EU Risk Management Plan

For

mCOMBRIAX

(Influenza and COVID-19, mRNA Vaccine)

Risk Management Plan (RMP) version to be assessed as part of this application:

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Not applicable for initial marketing authorisation application (MAA) submission

Summary of significant changes in this RMP:

Not applicable for initial MAA submission.

Other RMP versions under evaluation:

RMP version number	Date submitted to EMA	Procedure number
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EU QPPV name[1]: Marie-Pierre Caby-Tosi, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Moderna EU QPPV. The electronic signature is available on file.

[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
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CEE	Central and Eastern European
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	COVID-19 disease caused by the 2019 coronavirus
CSR	clinical study report
DP	drug product
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EOS	end of study
EPAR	European Public Assessment Report
ERVISS	European Respiratory Virus Surveillance System
EU	European Union
FDA	United States Food and Drug Administration
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
HA	haemagglutinin
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IM	intramuscular
LNP	lipid nanoparticle
LRTI	lower respiratory tract infection

Acronym	Definition
MAA	marketing authorisation application
MMG	monomyristoyl glycerol
mRNA	messenger ribonucleic acid
NHP	nonhuman primate
NOAEL	no observed adverse effect level
NPI	nascent peptide imaging
NTD	N-terminal domain
O/E	observed to expected
PASS	post-authorisation safety study
PEG	polyethylene glycol
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PFS	pre-filled syringe
PL	package leaflet
PSUR	periodic safety update report
PV	pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RBD	receptor-binding domain
RMP	risk management plan
RNA	ribonucleic acid
S	spike
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
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
SSP	Signalling Strategy Plan
US	United States
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Influenza and COVID-19, mRNA vaccine
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
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(s) in the European Economic Area (EEA)	mCOMBRIAX
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** The mRNA drug substance in mRNA-1083 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 mRNA-1083 drug substance in place of the normal uridine base to minimise the indiscriminate recognition of the mRNA-1083 mRNA by pathogen-associated molecular pattern receptors (e.g., 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: mCOMBRIAX encodes influenza and SARS-CoV-2 antigens: • The influenza antigens encoded are the full-length, membrane-bound HA glycoproteins of seasonal influenza virus types A (H1N1 and H3N2) and B (Victoria lineage). • The SARS-CoV-2 antigen encoded is the membrane-bound, linked NTD and RBD of the spike (S) glycoprotein from SARS-CoV-2 strains. After delivery into cells, the mRNA serves as a template for the synthesis of the intended proteins. The vaccine elicits immune responses to the HA antigens and NTD-RBD of the S antigen, which contribute to protection against influenza and COVID-19.

	Important information about its composition: mCOMBRIAX is a nucleoside-modified mRNA-based vaccine formulated in LNPs encoding influenza and SARS-CoV-2 antigens. The influenza antigens encoded are the full-length, membrane-bound HA glycoproteins of seasonal influenza virus types A (H1N1 and H3N2) and B (Victoria lineage). The SARS-CoV-2 antigen encoded is the membrane-bound, linked NTD and RBD of the spike (S) glycoprotein from SARS-CoV-2 strains.
Hyperlink to the Product Information	Product Information (Module 1.3.1)
Indication(s) in the EEA	**Current:** mCOMBRIAX is indicated for active immunisation for the prevention of influenza disease and COVID-19 caused by SARS-CoV-2 in individuals 50 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:** Posology *Adults 50 years of age and older* One dose of 0.32 mL. If previously vaccinated with a COVID-19 vaccine, this vaccine 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 mCOMBRIAX in children less than 18 years of age have not yet been established. No data are available.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Dispersion for injection White to off-white dispersion (pH: 7.1 to 7.8). One dose (0.32 mL) contains nucleoside modified mRNAs encoding seasonal influenza HA glycoproteins and the linked NTD and RBD of the spike glycoprotein of SARS-CoV-2 encapsulated in LNPs (31.7 micrograms of total RNA).
	Proposed: Not applicable
Vaccine Construct and the formulation	mCOMBRIAX is an LNP-encapsulated, mRNA-based vaccine encoding antigens from seasonal influenza viruses and from SARS-CoV-2. The other ingredients are heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate (SM-102), 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(s) and Target Population(s)

Indication: mCOMBRIAX is indicated for active immunisation for the prevention of influenza disease and COVID-19 caused by SARS-CoV-2 in individuals 50 years of age and older.

Influenza and SARS-CoV-2 are both highly contagious respiratory infections that contribute significantly to global morbidity and mortality. While these viruses can infect multiple species, both viruses are predominantly transmitted human-to-human via respiratory droplets from coughing or sneezing but can also persist in secretions on surfaces (ECDC 2022, ECDC 2024). Airborne transmission may be possible during certain medical procedures and in indoor, crowded, and poorly ventilated environments (WHO 2021).

Seasonality has been observed for both viruses, due to enhanced survival of the influenza and SARS-CoV-2 viruses in drier and colder winter conditions and due to behavioural factors (populations spend more time indoors in closer proximity during the winter) (CDC 2024c, Lowen et al 2007). However, peaks of SARS-CoV-2 transmission have been observed both in winter months and in late summer (WHO 2024). Both viruses are prone to mutation, requiring periodic vaccine updates.

Influenza

Human influenza viruses are segmented, negative-sense, single-stranded RNA viruses belonging to the Orthomyxoviridae virus family that are prone to change through antigenic drift or antigenic shifts (Bouvier and Palese 2008). Influenza type A and B viruses are responsible for seasonal influenza epidemics in humans each year (CDC 2023a). Influenza A viruses are classified into subtypes according to the combination of HA and NA glycoproteins they express on the viral surface, while influenza B viruses are classified into 2 lineages: B/Victoria and B/Yamagata (CDC 2023a). HA proteins bind to specific sialic acid moieties on epithelial cells in the mammalian respiratory tract, which facilitates cellular entry (Bouvier and Palese 2008). Substantial antigenic drift occurs, particularly among influenza A subtypes (eg, A/H3N2, A/2009H1N1 pdm09) leading to frequent changes in circulating clades (Chen et al 2020, CDC 2022a). This results in the need for periodic updates to the strains included in seasonal influenza vaccines. In the time since the mRNA-1083 studies were initiated, the WHO recommendation has been updated to exclude B/Yamagata because the strain no longer circulates (Clinical Overview 2.5, Section 2.5.1.6.3).

COVID-19

Coronaviruses are a large family of double stranded RNA viruses that cause illness ranging from the common cold (CoV species OC43, HKU1, NL63, and 229E) to more severe diseases (MERS-CoV and SARS-CoV) (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).

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:

Influenza

Influenza disease, most often caused by influenza A and influenza B viruses, is a substantial cause of acute viral respiratory tract infections worldwide, causing a major burden to public health. The WHO estimates that seasonal influenza viruses cause around 1 billion infections, 3 to 5 million cases of severe illness and up to 650,000 deaths globally each year (WHO 2023). In the EU/EEA, seasonal influenza is responsible for up to 50 million symptomatic cases and 15,000 to 70,000 deaths annually (ECDC 2022). In the US, influenza has resulted in up to 41 million illnesses, up to 710,000 hospitalisations and up to 51,000 deaths annually between 2010 and 2023 (CDC 2023b).

Estimates of influenza incidence vary according to the conditions (season, region, access to care, availability of testing, hospital admission practices, etc.) under which they were estimated. In a typical year, seasonal influenza has attack rates estimated of 5% to 10% in adults and 20% to 30% in children (de Fougerolles et al 2022). In the Global Burden of Disease Study, the incidence rate of LRTIs attributable to influenza was estimated to be 713.1 per 100,000 in 2017, leading to 54.5 million cases, 9.5 million hospitalisations and 145,000 deaths across all ages worldwide. The highest influenza LRTI mortality rate among all ages occurred in eastern Europe (5.2 per 100,000), where influenza LRTI hospitalisations were also high (488.7 per 100,000). By comparison, the mortality and hospitalisation rates were 2.1 and 59.9 per 100,000, respectively, in high-income western European countries; 4.0 and 84.0 per 100,000, respectively, in high-income Asian-Pacific countries; and 1.1 and 55.0 per 100,000, respectively, in the US (GBD 2017 Influenza Collaborators, 2019).

COVID-19

The first cases of SARS-CoV-2 were detected in 2019 in Wuhan, Hubei Province, China in December 2019, and have 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 10th 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 Fall (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-Fall 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 Disease Outcomes:

Influenza

The proportion of age groups affected varies annually based on the dominant viruses and the level of population immunity, but in general older adults are at greater risk of developing severe influenza complications. Globally, the highest influenza mortality rate from LRTI in 2017 occurred among adults >70 years (16.4 deaths per 100,000) (GBD 2017 Influenza Collaborators 2019). In an analysis over 9 seasons (2002 to 2011), 88% of influenza-associated respiratory deaths in the EU occurred in those >65 years (Paget et al 2022). Similarly in the US, adults ≥65 years accounted for 70% to 85% of influenza-related deaths and 50% to 70% of influenza-related hospitalisations between the 2010 and 2020 seasons (CDC 2022c). A significant burden of influenza has also been reported in adults 50 to 64 years who account for a large proportion of the workforce and play a key economic role. According to a study in 5 European countries (Netherlands, France, England, Portugal, Spain), the percentage of mortality due to respiratory disease caused by influenza activity was equal for the age groups 50 to 64 years and ≥65 years (9.4% to 19.4% vs. 9.4% to 19.3%, respectively) (Nielen et al 2010). During the 2022/2023 season in the US, the rates of hospitalisation and mortality were 105.9 and 7.2 per 100,000 among adults 50 to 64 years and 332.4 and 26.6 per 100,000 among adults ≥65 years, compared to 44.7 and 0.7 per 100,000 among those 18 to 49 years (CDC 2023c). Apart from age-related increased risk, existence of certain medical conditions increases the risk of influenza complications for people of any age. These high-risk groups include individuals with chronic medical conditions (such as metabolic diseases, chronic lung conditions, heart disease, liver disease, blood conditions, BMI ≥40 kg/m^2, genetic conditions, chronic kidney diseases, or treatments that suppress the immune function), pregnant women, and children <5 years (ECDC 2022).

COVID-19

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 between Week 36 and Week 50 2023 (Dec 2023), the cumulative rate of non-sentinel 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 to 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:

Interventions for both influenza and SARS-CoV-2 infection include prophylactic vaccination, supportive care for symptomatic infection, and treatments for the viral infection, including antivirals and monoclonal antibodies. Immune modulating medications can also be used for treatment of COVID-19.

Influenza

The availability of seasonal influenza vaccines can vary by country and season, depending on regulatory approvals and market decisions. Several different technologies have been utilised to create and administer vaccines, which may be on egg- or cell-culture growth or recombinant HA and may be delivered IM, intranasally, or via jet injector.

Influenza-specific antiviral drugs can be administered as therapy or prophylaxis against influenza disease although they should not be used to replace influenza vaccination. Currently, 3 drugs are authorised and recommended for the treatment of influenza in Europe: Tamiflu (oseltamivir), Relenza and Dectova (zanamivir), and Xofluza (baloxavir marboxil). These medications should be recommended as treatment for influenza for individuals considered to be ‘at risk’ of developing more serious complications: young children, the elderly or those living with co-morbid conditions, specifically including cardiopulmonary conditions, like COPD, asthma, or myocardial disease.

COVID-19

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), an interleukin-6 inhibitor; Ronapreve (casirivimab/imdevimab), a combination of 2 monoclonal antibodies; Veklury (remdesivir), an antiviral medication; Xevudy (sotrovimab), a human monoclonal antibody that neutralises SARS-CoV-2; Evusheld (tixagevimab/cilgavimab), a combination of 2 recombinant human IgG1monoclonal 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 The Indicated Condition in The Population, Including Mortality and Morbidity:

Influenza

Influenza virus is predominantly transmitted directly via droplets spread by coughing or sneezing, or indirectly via respiratory secretions on hands and tissues (ECDC 2022). Influenza virus can affect any organ system but typically manifests as an acute febrile illness with variable systemic and respiratory symptoms (Krammer et al 2018). Influenza can manifest as a mild to moderate illness, such as sinusitis or otitis media, or as a severe disease, including pneumonia, multi-organ failure, and hyperinflammatory responses that may result in sepsis (CDC 2022b). Older adults might present with general symptoms only without fever, sore throat, and myalgia (Uyeki et al 2022). Complications of influenza can be severe or life-threatening, resulting either from the virus itself or secondary to a bacterial infection (ECDC 2022) and can extend beyond respiratory events, including increased risk of myocardial infarction and stroke (Kwong et al 2018, Ohland et al 2020). Long-term complications may also arise from influenza infection (Xie et al 2024, Quinn et al 2023).

Substantial variability in methods to estimate influenza-associated hospitalisation rates exist, resulting in the absence of reliable global estimates. Previously reported global rates of influenza-associated hospitalisation vary from 40.5 per 100,000 (Paget et al 2023) to 123.8 per 100,000 (GBD 2017 Influenza Collaborators, 2019). The estimated yearly rate of excess hospitalisation due to influenza and pneumonia in Germany, France, and England and Wales was 165, 189, and 219 per 100,000, respectively, which is far greater than those reported in Central and Eastern European countries (30 per 100,000) likely due to underreporting in CEE region (Kovács et al 2014). Rate of influenza-related hospitalisation in the US among all ages was estimated to be 55.0 per 100,000 in a global modelling study (GBD 2017 Influenza Collaborators, 2019). Similarly, estimates of influenza mortality from different studies should be interpreted with caution. Based on FluMOMO algorithm, influenza-attributable mortality in all ages ranged from 0.31 per 100,000 to 28.58 per 100,000 in European countries between 2012/13 and 2017/18 seasons (Nielsen et al 2019). Another modelling study estimated influenza-associated respiratory mortality in 28 EU countries to be 5.3 per 100,000 in all ages (Paget et al 2022). Influenza-related mortality in the US among all ages was estimated to be 1.8 per 100,000 based on mortality data from 2018 to 2022 (CDC WONDER 2024).

COVID-19

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, hematologic, 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, and 10% to 12% of vaccinated individuals have experienced Long COVID (Davis et al 2023). A population-based study conducted in the US between Jun and Jul 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 Aug and Nov 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 (10.0%). Long COVID therefore represents a long-term outcome that can result in significant impact to health.

Part II: Module SII – Non-Clinical Part of the Safety Specification

Table 2 summarises the key non-clinical findings and their relevance to safety in humans. In summary, the non-clinical package, which consisted of both studies performed with mRNA-1083 and with mRNA vaccines formulated in the same SM-102 LNP vaccine matrix to support mRNA-1083 use in humans, identified no safety concerns.

Table 2: Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Findings	Relevance to Human Use
Safety pharmacology and toxicology		
Consistent with the WHO regulatory guidelines on the nonclinical evaluation of vaccines (WHO 2005), no safety pharmacology studies have been performed with mRNA-1083 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-1083.2 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-1083, 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-1083. 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 DPs 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 lower limit of quantitation (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-1083.2 in male and female Sprague Dawley rats (administered IM two times at 0, 10, 20, and 36 µg/dose once every 4 weeks followed by a 2-week recovery period)	The GLP toxicity study utilised a DP encoding QIV HA influenza strain components (at individual mass ratios of 1:1:1:1) and bivalent (1:1) SARS CoV-2 components (Wuhan-Hu-1 and Omicron BA.4/BA.5 variant) at a total flu to SARS CoV-2 mass ratio of 10:1. There were no test article related clinical signs, injection site observations, or mortalities when administered IM followed by a 2-week recovery period. Microscopic target organs in this study included the injection site, spleen, and liver, the latter of which was limited to females. Injection site inflammation correlated with clinical pathology changes consistent with an inflammatory and/or acute phase response. Multifocal liver necrosis was observed in a small subset of females only (3 out of 10 animals) at 36 µg/dose, with corresponding increases in hepatocellular/ hepatobiliary parameters, which is what conservatively set the NOAEL at 20 µg/dose. At the end of the 2-week recovery period, there were no microscopic changes observed, including liver histopathology, and all clinical pathology changes were either fully or partially resolved.	Using the NOAEL in rats (20 µg/dose or 66.7 µg/kg based on a rat body weight of 0.3 kg) in the repeat-dose GLP toxicity study with mRNA-1083.2, there is a 126-fold safety margin when compared to the proposed marketed dose of mRNA-1083 (31.7 µg/dose or 0.53 µg/kg based on a conservative body weight estimate of 60 kg). Doses of each individual RNA (as well as the combined total RNA dose) evaluated in the pivotal GLP toxicity study with mRNA-1083 exceeded the proposed marketed dose on a µg/kg basis. 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

Study Type	Important Nonclinical Findings	Relevance to Human Use
		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. Clinical safety data derived across studies with mRNA-1083 showed no cases of drug-induced liver injury or other type of acute hepatic injury. No elevations in liver enzymes were considered related to mRNA-1083 up to the highest dose tested in the mRNA-1083-P101 study (82 µg/dose), indicating a lack of translation of the finding observed in rats.
Platform GLP toxicity studies evaluating mRNA vaccines formulated in the same SM-102 LNP vaccine matrix as mRNA-1083 in male and female Sprague Dawley rats (administered IM at doses ranging from 9 to 150 µg/dose once every 2 weeks for up to 6 weeks with a 2-week recovery period)	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 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).	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
Other nonclinical toxicology studies		
GLP perinatal/ postnatal developmental and reproductive toxicity studies where 0 and 80 µg/dose mRNA-1283 and 0 and 100 µg/dose mRNA-1010 were administered to female rats via IM injection 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 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 antibodies to offspring when females were immunised prior to and after mating.	Regarding the NOAELs from these studies with mRNA-1283 (80 µg/dose or 267 µg/kg) and mRNA-1010 (100 µg/dose or 333 µg/kg), the safety margins are 503-fold and 629-fold, respectively, relative to the proposed marketed human dose of 31.7 µg/dose of mRNA-1083 (or 0.53 µg/kg). The risk for adverse pregnancy outcomes after exposure is unknown in humans, but nonclinical findings do not suggest a specific risk.

There are no safety concerns for mRNA-1083 based on nonclinical data.

Part II: Module SIII – Clinical Trial Exposure

The safety and tolerability of mRNA-1083 have been assessed using an overall safety database of over 8000 participants, of which 4132 adult participants ≥50 years of age received at least 1 injection of mRNA-1083 at 30 µg, 40 µg, or 60 µg (Table 3). The Pivotal Phase 3 Study mRNA-1083-P301 provides the main clinical safety data for mRNA-1083.

The mRNA-1083 clinical development programme initiated with the Phase 1/2 Study mRNA-1083-P101. Safety and immunogenicity results of Part 1 of this Phase 1/2 study supported the dose selection for mRNA-1083 (40 µg) for further evaluation in the Phase 3 observer-blinded, randomised study mRNA-1083-P301.

Two clinical trials of mRNA-1083 are reported below.

Table 3: Clinical Studies Supporting the Safety of mRNA-1083

Study Number (Country)	Study Design	Study Population	Regimen (Participants in the Safety Set)		Number of participants exposed	Safety Objectives
mRNA-1083-P101 Part 1[a] (US)	Phase 1/2 randomised, observer-blind, active-controlled study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083. Follow-up through EOS/Day 181.	Healthy adults ≥18 to <80 years. Cohort A: ≥65 to <80 years. Cohort B: ≥18 to <65 years. Randomisation stratification: by age (≥18 to <50 and ≥50 to <65 years, Cohort B only) and by influenza vaccine status in the most recent season.	Single IM injection into the deltoid muscle on Day 1.[b]		Cohort A (≥65 to <80 years) mRNA-1083 (30 µg or 60 µg) = 84 Cohort B (≥50 to <65 years) mRNA-1083 (30 µg or 60 µg) = 44	To evaluate the safety and reactogenicity of study intervention administration across groups.
			Cohort A (≥65 to <80 years):	Cohort B (≥18 to <65 years):		
			mRNA-1083.1 30 µg (51) mRNA-1083.1 60 µg (33) mRNA-1083.2 27.5 µg (55) mRNA-1083.2 55 µg (53) mRNA-1083.2 82 µg (33) mRNA-1083.3 52.5 µg (53) mRNA-1010.4 50 µg (51) mRNA-1283.222 10 µg (52) mRNA-1273.222 50 µg (54) mRNA-1010 50 µg (54) Fluarix (54) Fluzone HD (53)	mRNA-1083.1 15 µg (56) mRNA-1083.1 30 µg (55) mRNA-1083.1 60 µg (37) mRNA-1083.2 27.5 µg (56) mRNA-1083.2 55 µg (54) mRNA-1083.2 82 µg (38) mRNA-1083.3 52.5 µg (54) mRNA-1010.4 50 µg (55) mRNA-1283.222 10 µg (55) mRNA-1273.222 50 µg (53) mRNA-1010[b] 50 µg (55) Fluarix (52)		
mRNA-1083-P301 (US)	Phase 3 randomised, observer-blind, active-controlled study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083. Follow-up through EOS/Day 181.	Healthy adults ≥50 years. Cohort A: ≥65 years. Cohort B: ≥50 to <65 years. Randomisation stratification by age (65 to <75 and ≥75 years, Cohort A only) and by influenza vaccine status in the most recent season.	Two single IM injections, 1 into each deltoid muscle, on Day 1.[c] Cohort A (≥65 years): mRNA-1083 40 µg + placebo (2011) or Fluzone HD + Spikevax (2006) Cohort B (≥50 to <65 years): mRNA-1083 40 µg + placebo (1993) or Fluarix + Spikevax (2005).		Cohort A (≥65 years) mRNA-1083 40 µg + placebo = 2011 Cohort B (≥50 to <65 years) mRNA-1083 40 µg + placebo = 1993	To evaluate the safety and reactogenicity of study intervention administration across groups.

Abbreviations: EOS = end of study; HD = high dose; IM = intramuscular; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; US = United States.
Participants remain in all studies to all protocol-specified assessments of efficacy, immunogenicity, and safety through the scheduled end of study.

[a] Part 1 of the study was conducted in cohorts for adults ≥65 to <80 years and ≥18 to <65 years (further stratified into ≥18 to <50 years and ≥50 to <65 years) and informed composition and dose selection for clinical development in adults ≥50 years. Part 2 of the study is being conducted in adults ≥18 to <50 years and is not summarised in this submission and remains ongoing.

[b] The influenza component of mRNA-1083 (all compositions) and mRNA-1010 (all compositions) in Study mRNA-1083-P101 Part 1 used the WHO 2022/2023 NH cell- or recombinant-based vaccine strain composition. The SARS-CoV-2 component of mRNA-1083 (all compositions) and mRNA-1283 in Part 1 used the original (Wuhan-Hu-1) and Omicron BA.4/BA.5 variants recommended for 2022/2023.

[c] The influenza component of mRNA-1083 in Study mRNA-1083-P301 used the WHO 2023/2024 NH cell- or recombinant-based vaccine strain composition. The SARS-CoV-2 component used the fall/winter 2023/2024 recommended Omicron XBB.1.5 variant. The comparators used the same recommended strain compositions.

Source: Module 2.5, Section 72.5.1.4, Table 1.

Study mRNA-1083-P301

Study mRNA-1083-P301 is a randomised, observer-blind, single-dose, 2-cohort, active-control Phase 3 study to assess the effectiveness (immunogenicity), reactogenicity, and safety of a single 40-µg dose of mRNA-1083 as compared to co-administered licensed influenza vaccine and Spikevax:

- Cohort A substudy (≥65 years) is evaluating the safety, reactogenicity, and immunogenicity of the selected mRNA-1083 vaccine and dose level as compared with co-administered active licensed comparator vaccines, Fluzone HD and Spikevax. Approximately 4000 participants have been randomised (in a 1:1 ratio) into the investigational vaccine and control arms and stratified by age groups (65 to <75 years and ≥75 years of age; where at least 10% of participants are ≥75 years of age) and influenza vaccine status in the most recent influenza season (received or not received since September 2022).
- Cohort B substudy (50 to <65 years) is evaluating the safety, reactogenicity, and immunogenicity of the selected mRNA-1083 vaccine and dose level as compared with co-administered active licensed comparator vaccines, Fluarix and Spikevax. Approximately 4000 participants have been randomised (in a 1:1 ratio) into the investigational vaccine and control arms and stratified by influenza vaccine status in the most recent influenza season (received or not received since September 2022).

Clinical trial exposure data for Study mRNA-1083-P301 are presented by duration of exposure, age and sex, race, and ethnicity in Table 4 to Table 7 for Cohort A and in Table 8 to Table 11 for Cohort B.

Table 4: Summary of Study Duration for mRNA-1083-P301 - Cohort A ≥65 Years (Safety Set)

Duration of exposure	mRNA-1083 40 µg + Placebo (N=2011)	Fluzone HD + Spikevax (N=2006)	Overall (N=4017)
Number of participants, n (%)			
Received both injections at Day 1	2011 (100)	2006 (100)	4017 (100)
With study duration ≥7 days since injection	2010 (>99.9)	2004 (>99.9)	4014 (>99.9)
With study duration ≥28 days since injection	2001 (99.5)	1999 (99.7)	4000 (99.6)
With study duration ≥90 days since injection	1986 (98.8)	1984 (98.9)	3970 (98.8)
With study duration ≥180 days since injection[a]	373 (18.5)	361 (18.0)	734 (18.3)
Study duration from injection (days)			
Mean (SD)	171.0 (17.47)	171.3 (16.46)	171.2 (16.97)
Median	171.0	171.0	171.0
Min, max	1, 201	1, 203	1, 203

Abbreviations: EOS = end of study; Max = maximum; Min = minimum; SD = standard deviation.
Numbers were based on actual vaccination group and percentages were based on the number of participants in the Safety Set.
Duration from study injection was calculated as EOS date – earliest injection date + 1.
[a] Durations of follow-up did not reach 180 days for many participants because participants had a window of ±14 days from Day 181 for the EOS visit.
Source: Study mRNA-1083-P301 CSR Table 14.1.7.1a (01 Jul 2024).

Table 5: Participant Age and Sex in Study mRNA-1083-P301 - Cohort A ≥65 Years (Safety Set)

Characteristic	mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	Overall (N=4017) n (%)
Age (years)[a]			
n	2011	2006	4017
Mean (SD)	70.9 (4.96)	70.7 (4.70)	70.8 (4.83)
Median	70.0	70.0	70.0
Min, Max	63, 92	65, 98	63, 98
Age group (years), n (%)[a]			
≥50 to <65 years[b]	2 (<0.1)	0	2 (<0.1)
≥65 to <75 years	1593 (79.2)	1591 (79.3)	3184 (79.3)
≥75 years	416 (20.7)	415 (20.7)	831 (20.7)
Sex, n (%)			
Male	933 (46.4)	908 (45.3)	1841 (45.8)
Female	1078 (53.6)	1098 (54.7)	2176 (54.2)

Abbreviations: eCRF = electronic case report form; Max = maximum; Min = minimum; SD = standard deviation.
Numbers were based on planned study intervention group and percentages were based on the number of participants in the Safety Set.
[a] Based on age and vaccination status collected on eCRFs.
[b] Mis-randomised participants.
Source: Study mRNA-1083-P301 CSR Table 14.1.4.4a (01 Jul 2024).

Table 6: Participant Race in Study mRNA-1083-P301 - Cohort A ≥65 Years (Safety Set)

Race, n (%)	mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	Overall (N=4017) n (%)
White	1577 (78.4)	1565 (78.0)	3142 (78.2)
Black or African American	370 (18.4)	370 (18.4)	740 (18.4)
Asian	25 (1.2)	36 (1.8)	61 (1.5)
American Indian or Alaska Native	9 (0.4)	12 (0.6)	21 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	4 (0.2)	5 (0.1)
Other	4 (0.2)	3 (0.1)	7 (0.2)
Multiple	14 (0.7)	4 (0.2)	18 (0.4)
Unknown/Not reported	11 (0.5)	12 (0.6)	23 (0.6)

Abbreviations: eCRF = electronic case report form; Max = maximum; Min = minimum; SD = standard deviation.
Numbers were based on planned study intervention group and percentages were based on the number of participants in the Safety Set.
Source: Study mRNA-1083-P301 CSR Table 14.1.4.4a (01 Jul 2024).

Table 7: Participant Ethnicity in Study mRNA-1083-P301 - Cohort A ≥65 Years (Safety Set)

Ethnicity, n (%)	mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	Overall (N=4017) n (%)
Hispanic or Latino	283 (14.1)	275 (13.7)	558 (13.9)
Not Hispanic or Latino	1688 (83.9)	1689 (84.2)	3377 (84.1)
Not reported/Unknown	40 (2.0)	42 (2.1)	82 (2.0)

Abbreviations: eCRF = electronic case report form; Max = maximum; Min = minimum; SD = standard deviation.
Numbers were based on planned study intervention group and percentages were based on the number of participants in the Safety Set.
Source: Study mRNA-1083-P301 CSR Table 14.1.4.4a (01 Jul 2024).

Table 8: Summary of Study Duration for mRNA-1083-P301 - Cohort B ≥50 to <65 Years (Safety Set)

Duration of exposure	mRNA-1083 40 µg + Placebo (N=1993)	Fluarix + Spikevax (N=2005)	Overall (N=3998)
Number of participants, n (%)			
Received both injections at Day 1	1993 (100)	2005 (100)	3998 (100)
With study duration ≥7 days since injection	1992 (>99.9)	2003 (>99.9)	3995 (>99.9)
With study duration ≥28 days since injection	1983 (99.5)	1987 (99.1)	3970 (99.3)
With study duration ≥90 days since injection	1965 (98.6)	1968 (98.2)	3933 (98.4)
With study duration ≥180 days since injection[a]	466 (23.4)	434 (21.6)	900 (22.5)
Study duration from injection (days)			
Mean (SD)	171.0 (18.34)	170.4 (20.66)	170.7 (19.54)
Median	171.0	170.0	170.0
Min, max	3, 197	1, 201	1, 201

Abbreviations: EOS = end of study; Max = maximum; Min = minimum; SD = standard deviation.
Numbers were based on actual vaccination group and percentages were based on the number of participants in the Safety Set.
Duration from study injection was calculated as EOS date – earliest injection date + 1.
[a]. Durations of follow-up did not reach 180 days for many participants because participants had a window of ±14 days from Day 181 for the EOS visit.
Source: Study mRNA-1083-P301 CSR Table 14.1.7.1b (01 Jul 2024).

Table 9: Participant Age and Sex in Study mRNA-1083-P301 - Cohort B ≥50 to <65 Years (Safety Set)

Characteristic	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)	Overall (N=3998) n (%)
Age (years)[a]			
N	1993	2005	3998
Mean (SD)	57.5 (4.25)	57.4 (4.21)	57.5 (4.23)
Median	58.0	58.0	58.0
Min, Max	50, 79	50, 77	50, 79
Sex, n (%)			
Male	837 (42.0)	811 (40.4)	1648 (41.2)

Characteristic	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)	Overall (N=3998) n (%)
Female	1156 (58.0)	1194 (59.6)	2350 (58.8)
Not reported/Unknown	25 (1.3)	21 (1.0)	46 (1.2)

Abbreviations: eCRF = electronic case report form; Max = maximum; Min = minimum; SD = standard deviation.
Numbers were based on planned vaccination group and percentages were based on the number of participants in the Randomisation Set.
[a.] Based on age and vaccination status collected on eCRFs. Note that 3 participants in the Safety Set had been mis-randomised to Cohort B with ages >65 years (Listing 16.2.1.1 [01 Jul 2024]).
Source: Study mRNA-1083-P301 CSR Table 14.1.4.4b (01 Jul 2024).

Table 10: Participant Race in Study mRNA-1083-P301 - Cohort B ≥50 to <65 Years (Safety Set)

Race, n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)	Overall (N=3998) n (%)
White	1374 (68.9)	1344 (67.0)	2718 (68.0)
Black or African American	516 (25.9)	551 (27.5)	1067 (26.7)
Asian	50 (2.5)	39 (1.9)	89 (2.2)
American Indian or Alaska Native	12 (0.6)	13 (0.6)	25 (0.6)
Native Hawaiian or Other Pacific Islander	3 (0.2)	5 (0.2)	8 (0.2)
Other	4 (0.2)	8 (0.4)	12 (0.3)
Multiple	19 (1.0)	21 (1.0)	40 (1.0)
Unknown/Not reported	15 (0.8)	24 (1.2)	39 (1.0)

Abbreviations: eCRF = electronic case report form; Max = maximum; Min = minimum; SD = standard deviation.
Numbers were based on planned vaccination group and percentages were based on the number of participants in the Randomisation Set.
Source: Study mRNA-1083-P301 CSR Table 14.1.4.4b (01 Jul 2024).

Table 11: Participant Ethnicity in Study mRNA-1083-P301 - Cohort B ≥50 to <65 Years (Safety Set)

Ethnicity, n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)	Overall (N=3998) n (%)
Hispanic or Latino	392 (19.7)	381 (19.0)	773 (19.3)
Not Hispanic or Latino	1576 (79.1)	1603 (80.0)	3179 (79.5)
Not reported/Unknown	25 (1.3)	21 (1.0)	46 (1.2)

Abbreviations: eCRF = electronic case report form; Max = maximum; Min = minimum; SD = standard deviation.
Numbers were based on planned vaccination group and percentages were based on the number of participants in the Randomisation Set.
Source: Study mRNA-1083-P301 CSR Table 14.1.4.4b (01 Jul 2024).

Study mRNA-1083-P101

Study mRNA-1083-P101 is a 2-part Phase 1/2 randomised, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of multiple mRNA-1083 formulations and dose levels compared with active control vaccines.

The study is divided into 2 parts:

- Part 1 consists of 2 age sub-studies, Cohort A comprises adults ≥65 to <80 years of age and Cohort B comprises adults ≥18 to <65 years of age.
- Part 2 is a Phase 2 extension in adults ≥18 to <50 years of age and is not covered in this RMP.

The mRNA-1083 formulations included different ratios of total combined influenza RNA mass to total combined SARS-CoV-2 RNA mass; those used in Part 1 were mRNA-1083.1 (5:1), mRNA-1083.2 (10:1), and mRNA-1083.3 (20:1). The influenza component included 4 RNAs that encode the seasonal influenza HA glycoproteins, each RNA corresponding to 1 influenza strain recommended by the WHO, with the 4 RNAs in an equivalent mass ratio. The SARS-CoV-2 component included 2 RNAs that encode the NTD and RBD of the SARS-CoV-2 spike glycoprotein, 1 RNA corresponding to the original (Wuhan-Hu 1) and 1 RNA corresponding to the BA.4/BA.5 variants, with the 2 RNAs in an equivalent mass ratio. The comparators in both study parts were licensed non-mRNA influenza vaccines, licensed mRNA SARS-CoV-2 vaccines, an investigational mRNA influenza vaccine (mRNA-1010), and an investigational SARS-CoV-2 vaccine (mRNA-1283).

To support dose selection for the pivotal Phase 3 study, a planned interim analysis was conducted at Day 29 (data cutoff 18 Jul 2023) in Part 1 of the study.

Clinical trial exposure data for Study mRNA-1083-P101 are presented by duration of exposure, age and sex, race and ethnicity in Table 12 to Table 15.

Table 12: Summary of Exposure and Follow-Up Duration After Study Injection (Days) in mRNA-1083-P101 (Safety Set)

Duration of exposure	Fluarix	Fluzone HD	mRNA-1273.222 50 µg	mRNA-1083.1 30 µg	mRNA-1083.1 60 µg
Cohort A (≥65 to <80 years), n (%)	54	53	54	51	33
≥7 days since injection	54 (100)	53 (100)	54 (100)	51 (100)	33 (100)
≥28 days since injection	54 (100)	53 (100)	54 (100)	51 (100)	33 (100)
≥90 days since injection	53 (98.1)	53 (100)	54 (100)	51 (100)	33 (100)
≥EOS (Day181) since injection[a]	10 (18.5)	15 (28.3)	7 (13.0)	7 (13.7)	8 (24.2)
Time on Study (days)					
Mean (SD)	171.1 (20.74)	175.2 (7.61)	171.8 (6.88)	172.4 (6.23)	173.9 (6.04)
Median	170.0	174.0	169.0	169.0	172.0
Min, max	35, 204	167, 197	167, 197	167, 188	167, 187
Cohort B (≥50 to <65 years), n (%)	26	-	27	28	16
≥7 days since injection	28 (100)	-	27 (100)	28 (100)	16 (100)
≥28 days since injection	28 (100)	-	27 (100)	28 (100)	16 (100)
≥90 days since injection	28 (100)	-	27 (100)	28 (100)	16 (100)
≥EOS (Day181) since injection	9 (32.1)	-	2 (7.4)	6 (21.4)	3 (18.8)

Duration of exposure	Fluarix	Fluzone HD	mRNA-1273.222 50 µg	mRNA-1083.1 30 µg	mRNA-1083.1 60 µg
Time on Study (days)					
Mean (SD)	174.4 (6.95)	-	171.4 (5.09)	173.5 (7.50)	173.2 (6.76)
Median	172.5	-	169.0	169.5	170.5
Min, max	167, 189	-	167, 181	167, 191	167, 188

Abbreviations: CSR = clinical study report; EOS = end of study; HD = high dose; max = maximum; min = minimum; SD = standard deviation.
Duration from study injection was calculated as end of study date – injection date +1.
Numbers were based on actual study intervention group and percentages were based on the number of participants (n) in the Safety Set.
[a.] Durations of follow-up did not reach 180 days for many participants because participants had a window of ±14 days from Day 181 for the EOS visit.
Source: Study mRNA-1083-P101 CSR Table 14.1.2.1, Table 14.1.2.2, Table 14.1.5.1, and Table 14.1.5.2.

Table 13: Participant Age and Sex in Study mRNA-1083-P101 (Full Analysis Set)

Characteristic	Fluarix	Fluzone HD	mRNA-1273.222 50 µg	mRNA-1083.1 30 µg	mRNA-1083.1 60 µg
Cohort A (≥65 to <80 years), n	54	53	54	51	33
Age (years)					
Mean (SD)	70.7 (3.70)	69.4 (3.68)	70.3 (3.84)	70.5 (3.72)	70.5 (3.72)
Median	70.5	68.0	70.0	69.0	70.0
Q1, Q3	67.0, 73.0	67.0, 71.0	66.0, 73.0	67.0, 73.0	67.0, 74.0
Min, max	65, 78	65, 79	65, 79	65, 79	65, 79
Sex, n (%)					
Male	22 (40.7)	23 (43.4)	21 (38.9)	24 (47.1)	17 (51.5)
Female	32 (59.3)	30 (56.6)	33 (61.1)	27 (52.9)	16 (48.5)
Cohort B (≥50 to <65 years), n	26	-	27	28	16
Age (years)					
Mean (SD)	57.7 (4.17)	-	58.6 (4.06)	57.5 (4.57)	58.2 (4.04)
Median	59.0	-	59.0	56.5	58.0
Q1, Q3	54.0, 60.0	-	56.0, 62.0	53.0, 62.0	54.5,61.5
Min, max	50, 64	-	50, 64	50, 64	50, 64
Sex, n (%)					
Male	13 (50.0)	-	12 (44.4)	16 (57.1)	11 (68.8)
Female	13 (50.0)	-	15 (55.6)	12 (42.9)	5 (31.3)

Abbreviations: CSR = clinical study report; HD = high dose; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
Source: Study mRNA-1083-P101 CSR Table 14.1.3.1.2.1 and Table 14.1.3.1.2.2.

Table 14: Participant Race in Study mRNA-1083-P101 (Full Analysis Set)

Characteristic	Fluarix	Fluzone HD	mRNA-1273.222 50 µg	mRNA-1083.1 30 µg	mRNA-1083.1 60 µg
Cohort A (≥65 to <80 years), n	54	53	54	51	33
Race, n (%)					
White	48 (88.9)	47 (88.7)	44 (81.5)	46 (90.2)	28 (84.8)
Black or African American	6 (11.1)	5 (9.4)	9 (16.7)	5 (9.8)	5 (15.2)
Asian	0	1 (1.9)	1 (1.9)	0	0
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Multiracial	0	0	0	0	0
Other	0	0	0	0	0
Unknown	0	0	0	0	0
Not reported	0	0	0	0	0
Cohort B (≥50 to <65 years), n	26	-	27	28	16
Race, n (%)					
White	20 (76.9)	-	23 (85.2)	20 (71.4)	14 (87.5)
Black or African American	6 (23.1)	-	4 (14.8)	8 (28.6)	1 (6.3)
Asian	0	-	0	0	1 (6.3)
American Indian or Alaska Native	0	-	0	0	0
Native Hawaiian or Other Pacific Islander	0	-	0	0	0
Multiracial	0	-	0	0	0
Other	0	-	0	0	0
Unknown	0	-	0	0	0
Not reported	0	-	0	0	0

Source: Study mRNA-1083-P101 CSR Table 14.1.3.1.2.1 and Table 14.1.3.1.2.2.

Table 15: Participant Ethnicity in Study mRNA-1083-P101 (Full Analysis Set)

Characteristic	Fluarix	Fluzone HD	mRNA-1273.222 50 µg	mRNA-1083.1 30 µg	mRNA-1083.1 60 µg
Cohort A (≥65 to <80 years), n	54	53	54	51	33
Ethnicity, n (%)					
Hispanic or Latino	4 (7.4)	4 (7.5)	4 (7.4)	8 (15.7)	4 (12.1)
Not Hispanic/Latino	50 (92.6)	49 (92.5)	50 (92.6)	43 (84.3)	28 (84.8)
Not reported	0	0	0	0	0
Unknown	0	0	0	0	1 (3.0)
Cohort B (≥50 to <65 years), n	26	-	27	28	16
Ethnicity, n (%)					
Hispanic or Latino	5 (19.2)	-	3 (11.1)	2 (7.1)	2 (12.5)
Not Hispanic/Latino	21 (80.8)	-	24 (88.9)	26 (92.9)	14 (87.5)
Not reported	0	-	0	0	0
Unknown	0	-	0	0	0

Source: Study mRNA-1083-P101 CSR Table 14.1.3.1.2.1 and Table 14.1.3.1.2.2.

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-1083-P301 according to the general criteria listed below (Table 16). Detailed descriptions of all exclusion criteria are provided in the individual protocols.

Table 16: Important Exclusion Criteria in the Pivotal Study

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing)
Pregnant women	Clinical development generally first demonstrates safety and efficacy in non-pregnant women.	No	The indication is for individuals 50 years of age and older. The mCOMBRIAX SmPC advises that as a precautionary measure, it is preferrable to avoid the use of mCOMBRIAX during pregnancy.
Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) 72 hours prior to or at the Screening Visit or Day 1.	Allowance of these conditions would confound assessment of safety and these febrile participants might already be infected with seasonal influenza virus or 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. The mCOMBRIAX 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.
Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of any mRNA or influenza vaccines or any components of the mRNA or influenza vaccines, including egg protein.	Participants with medical history significant for allergic reactions following the vaccine or its excipients are at increased risk for hypersensitivity reactions when receiving another vaccine.	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. The mCOMBRIAX SmPC contraindicates vaccination in individuals with known hypersensitivity to the active substances or to any of the excipients. Furthermore, appropriate medical treatment and supervision should always be readily available in case of severe hypersensitivity reaction, including anaphylaxis, following administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of the vaccine.

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing)
Reported history of coagulopathy or 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. The mCOMBRIAX 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.
Received or plans to receive any vaccine authorised or approved by a local health agency ≤28 days prior to study injections or plans to receive a vaccine authorised or approved by a local health agency within 28 days after the study injections.	Allowance of these vaccinations would confound assessment of safety and efficacy.	No	The study included participants with prior influenza immunisation and/or prior COVID-19 immunisation, including different number of vaccination doses (mRNA-1083-P301 CSR, Table 14.1.4.4a and Table 14.1.4.4b). The mCOMBRIAX SmPC advises that if previously vaccinated with a COVID-19 vaccine, this vaccine should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. No interaction studies with other medicinal products have been performed. Concomitant administration of mCOMBRIAX with other vaccines has not been studied.
Has received systemic immunosuppressants for >14 days in total within 180 days prior to Day 1 (for corticosteroids, ≥10 mg/day of prednisone or equivalent) or is anticipating the need for systemic immunosuppressive treatment at any time during participation in the study. Inhaled nasal and topical steroids are allowed. Intra-articular and epidural steroid injections are not allowed within 28 days before and/or after study injection.	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 either a COVID-19 vaccine or influenza vaccine. Countries have amended/approved an additional primary series dose in immunocompromised patients to achieve an adequate, more robust immune response. The mCOMBRIAX SmPC states that safety and immunogenicity data on the vaccine 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.

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing)
Has received systemic immunoglobulins or blood products ≤90 days prior to the Screening Visit or plans to receive systemic immunoglobulins or blood products during the clinical 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. The mCOMBRIAX SmPC states that safety and immunogenicity data on the vaccine 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 the Screening Visit or plans to donate blood products during the study.	Allowance of these conditions would confound assessment of efficacy.	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 mCOMBRIAX in these participants would be different from the rest of the population receiving mCOMBRIAX.
Has a history of myocarditis or pericarditis or myopericarditis within 90 days prior to the Screening Visit.	Including this population could have impacted the safety outcome of the study.	No	Myocarditis and pericarditis are important potential risks (Module SVII.1.2).
Has a history of Guillain-Barre syndrome.	Allowance of this condition would confound assessment of safety and efficacy.	No	New onset of or worsening of neurologic diseases, including Guillain-Barré syndrome, were adverse events of special interest (AESI) in the study as they are recognised to occur with some vaccines.
Dermatologic conditions that could affect local solicited adverse reaction assessments (eg, tattoos, 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. However, there is no suspected reason to expect the safety or efficacy of mCOMBRIAX in these individuals would be different from the rest of the population receiving mCOMBRIAX.
Diagnosis of malignancy within the previous 2 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 mCOMBRIAX in these individuals would be different from the rest of the population receiving mRNA-1083. However, if the individual is immunocompromised the efficacy of mCOMBRIAX could be impacted. The mCOMBRIAX SmPC states that safety and immunogenicity data on the vaccine 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.

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing)
Reported history of congenital or acquired immunodeficiency (eg, HIV), immunocompromising/immunosuppressive condition, asplenia, or recurrent severe infections.	Allowance of these conditions would confound assessment of safety and efficacy.	No	No significant safety concerns have been identified in the literature to date for vaccination of immunocompromised patients with an influenza or COVID-19 vaccine. The mCOMBRIAX SmPC states that safety and immunogenicity data on the vaccine are not available for immunocompromised individuals and that 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-1083 in the clinical development programme are unlikely to detect certain types of adverse reactions such as rare (<1/1,000) adverse reactions or adverse reactions with a long latency. There is no prolonged exposure to mRNA-1083.

The safety profile is based on the randomised, observer-blind, active-controlled Phase 3 Study mRNA-1083-P301, in which 2011 participants aged ≥65 years of age and 1993 participants aged 50 to <65 years of age received 1 injection of 40 µg mRNA-1083, and supported by safety data from Phase 1/2 Study mRNA-1083-P101 wherein a total 128 participants aged 50 years or older received 1 injection of 30 or 60 µg mRNA-1083. In these 2 studies combined, a total of 4132 participants ≥50 years have received mRNA-1083 (5:1 ratio) at 30 µg, 40 µg, or 60 µg, including 4004 participants in Study mRNA-1083-P301 who have received mRNA-1083 40 µg.

In Study mRNA-1083-P301, the median duration of follow-up in both groups was 171 days among participants ≥65 years (Cohort A), and 171 days in the mRNA-1083 group and 170 days in the Fluarix + Spikevax group among participants ≥50 to <65 years (Cohort B) (Table 4, Table 8; Module SIII). In Study mRNA-1083-P101, the median duration of follow-up after injection on Day 1 was approximately 170 days in mRNA-1083 30 µg and 60 µg groups in both age cohorts (Table 12; Module SIII).

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

Table 17: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Paediatric participants	Paediatrics <18 years of age were not included in the clinical development programme to support the indication in individuals ≥50 years.
Pregnant women	Not included in the clinical development programme to support the indication in individuals ≥50 years.

Type of Special Population	Exposure
Breastfeeding women	Not included in the clinical development programme to support the indication in individuals ≥50 years.
Participants with relevant comorbidities	
Participants with hepatic impairment	Hepatic impairment at baseline was not evaluated in the clinical development programme, however, in Study mRNA-1083-P301 participants had a medical history of hepatobiliary disorders (8.9% and 6.4%) in the mRNA-1083 group of Cohort A and Cohort B, respectively. The most frequently reported hepatobiliary disorders were cholelithiasis 5.0%, cholecystitis 1.9%, and non-alcoholic fatty liver 0.6% in Cohort A; and cholelithiasis 3.9%, cholecystitis 1.8%, and hepatic steatosis 0.5% in Cohort B (mRNA-1083-P301 CSR, Table 14.1.5.1a and Table 14.1.5.1b).
Participants with renal impairment	Renal impairment at baseline was not evaluated in the clinical development programme, however, in Study mRNA-1083-P301 participants had a medical history of renal and urinary disorders (13.1% and 5.1%) in the mRNA-1083 group of Cohort A and Cohort B, respectively. The most frequently reported renal and urinary disorders were hypertonic bladder 3.4%, urinary incontinence 2.9%, chronic kidney disease 2.5%, and nephrolithiasis 2.4% in Cohort A; and urinary incontinence 1.3%, nephrolithiasis 1.3%, hypertonic bladder 1.2%, and chronic kidney disease 0.9% in Cohort B (mRNA-1083-P301 CSR, Table 14.1.5.1a and Table 14.1.5.1b).
Participants with cardiovascular impairment	In Study mRNA-1083-P301, participants had a medical history of cardiac disorders (13.9% and 5.5%) in the mRNA-1083 group of Cohort A and Cohort B, respectively. The most frequently reported cardiac disorders were atrial fibrillation 4.3%, coronary artery disease 4.2%, and myocardial infarction 1.9% in Cohort A; and coronary artery disease 1.3%; atrial fibrillation 1.1.%; cardiac failure congestive 0.7% in Cohort B (mRNA-1083-P301 CSR, Table 14.1.5.1a and Table 14.1.5.1b).
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-1083-P301 are presented in Table 6 and Table 7 for Cohort A, and Table 10 and Table 11 for Cohort B (Module SIII), respectively. In this study, the majority of participants in Cohort A and Cohort B were White (78.4% and 68.9%) followed by Black or African American (18.4% and 25.9%), Asian (1.2% and 2.5%), American Indian or Alaska Native (0.4% and 0.6%), Native Hawaiian or Other Pacific Islander (<0.1% and 0.2%), multiple (0.7% and 1.0%), other (0.2% and 0.2%); in 0.5% and 0.8% of participants the race was unknown/not reported, respectively (mRNA-1083-P301 CSR, Table 14.1.4.4a and Table 14.1.4.4b). In terms of ethnicity, the majority of participants in Cohort A and Cohort B of mRNA-1083-P301 were Not Hispanic or Latino (83.9% and 79.1%), followed by Hispanic or Latino (14.1% and 19.7%); in 2.0% and 1.3% of participants ethnicity was unknown/not reported, respectively (mRNA-1083-P301 CSR, Table 14.1.4.4a and Table 14.1.4.4b).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.

Type of Special Population	Exposure
Others	
Participants ≥75 years of age	Participant exposure by age in Study mRNA-1083-P301 is presented in Table 5 and Table 9 (Module SIII). In this study, 20.7% of participants were ≥75 years of age in the mRNA-1083 40 µg group of Cohort A (mRNA-1083-P301 CSR, Table 14.1.4.4a). One participant was ≥75 years of age in the mRNA-1083 40 µg group of Cohort B (mRNA-1083-P301 CSR, Listing 16.2.4.1).
Diabetes (Type I, Type II)	In Study mRNA-1083-P301, participants had a medical history of Type I diabetes mellitus (<0.1% and 0.3%), Type II diabetes mellitus (21.6% and 14.4%), and diabetes mellitus (<0.1% and 0.4%) in Cohort A and Cohort B, respectively (mRNA-1083-P301 CSR, Table 14.1.5.1a and Table 14.1.5.1b).
Chronic lung disease	In Study mRNA-1083-P301, participants had a medical history of asthma (7.6% and 7.2%), COPD (4.5% and 2.2%), emphysema (0.3% and 0.0%), bronchitis chronic (0.4% and 0.1%), and chronic respiratory failure (<0.1% and <0.1%) in Cohort A and Cohort B, respectively (mRNA-1083-P301 CSR, Table 14.1.5.1a and Table 14.1.5.1b)
Severe obesity (BMI ≥40 kg/m^2)	In study mRNA-1083-P301, 922 (45.8%) participants in Cohort A and 1024 (51.4%) participants in Cohort B had a BMI of ≥30 kg/m^2 (mRNA-1083-P301 CSR, Table 14.1.4.1a and Table 14.1.4.1b).
HIV infection	History of congenital or acquired immunodeficiency (eg, HIV) was an exclusion criterion in studies mRNA-1083-P101 and mRNA-1083-P301. One participant had a medical history of HIV infection in Study mRNA-1083-P301, and was randomised to the control arm of Cohort B (mRNA-1083-P301 CSR, Table 14.1.5.1a and Table 14.1.5.1b).

Part II: Module SV – Post-Authorisation Experience

SV.1 Post-Authorisation Experience

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	None

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 an LNP-encapsulated mRNA-based vaccine for active immunisation to prevent COVID-19 caused by SARS-CoV-2 (SPIKEVAX^{TM}). The vaccine is updated seasonally to provide immunity to circulating variants.

Myocarditis and pericarditis are important identified risks for currently approved COVID-19 vaccines including non-mRNA-based 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).

The mCOMBRIAX vaccine is an LNP-encapsulated, mRNA-based, multi-component vaccine encoding antigens from seasonal influenza viruses and SARS-CoV-2. For SARS-CoV-2 component, mCOMBRIAX has an improved formulation encoding 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 mCOMBRIAX immunogen is expected to be released into systemic circulation. Therefore, it is hypothesised that limited quantity of circulating spike protein that can interact with heart tissue has the potential to mitigate the risk of myocarditis and/or pericarditis. No events of myocarditis or/and pericarditis have been observed in mRNA-1083 programme. Hence, myocarditis and pericarditis are considered important potential risks (Module SVII.1.2.)

Degradation

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

Adjuvant statement

The mCOMBRIAX 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 mCOMBRIAX, 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

  In the mRNA-1083-P301 pooled cohort, solicited local and systemic ARs were predominantly mild to moderate, transient and of minimal clinical impact. Solicited local ARs were reported in 77.5% of participants, the majority being mild to moderate (42.8% Grade 1 and 31.6% Grade 2). Grade 3 solicited local ARs were infrequent (3.1%) with injection site pain being most frequent (2.1%). Grade 3 solicited local ARs were transient and no Grade 4 solicited local ARs were reported.

  Similarly, solicited systemic ARs were reported in 72.6% of participants, the majority being mostly mild to moderate (26% Grade 1 and 37.3% Grade 2). Grade ≥3 solicited systemic ARs occurred in 9.2% of participants, most frequently fatigue (5.6%). Grade ≥3 solicited systemic ARs were transient. Fever >40°C was the only Grade 4 systemic solicited AR reported and occurred in 0.1% of participants. No safety concern was observed, as none of these Grade 4 fever events were MAAEs, met SAE criteria or persisted beyond Day 7. These transient local and systemic Grade ≥3 ARs were primarily self-limiting, manageable with standard symptomatic care, and less severe than the clinical manifestations of the target diseases, particularly those that require hospitalisation or are potentially life-threatening.

  Overall, the observed solicited local and systemic ARs are consistent with the known reactogenicity of intramuscularly administered vaccines, and the safety profile of mRNA-1083 remains acceptable. No significant safety concerns have been identified, and therefore, routine risk minimisation activities are considered sufficient to manage the expected reactogenicity.

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

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 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 (e.g. actions being part of standard clinical practice in each country where the product is authorised):

- Anaphylaxis

  Anaphylaxis is not an important risk of mCOMBRIAX.

  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 mCOMBRIAX 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.

  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-1083-P301 and supportive Study mRNA-1083-P101 as it is a recognised immediate systemic allergic reaction that can occur after any injectable vaccine.

  In Study mRNA-1083-P301, no cases of anaphylactic reaction were reported in either Cohort A or Cohort B throughout the study (mRNA-1083-P301 CSR Section 7.1.2, Table 14.3.2.12.2a, Table 14.3.2.12.2b). In Study mRNA-1083-P101, no case of anaphylaxis were reported throughout the study (mRNA-1083-P101 CSR, Section 7.1.2).

  Anaphylaxis can be managed post-authorisation with the guidance presented in the product information which contraindicates administration of mCOMBRIAX 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 severe hypersensitivity reactions, including anaphylaxis, following administration of the vaccine as recommended in the mCOMBRIAX SmPC. The SmPC recommends 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.2).

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 mCOMBRIAX.

Myocarditis and myopericarditis are AESI in pivotal Study mRNA-1083-P301 and supportive Study mRNA-1083-P101.

In Study mRNA-1083-P301, there were no events of myocarditis reported in Cohort A (mRNA-1083-P301 CSR Section 7.1.1, Table 14.3.2.14.2a) or Cohort B (mRNA-1083-P301 CSR Section 7.2.1, Table 14.3.2.14.2b) throughout the study. In Study mRNA-1083-P101, no events of myocarditis were reported throughout the study in individuals 50 years of age and older (mRNA-1083-P101 CSR, Section 7.1.2.5).

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). mCOMBRIAX 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 mCOMBRIAX immunogen is expected to be released into systemic circulation. mCOMBRIAX does not include the full S1 spike protein. Therefore, it is hypothesised that limited quantity of circulating S1 spike protein that can interact with heart tissue has the potential to mitigate the risk of myocarditis and/or pericarditis.

Based on the current available safety information for mCOMBRIAX, there is insufficient evidence at this time to confirm a temporal or causal association between myocarditis and mCOMBRIAX 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. Non-infectious triggers have been identified such as toxins, autoimmune 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 some other 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 mCOMBRIAX. The benefit of mCOMBRIAX as a preventive vaccine for seasonal influenza and 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 mCOMBRIAX.

The mCOMBRIAX SmPC advises healthcare professionals that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines. Healthcare professionals are advised to be alert to the signs and symptoms of myocarditis and pericarditis and to instruct vaccine recipients (including caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.

Myocarditis will be further characterised through planned post-authorisation safety study mRNA-1083-P907 and routine pharmacovigilance activities (Part III).

Important Potential Risk 2: Pericarditis

Pericarditis is an important potential risk of mCOMBRIAX.

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).

Pericarditis and myopericarditis are AESI in pivotal Study mRNA-1083-P301 and supportive Study mRNA-1083-P101.

In Study mRNA-1083-P301, there were no pericarditis events reported in Cohort A (mRNA-1083-P301 CSR Section 7.1.1, Table 14.3.2.14.1a, Table 14.3.2.14.2a) throughout the study nor in Cohort B up to 28 days after injection (mRNA-1083-P301 CSR Section 7.2.1, Table 14.3.2.14.1b). Up to EOS/Day 181, 1 participant in the mRNA-1083 group of Cohort B had an SAE of acute pericarditis with onset on Day 148 after study injection. The participant had the following ongoing medical conditions: essential hypertension, anxiety, attention deficit hyperactivity disorder, depression, insomnia, seasonal allergy, and micturition urgency. The event resolved with sequelae (to be followed up by cardiologist) on Day 158, and was assessed as not related to the study injection by the Investigator (Clinical Safety Summary 2.7.4 Section 2.7.4.2.2.2.4.4.2; mRNA-1083-P301 CSR Table 56; Table 14.3.2.12.3b, Table 14.3.2.14.2b; Listing 16.2.7.6). In Study mRNA-1083-P101, no events of pericarditis were reported throughout the study in individuals 50 years of age and older (mRNA-1083-P101 CSR, Section 7.1.2.5.2.13).

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). mCOMBRIAX 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 mCOMBRIAX immunogen is expected to be released into systemic circulation. mCOMBRIAX does not include the full S1 spike protein. Therefore, it is hypothesised that limited quantity of circulating S1 spike protein that can interact with heart tissue has the potential to mitigate the risk of myocarditis and/or pericarditis.

Based on the current data there is insufficient evidence at this time to confirm a temporal or causal association between pericarditis and mCOMBRIAX 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, only 1 event of pericarditis (considered unrelated) has been observed in the clinical studies to date with mCOMBRIAX.

The benefit of mCOMBRIAX as a preventive vaccine for seasonal influenza and 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 mCOMBRIAX.

The mCOMBRIAX SmPC advises healthcare professionals that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines. Healthcare professionals are advised to be alert to the signs and symptoms of myocarditis and pericarditis and to instruct vaccine recipients (including caregivers) to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.

Pericarditis will be further characterised through planned post-authorisation safety study mRNA-1083-P907 and routine pharmacovigilance activities (Part III).

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 18: Presentation of Important Potential Risks

Important Potential Risk	Myocarditis
Potential mechanism(s)	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% to 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 male 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 mRNA COVID-19 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). mCOMBRIAX 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 mCOMBRIAX COVID-19 immunogen is expected to be released into systemic circulation. Therefore, it is hypothesised that limited quantity of circulating S1 spike protein that can interact with heart tissue has the potential to mitigate the risk of myocarditis and/or pericarditis. This is anticipated to decrease the risk of myocarditis with mCOMBRIAX.

Important Potential Risk	**Myocarditis**
Evidence source(s) 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 mCOMBRIAX 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 can interact with heart tissue. In Study mRNA-1083-P301, there were no myocarditis events in either mRNA-1083 or Fluzone HD + Spikevax vaccinated participants. Likewise in study mRNA-1083-P101, no events of myocarditis were observed.
Characterisation of risk	In Study mRNA-1083-P301, there were no myocarditis events in participants in either Cohort A (≥65 years) or Cohort B (≥50 to <65 years) (mRNA-1083-P301 CSR, Section 7.1.1 and Section 7.2.1). In Study mRNA-1083-P101, the narrow scope SMQ for non-infectious myocarditis/pericarditis identified no events of myocarditis throughout the study among participants ≥50 years (mRNA-1083-P101 CSR, Section 7.1.2.5).
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 dilated cardiomyopathy 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 yet to be confirmed as causally associated with mCOMBRIAX but can be managed in clinical practice with supportive treatment should it occur. The mCOMBRIAX SmPC advises healthcare professionals that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines. These conditions can develop within a few days and primarily occurred within 14 days. They 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 caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.
Impact on the benefit-risk balance of the product	The benefit of mCOMBRIAX as a preventive vaccine for seasonal influenza and COVID-19 caused by SARS-CoV-2 is considered to outweigh the risk of myocarditis, a risk for which a causal association with mCOMBRIAX 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 mCOMBRIAX. 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(s)	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,

Important Potential Risk	**Pericarditis**
	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 male 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 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). mCOMBRIAX 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 mCOMBRIAX immunogen is expected to be released into systemic circulation. Therefore, it is hypothesised that lack of circulating spike protein that can interact with heart tissue has the potential to mitigate the risk of myocarditis and/or pericarditis. This is anticipated to decrease the risk of pericarditis with mCOMBRIAX.
Evidence source(s) 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 mCOMBRIAX 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 can interact with heart tissue. In Study mRNA-1083-P301, there was 1 pericarditis event in a mRNA-1083 vaccinated participant but which was assessed as not related to the study injection by the Investigator. In study mRNA-1083-P101, no events of pericarditis were observed throughout the study.
Characterisation of risk	In Study mRNA-1083-P301, there was 1 CEAC-confirmed pericarditis event. Among participants ≥50 to <65 years (Cohort B), there was 1 event of acute pericarditis in a 59-year-old male participant with onset on Day 148 that resolved on Day 158 with sequelae (to be followed up by cardiologist) and was assessed as not related to the study injection by the Investigator (Clinical Safety Summary 2.7.4 Section 2.7.4.2.2.2.4.4.2; Study mRNA-1083-P301 CSR Table 14.3.2.12.3b, Table 14.3.2.14.2b, and Listing 16.2.7.6). In study mRNA-1083-P101, no events of pericarditis were observed throughout the study (mRNA-1083-P101 CSR, Section 7.1.2.5.2.13).
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 2016).
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 1 of 2 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 yet to be confirmed as causally associated with mCOMBRIAX but can be managed in clinical practice with supportive treatment should it occur.

Important Potential Risk	**Pericarditis**
	The mCOMBRIAX SmPC advises healthcare professionals that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines. These conditions can develop within a few days and primarily occurred within 14 days. They 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 caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.
Impact on the benefit-risk balance of the product	The benefit of mCOMBRIAX as a preventive vaccine for seasonal influenza and COVID-19 caused by SARS-CoV-2 is considered to outweigh the risk of pericarditis, a risk for which a causal association with mCOMBRIAX 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 mCOMBRIAX. 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

Not applicable.

Part II: Module SVIII – Summary of the Safety Concerns

Table 19: Summary of Safety Concerns

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

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 principles of the Guideline on Good Pharmacovigilance Practices Module IX for Signal Management (Rev.1) (GVP Module IX - Signal Management). During signal detection, data sources will be screened for new safety information related to mCOMBRIAX. 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 non-interventional 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 PV activities, Moderna performs periodic signal detection analyses, in line with the product’s SSP. These analyses include but are not limited to safety concerns, 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 mCOMBRIAX, 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 2023)
- 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 20.

Table 20: 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 mCOMBRIAX. 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 (Only if product is approved in EU)	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).

Data Source	Frequency of Safety Evaluations
VAERS (Only if product is approved in US)	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 the Moderna electronic signal detection and management system.
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 21: Product Surveillance List of Signalling Strategy by Category

Category	Safety Topics (Updates may be Needed if New Adverse Events Emerge)
Safety concerns	Myocarditis Pericarditis
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 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

As support to signal detection, when relevant, observed rates of AEs will be compared with the expected rates which will be available from the scientific literature or other sources (Willame et al 2021).

During the evaluation of validated signals, Moderna is planning to use globally representative and/or EU-specific background incidence rates from high-quality epidemiologic publications where feasible and available. Should such data not be available or feasible to access in a timely manner, available US-based data will be used, and a discussion of demographic comparability will be included.

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 influenza or COVID-19 cases requiring hospitalisation, and vaccination administration errors that may have been reported to occur in vaccinees.

Potential medication errors

Potential storage, handling, dosing, and administration medication errors with mCOMBRIAX are very limited and mitigated through the guidance in the mCOMBRIAX SmPC.

Traceability

mCOMBRIAX 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.

Moderna will ensure end-to-end traceability so that ADRs can be attributed to the original versus updated formulation/strain. Moderna's approach combines distinct identifiers and EU Hub connectivity with point-of-care traceability tools and product-stratified surveillance.

III.2 Additional Pharmacovigilance Activities

The planned additional pharmacovigilance activities are presented in Table 22.

Table 22: Additional Pharmacovigilance Activities

Study Number, Title, and Status	Rationale and Study Objectives	Study Design	Study Population	Milestones
mRNA-1083-P907 Post-marketing safety of the mRNA-1083 vaccine in Europe Planned	Primary Objectives: • Monitor the distribution of mRNA-1083 in Europe • Describe the uptake of mRNA-1083, characterise vaccine recipients, and estimate the incidence of myocarditis and pericarditis among them • Compare the risk of myocarditis and pericarditis between mRNA-1083 recipients and an unexposed reference population	Retrospective EU cohort study in a staged approach	Vaccinated adults	Protocol submission: Sep 2026 Final report: May 2030

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 23: 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-1083-P907 Post-marketing safety of the mRNA-1083 vaccine in Europe Planned	Primary Objectives: • Monitor the distribution of mRNA-1083 in Europe • Describe the uptake of mRNA-1083, characterise vaccine recipients, and estimate the incidence of myocarditis and pericarditis among them • Compare the risk of myocarditis and pericarditis between mRNA-1083 recipients and an unexposed reference population	Myocarditis Pericarditis	Protocol submission Final report	Sep 2026 May 2030

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 24: 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 mCOMBRIAX 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. These conditions can develop within a few days and primarily occurred within 14 days. They have been observed more often in younger males (SmPC Section 4.4). • Warning for patients to be alert to signs of myocarditis and pericarditis following vaccination, such as breathlessness, palpitations and chest pain, 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 mCOMBRIAX 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. These conditions can develop within a few days and primarily occurred within 14 days. They have been observed more often in younger males (SmPC Section 4.4). • Warning for patients to be alert to signs of myocarditis and pericarditis following vaccination, such as breathlessness, palpitations and chest pain, and to seek immediate medical attention should these occur (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-1083.

V.3 Summary of Risk Minimisation Measures

Table 25: 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 to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines in SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study mRNA-1083-P907

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Warning for patients to be alert to signs of myocarditis and pericarditis following vaccination and to seek immediate medical attention should these occur in SmPC Section 4.4 and PL Section 2. Additional risk minimisation measures: • None	
Pericarditis (Important potential risk)	Routine risk minimisation measures: • Warning to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines in SmPC Section 4.4 • Warning for patients to be alert to signs of myocarditis and pericarditis following vaccination and to seek immediate medical attention should these occur in SmPC Section 4.4 and PL Section 2. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study mRNA-1083-P907

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for mCOMBRIAX (influenza and COVID-19 mRNA vaccine)

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

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

This summary of the RMP for mCOMBRIAX 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 mCOMBRIAX's RMP.

I. The Medicine and What It Is Used For

mCOMBRIAX is indicated for active immunisation for the prevention of influenza disease and COVID-19 caused by SARS-CoV-2 in individuals 50 years of age and older. The active substance is nucleoside modified mRNAs encoding seasonal influenza HA glycoproteins and 2 key subdomains of the SARS-CoV-2 spike glycoprotein, and it is given by intramuscular route.

Further information about the evaluation of mCOMBRIAX's benefits can be found in mCOMBRIAX'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 mCOMBRIAX, together with measures to minimise such risks and the proposed studies for learning more about mCOMBRIAX'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 (e.g., 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 periodic safety update report (PSUR) assessment - so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of mCOMBRIAX 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 mCOMBRIAX. 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 26: 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	None

II.B Summary of Important Risks

Table 27: 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 mCOMBRIAX 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 can interact with heart tissue. In Study mRNA-1083-P301, there were no myocarditis events in either mRNA-1083 or Fluzone HD + Spikevax vaccinated participants. Likewise in study mRNA-1083-P101, no events of myocarditis were observed.
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).
Risk minimisation measures	Routine risk minimisation measures: Warning to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines in SmPC Section 4.4. Warning for patients to be alert to signs of myocarditis and pericarditis following vaccination and to seek immediate medical attention should these occur in SmPC Section 4.4 and PL Section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1083-P907 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 28: 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 mCOMBRIAX 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 can interact with heart tissue. In Study mRNA-1083-P301, there was 1 pericarditis event in a mRNA-1083 vaccinated participant but which was assessed as not related to the study injection by the Investigator. In study mRNA-1083-P101, no events of pericarditis were observed throughout the study.
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 2016).

Important Potential Risk: Pericarditis	
Risk minimisation measures	Routine risk minimisation measures: Warning to be aware that an increased risk of myocarditis and pericarditis has been observed following vaccination with some other COVID-19 vaccines in SmPC Section 4.4. Warning for patients to be alert to signs of myocarditis and pericarditis following vaccination and to seek immediate medical attention should these occur in SmPC Section 4.4 and PL Section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1083-P907 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 mCOMBRIAX.

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

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

Table 29: Other Studies in the Post-Authorisation Development Plan

Study Title and Number ***Status***	**Purpose of the Study**
mRNA-1083-P907 Post-marketing safety of the mRNA-1083 vaccine in Europe *Planned*	Primary Objectives: • Monitor the distribution of mRNA-1083 in Europe • Describe the uptake of mRNA-1083, characterise vaccine recipients, and estimate the incidence of myocarditis and pericarditis among them • Compare the risk of myocarditis and pericarditis between mRNA-1083 recipients and an unexposed reference population

Abbreviations: mRNA = messenger ribonucleic acid

Part VII: Annexes

Table of Contents (Annexes)

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

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

Not applicable.