleavage site, potentially eliminating circulating spike protein antigen that may interact with heart tissue. In Study mRNA-1283-P301, there were no pericarditis events in either mRNA-1283 or mRNA-1273 vaccinated participants within 28 days post injection. Up to the data cutoff (23 Feb 2024), 1 event of suspected pericarditis was reported in the mRNA-1273 group that was assessed as not related to study injection; no pericarditis events were observed in the mRNA-1283 group. In Study mRNA-1283-P301-Japan, no events of pericarditis were reported in either vaccine group up to the data cutoff (02 May 2024). In studies mRNA-1283-P201 and mRNA-1283-P101, no events of pericarditis were observed throughout the studies.
Risk factors and risk groups	Acute pericarditis is overall more common in men than in women. However, the gender difference is reduced with advancing age and became nominal in persons aged >65 years (Kytö et al 2014). In males, the incidence rate of acute pericarditis declines between 16 to 45 years followed by an increase in older individuals aged >50 years (Kytö et al 2014). In females, the incidence rate of acute pericarditis gradually increases with age, with a peak in the population aged 65 to 74 years (Kytö et al 2014; Kumar et al 2016).

Important Potential Risk: Pericarditis	
Risk minimisation measures	Routine risk minimisation measures: Warning for healthcare professionals to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines and to be alert to the signs and symptoms of myocarditis and pericarditis in SmPC Section 4.4 Warning for healthcare professionals to instruct vaccine recipients (including parents or caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis in SmPC Section 4.4 Warning for users to be aware that cases of myocarditis and pericarditis (inflammation of the heart muscle or the membrane around the heart) have been reported for other authorised COVID-19 vaccines in PL Section 2 Warning for users to be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, following vaccination and to seek immediate medical attention should these occur in PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1283-P901 mRNA-1283-P906 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table Part VI.4: Missing Information: Use in pregnancy

Missing Information: Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 SmPC Section 5.3 Precautionary guidance to avoid the use of mNEXSPIKE during pregnancy in SmPC Section 4.6 Guidance for the user to tell their doctor, nurse or pharmacist if they are pregnant or think they may be pregnant before they receive this vaccine in PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1283-P902 See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of mNEXSPIKE.

II.C.2 Other Studies in Post-Authorisation Development Plan

The following studies are considered ongoing and/or planned additional pharmacovigilance activities:

Table Part VI.5: Other Studies in the Post-Authorisation Development Plan

Study Title and Number ***Status***	**Purpose of the Study**
mRNA-1283-P901 Post-marketing safety of the mRNA-1283 vaccine in the United States *Planned*	Primary Objectives: • Estimate the incidence of myocarditis and pericarditis among recipients of mRNA-1283 and among individuals who have not received the prior seasonal formulation of COVID-19 vaccine within the past 90 days or the same seasonal formulation previously • Compare the risk of myocarditis and pericarditis among the recipients of mRNA-1283 with the risk among individuals who have not received the prior seasonal formulation of COVID-19 vaccine within the past 90 days or the same seasonal formulation previously
mRNA-1283-P902 An observational cohort study to assess maternal and infant outcomes following exposure to mRNA-1283 during pregnancy *Planned*	Primary Objectives: • Describe the utilisation of the mRNA-1283 vaccine in routine clinical practice and estimate incidence rates of pregnancy complications (gestational hypertensive disorders and gestational diabetes), adverse pregnancy outcomes (medically attended spontaneous abortion, stillbirth, and preterm birth), and infant major congenital malformations among mRNA-1283 vaccine recipients using large-scale administrative claims data in the US. • Upon accrual of a sufficient number of exposed pregnancies: o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of pregnancy complications. o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased rate of adverse pregnancy outcomes. o Assess whether exposure to mRNA-1283 during pregnancy is associated with an increased prevalence of infant MCM.
mRNA-1283-P904 Long-term outcomes of myocarditis following administration of the mRNA-1283 vaccine *Planned*	Primary Objectives: • Characterise the presentation and clinical course of vaccine-associated myocarditis • Characterise potential long-term outcomes following vaccine-associated myocarditis
mRNA-1283-P906 Post-marketing safety of the mRNA-1283 vaccine in Europe *Planned*	Primary Objectives: • Monitor the distribution of mRNA-1283 in Europe. • Describe the uptake of mRNA-1283, characterise vaccine recipients, and estimate the incidence of myocarditis and pericarditis among them. • Compare the risk of myocarditis and pericarditis among the recipients of mRNA-1283 with the risk among individuals who have not received a COVID-19 vaccine within the past 90 days.

Abbreviations: COVID-19 = coronavirus disease 2019; MCM = major congenital malformation; mRNA = messenger ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; US = United States.

PART VII: ANNEXES

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Annex 6. Details of proposed additional risk minimisation activities (if applicable)

Annex 7. Other supporting data (including referenced material)

Annex 8. Summary of changes to the risk management plan over time

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable.