26 February 2026
EMADOC-1829012207-46393
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

mCOMBRIAX

Common name: Influenza and COVID-19, mRNA vaccine

Procedure No. EMEA/H/C/006472/0000

Note

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

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AET	Analytical evaluation threshold
AEX-HPLC	Anion exchange - high performance liquid chromatography
AF4-MALS	Asymmetric flow field flow fractionation - multiangle light scattering
ANCOVA	Analysis of covariance
AR	Adverse reaction
BF/GF	Break-loose/Gliding force
BMI	Body mass index
CCI	Container closure integrity
CCS	Container closure system
CD	Circular dichroism
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFT	Cell-free translation
CI	Confidence interval
cIEF	Capillary isoelectric focussing
CIP	Clean in place
CIPC	Critical in-process control
CNS	Central nervous system
COC	Cyclic olefin copolymer
COVID-19	Coronavirus disease 2019
CPD	Cumulative process duration
CPP(s)	Critical process parameter(s)
CQA	Critical quality attribute
CRO	Clinical research organization
CSR	Clinical study report
DBL	Database lock
DLS	Dynamic light scattering
DOE	Design-of-experiments
DP	Drug product
DS	Drug substance
DSC	Differential scanning calorimetry
DSMB	Drug Safety Monitoring Board
DSPC	(1,2-distearoyl-sn-glycero-3-phosphocholine) (excipient)
eCRF	Electronic case report form
eDiary	Electronic diary
EM	Electron microscopy
EOS	End of study
EOSL	End of shelf-life
EQ-5D-5L	EuroQol 5dimension 5level
EQ-VAS	EuroQol – visual analog scaleg
FAS	Full Analysis Setg
FMEA	Failure Modes and Effects Analysisg
GC-MS	Gas chromatography - mass spectrometry
GCP	Good Clinical Practice
GLSM	Geometric least squares mean
GM	Geometric mean
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMR	Geometric mean ratio
GMT	Geometric mean titre
HA	Haemagglutinin glycoprotein (of Influenza virus)
HAI	Haemagglutination inhibition
HD	High dose
HPLC-CAD	High performance liquid chromatography - charged aerosol detection
HPLC-MS	High performance liquid chromatography – mass spectrometry
HRMS	High-resolution mass spectrometry
ICF	Informed consent form
ICH	International Council for Harmonisation

ICP-MS	Inductively coupled plasma - mass spectrometry
IM	Intramuscular(ly)
IPC(s)	In-process control(s)
IRB	Institutional review board
IRM	Interim reference material
ITC	Isothermal calorimetry
IVRPE	In vitro relative protein expression
IVT	In vitro transcription
LC-MS	Liquid chromatography - mass spectrometry
LC-UV-MS	Liquid chromatography – ultraviolet – mass spectrometry
LDP	Labelled drug product
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle (intermediate)
LOD	Limit of detection
LOQ	Limit of quantitation
MAAE	Medically attended adverse event
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralisation
mRNA	Messenger ribonucleic acid
mRNA-1083	Quadrivalent Influenza and COVID-19, mRNA Vaccine (similar to mCOMBRIAX with B/Yamagata in its composition)
mRNA-1273	Moderna´s authorised SARS-CoV-2 vaccine Spikevax
mRNA-1283	Moderna´s 2nd generation SARS-CoV-2 vaccine mNEXSPIKE
mRNA-1345	Moderna´s authorised RSV vaccine mRESVIA
nAb	Neutralising antibody
NGS	Next generation sequencing
NH	Northern Hemisphere
NI	Noninferiority
NIM	Noninferiority margin
NoB	Notified body
NP	Nasopharyngeal
NTA	Nanoparticle tracking analysis
NTD	N-terminal domain
OOS	Out of specification
OOT	Out of trend
OQ	Operational qualification
ORF	Open reading frame
PAR(s)	Proven acceptable range(s)
PCR	Polymerase chain reaction
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (excipient)
PETG	Polyethylene terephthalate glycol
PFS	Prefilled syringe
PP(s)	Process parameter(s)
PPIS	Per-Protocol Immunogenicity Set
PPQ	Process performance qualification
PQ	Performance qualification
PRM	Primary reference material
PSB(s)	Primary stability batch(es)
PSL(s)	Primary stability lot(s)
PsVNA	Pseudovirus neutralisation assay
PT	Preferred term
QA(s)	Quality attribute(s)
QC	Quality control
RBD	Receptor-binding domain
RNA	Ribonucleic acid
RP-IP-HPLC	Reversed phase – ion pair – high performance liquid chromatography
RT PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	Seroconversion rate
SCT	Safety concern threshold
SD	Standard deviation

SDM	Scale-down model
SH	Southern Hemisphere
SM-102	(heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octanoate
SOC	System organ class
S-protein	Spike glycoprotein (of SARS-CoV-2) (excipient)
SRR	Seroresponse rate
SST	System suitability test
TFF	Tangential flow filtration
TOR	Time out of refrigeration
TOST	Two one-sided test
UDP	Unlabelled drug product
ULDPE	Ultra-low-density polyethylene
ULOQ	Upper limit of quantification
UTR(s)	Untranslated region(s)
UV	Ultraviolet
WCB	Working cell bank
WHO	World Health Organization
WPAI:GH	Work Productivity and Activity Impairment: General Health
WRM	Working reference material

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	mCOMBRIAX
Active substance	single-stranded, 5'-capped messenger RNAs (mRNAs) produced using a cell-free in vitro transcription from the corresponding DNA template, encoding seasonal influenza haemagglutinin (HA) glycoproteins: A/H1N1, A/H3N2, B/Victoria, and the linked N terminal domain and receptor-binding domain of the viral spike (S) protein of SARS CoV 2.
INN or common name	Influenza and COVID-19, mRNA vaccine
Applicant	Moderna Biotech Spain S.L. Calle De Julian Camarillo 31 Poligono Julian Camarillo 28037 Madrid SPAIN
EMA Product Number	EMEA/H/C/006472
ATC code and Pharmacotherapeutic group	Not yet assigned
Pharmaceutical form(s) and strength (s)	Dispersion for injection A/Wisconsin/67/2022 (A/H1N1) ...8.3 micrograms RNA A/Darwin/6/2021 (A/H3N2) .....8.3 micrograms RNA B/Austria/1359417/2021 (B/Victoria lineage) 8.3 micrograms RNA SARS-CoV 2 Omicron XBB.1.5 .....6.7 micrograms RNA
Packaging	pre-filled syringe (cyclic olefin copolymer) in a tray.
Package size(s)	1 pre-filled syringe, 10 pre-filled syringes
Route of administration	Intramuscular use
Device or diagnostic	pre-filled syringe
Orphan designation	No
Orphan indication status confirmed	No
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final 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. The use of this vaccine should be in accordance with official recommendations.
New active substance status	Granted for the influenza active substances

1.2. Scientific advice

Table 1. Scientific Advice provided by CHMP regarding mRNA-1083 and/or the component vaccines mRNA-1010 and mRNA-1283.

Date	Topic (quality / non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
16 January 2023	Clinical Non-clinical	EMA/SA/0000121008 / Mair Powell	The Scientific advice pertained to the following aspects: • Non-clinical plan to support Phase 3 and submission of a Marketing Authorisation Application for mRNA-1283.222 vaccine • Dose selection • Design of the P301 study, as a pivotal safety and immunogenicity trial to support licensure of mRNA-1283.222 • Regulatory strategy
14 September 2023	Clinical	EMA/SA/0000143761 / Mair Powell	The Scientific advice pertained to the following clinical aspects: • Design of the pivotal mRNA-1083-P301 safety and immunogenicity trial • Strategy proposing statistically powered non-inferior immunogenicity of mRNA-1083 compared to co-administered standard of care (authorised influenza vaccine + SARS-CoV-2 Vaccine) to support MAA
9 November 2023	Clinical Quality	EMA/SA/0000149655 / Manuela Mura, Yuansheng Sun	The Scientific advice pertained to the following scientific aspects: • PPQ data package • CMC annual strain update submission package • Agreement that the proposed registration package consisting of complete 6 months of safety data from P301 (N=3035 exposed), P302 (N=11,211 exposed), and P303 (N=1221 exposed), is adequate to support mRNA-1010 licensure for the intended indication
12 December 2024	Clinical	EMA/SA/0000221399 / Eleonora Wijnans	The Scientific advice pertained to the following clinical aspects: • Acceptability of the HAI as the primary analysis endpoint and as a surrogate endpoint for clinical benefit for mRNA-based influenza vaccines including statistical analysis methodology used to establish the model to correlate vaccine efficacy with HAI surrogate endpoint, as well as the use of this model to demonstrate that the mRNA-based influenza vaccines perform no differently

			than a licensed SD and HD egg-based influenza vaccines.

1.3. Eligibility to the centralised procedure

The applicant Moderna Biotech Spain S.L. submitted on 19 December 2024 an application for Marketing Authorisation to the European Medicines Agency (EMA) for mCOMBRIAX, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

mCOMBRIAX is indicated for active immunisation for the prevention of diseases associated with seasonal influenza viruses represented in the vaccine and SARS-CoV-2 in individuals 50 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/PE/0000227301 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000227301 was not yet completed as some measures were deferred.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Applicant's request(s) for consideration

1.7.1. New active substance status

The applicant requested the active substance single-stranded, 5'-capped messenger RNAs (mRNAs) produced using a cell-free in vitro transcription from the corresponding DNA template, encoding seasonal influenza haemagglutinin (HA) glycoproteins: A/H1N1, A/H3N2, B/Victoria, and the linked N terminal domain and receptor-binding domain of the viral spike (S) protein of SARS-CoV-2 contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that single-stranded, 5'-capped messenger RNAs (mRNAs) produced using a cell-free in vitro transcription from the corresponding DNA template, encoding seasonal influenza haemagglutinin (HA) glycoproteins: A/H1N1, A/H3N2, B/Victoria, are to be qualified as new active substances in itself as they are not a constituent of a medicinal product previously authorised within the European Union.

Refer to the Appendix on new active substance status claim assessment report.

On 17 February 2026, the applicant withdrew their request for new active substance for 5'-capped messenger RNAs (mRNAs) produced using a cell-free in vitro transcription from the corresponding DNA template, encoding the linked N terminal domain and receptor-binding domain of the viral spike (S) protein of SARS-CoV-2.

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Daniela Philadelphy
Co-Rapporteur:	Patrick Vrijlandt

The Rapporteur and Co-Rapporteur appointed by the PRAC were:

PRAC Rapporteur:	Georgia Gkegka
PRAC Co-Rapporteur:	Sonja Hrabcik

The application was received by the EMA on	19 December 2024
The procedure started on	23 January 2025
The CHMP Rapporteur's first Assessment Report was received on	14 April 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	16 April 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	28 April 2025
The Emergency Task Force (ETF) agreed on the Assessment Overview during their meeting on	13 May 2025
The Biologics Working Party agreed on the Assessment Overview during their	14 May 2025

meeting on	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 May 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	08 October 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 January 2026
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation on	26 February 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	26 February 2026

1.9. CHMP outcome

1.9.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.9.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.9.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of mCOMBRIAX is favourable in the following indication(s):

"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."

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.9.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.9.5. Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory, or a laboratory designated for that purpose.

1.9.6. Other conditions and requirements of the marketing authorisation

Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.9.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.9.8. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.9.9. Proposed list of recommendations

Table 2: Proposed list of recommendations

Description of Recommendation(s)
1. Stability data for LDP PPQ lots manufactured according to Process flow 1 that have undergone an interim storage period at the UDP stage should be provided in a subsequent post-approval variation

Description of Recommendation(s)
submission. The corresponding stability studies should foresee LDP storage for 11 months at -25ºC to -15ºC, followed by storage for 30 days at 2°C to 8°C and 24 hours at ambient light conditions and 25°C. 2. Envisaging potential future annual strain updates, the applicant will perform in silico analysis (B strains) and confirm protein expression using the in vitro protein expression assay (IVRPE). To further support annual strain updates, the applicant should evaluate immunogenicity of HA antigens in a suitable animal model as well. Generated antisera should be tested for their activity towards the recommended wild type influenza strains or recommended influenza candidate vaccine virus strains. Comparison to data from strains that were actually tested in clinical trials is recommended. Small scale monovalent vaccine formulations (LNP containing only one single HA mRNA) may be used for these characterisation studies. It is also strongly recommended to evaluate whether the HA antigens expressed by the mRNA (e.g. by analysing cells with membrane-associated expression of HA, after transfection of cells with the mRNA vaccine, possibly with monovalent formulations) are sufficiently recognised by antisera against the recommended influenza strains (available from WHO collaborating centres or Essential regulatory laboratories). 3. The Applicant should provide full method validation data for the CCI test method at the intended commercial manufacturing site in a post-approval variation. 4. The release specification for IVRPE should be further evaluated upon availability of data from 30 additional commercial scale data lots and submit any updates to the control strategy in a postapproval variation. 5. The applicant should explore orthogonal methods for characterization of DNA content and size and provide supporting characterization data within 18 months of market approval. 6. The applicant should implement an optimized method to quantify PolyA tailed RNA. The anticipated variation submission is planned for December 2026. A method validation report, method description, and bridging study summary should be provided at that time. 7. Supplementary method validation data covering an expanded assay range for IVRPE should be submitted before release of any mRNA-1083 to the EU market. 8. The lipid changes observed upon storage under refrigerated conditions should be further investigated. 9. mCOMBRIAX effectiveness of the influenza component for all included influenza strains should be confirmed over several seasons in a post-authorisation study. The applicant is advised to submit the protocol when available.

2. Introduction

2.1. Therapeutic Context

Both influenza and COVID-19 are diseases which primarily manifest respiratory symptoms, such as cough and nasal congestion, and systemic symptoms, such as fever and chills; symptoms may be mild to severe. Influenza can manifest 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. The clinical manifestations of COVID-19 may also include loss of taste or smell, and the spectrum of illness can range from asymptomatic infection to severe pneumonia, ARDS, respiratory failure, septic shock, multiple organ dysfunction or failure, and death. While COVID-19 is primarily a pulmonary disease, it can also lead to cardiac, dermatologic, haematologic, hepatic, neurologic, renal, and other complications, including thromboembolic events and peri- and myocarditis. Both influenza and COVID-19 are associated with health loss in the post-acute infection phase.

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. Influenza type A and B viruses are responsible for seasonal influenza epidemics in humans each year. Influenza A viruses are classified into subtypes according to the combination of HA and neuraminidase glycoproteins they express on the viral surface, while influenza B viruses are classified into 2 lineages: B/Victoria and B/Yamagata. B/Yamagata has not been detected in circulation since March 2020. HA proteins bind to specific sialic acid moieties on epithelial cells in the mammalian respiratory tract, which facilitates cellular entry. Substantial antigenic drift occurs, particularly among influenza A subtypes (e.g., A/H3N2, A/2009H1N1 pdm09) leading to frequent changes in circulating clades. This results in the need for periodic updates to the strains included in seasonal influenza vaccines.

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 2023b). 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 2020 (CDC 2023b). 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).

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 lower respiratory tract infection in 2017 occurred among adults >70 years (16.4 deaths per 100,000). 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 2022d). Similarly, 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).

Apart from age-related increased risk, presence 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/m2, genetic conditions, chronic diseases, or treatments that suppress the immune function), pregnant women, and children <5 years.

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. SARS-CoV-2 targets ACE2 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).

Since the outbreak of the pandemic, multiple SARS-CoV-2 variants (e.g., 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, requiring COVID-19 vaccine updates.

As of 8 February 2026, 779,125,257 COVID-19 cases and more than 7.1 million deaths had been reported globally. In Europe, as of 8 February 2026, 281,735,665 COVID-19 cases and 2,282,775 deaths had been reported.

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-fall and winter months. Globally in 2023, COVID-19 cases peaked in August (702,000 new cases the week of 06 August 2024) with another peak in December (382,000 new cases the week of 17 December 2024). COVID-19 cases rose again in the Summer of 2024, with 57,300 new weekly cases detected in late July 2024. 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 August 2024.

The majority of infections result in asymptomatic or mild disease with full recovery. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

The aetiology and pathogenesis of the main acute COVID-19 disease manifestations (i.e., pneumonia, myocarditis) are well understood. COVID-19 is also associated with a heterogenous group of post-acute, persistent symptoms and sequelae (currently described as long COVID), for which aetiology and pathogenesis are less well understood.

Available Interventions

For influenza, preventive strategies in the EU focus primarily on vaccination. A wide array of inactivated influenza vaccines is available, including split-virion and subunit vaccines produced using either egg-based or cell-based manufacturing processes. These are available in both trivalent and quadrivalent formulations, with each dose typically containing 15 micrograms of HA per strain. In addition, high-dose and adjuvanted trivalent vaccines are available for use in older adults, though these are not indicated for use in younger adult populations.

There are antiviral medicines approved in the EU to treat influenza. For the best clinical benefit, treatment with antivirals should be given early in the infection, within 48 hours (the earlier the better), to reduce the fever and flu-like symptoms. Antivirals may also reduce the risk of complications such as ear infections in children, respiratory complications requiring antibiotics, and hospitalisation in adults.

The use of antivirals can induce drug-resistant mutants. The level of antiviral resistance is closely followed by public health authorities.

The most effective way to prevent COVID-19 is vaccination. There are currently 6 vaccines authorised in the EU (i.e., Comirnaty, Spikevax, Nuvaxovid, Bimervax, Kostaive, mNEXSPIKE). COVID-19 vaccines have been shown to be effective in reducing the risk of disease and severe disease from SARS-CoV-2 infection.

The main treatment for most patients with severe disease is supportive care, which is often highly effective, antiviral medication (monoclonal antibodies and/or available antiviral drugs) where

appropriate, and immune modulators.

2.2. Aspects of development

The applicant is requesting a marketing authorisation for the vaccine candidate mCOMBRIAX, a multicomponent vaccine encoding antigens from seasonal influenza viruses and from SARS-CoV-2, which is intended for active immunisation for the prevention of diseases associated with seasonal influenza viruses represented in the vaccine and SARS-CoV-2 in persons 50 years of age and older.

The mRNA-1083 clinical development program includes a Phase 1/2 study (mRNA-1083-P101) and a Phase 3 study (mRNA-1083-P301). Supportive information comes from the clinical development programs for the component vaccines, mRNA-1010 (Moderna's seasonal influenza mRNA vaccine) and mRNA-1283 (Moderna´s 2nd generation SARS-CoV-2 mRNA vaccine, mNEXSPIKE). Of note, during the development of mRNA-1010, the mRNAs corresponding to the B strains were modified with the purpose of increasing the stability of the influenza B HAs (the optimized mRNA-1010 composition, which is also included in the mRNA-1083 vaccine, was first used in study mRNA-1010-P303).

2.3. Description of the product

mCOMBRIAX is an LNP-encapsulated, mRNA-based vaccine encoding antigens from seasonal influenza and SARS-CoV-2 viruses. The influenza antigens encoded by mCOMBRIAX are the full-length, membrane-bound HA glycoproteins of WHO-recommended seasonal influenza virus types A (H1N1 and H3N2) and B (Victoria lineage), although during the development the formulation investigated includes an additional strain B/Yamagata in the composition. The SARS-CoV-2 antigen encoded by mCOMBRIAX is a protein made up of the two key subdomains of the SARS-CoV-2 Spike glycoprotein, the NTD (linked N-terminal domain) and the RBD (receptor binding domain).

The applicant's mRNA-based vaccine platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express encoded antigens. After delivery into cells, the mRNA serves as a template for the synthesis of the intended proteins. In the case of mCOMBRIAX, the expressed, membrane bound HA proteins of the encoded influenza strains and NTD-RBD subdomains of the encoded SARS-CoV-2 Spike protein are recognised by immune cells as a foreign antigen, eliciting immune responses, which is intended to protection against influenza and COVID-19.

The proposed indication of mCOMBRIAX is for active immunisation for the prevention of diseases associated with seasonal influenza viruses represented in the vaccine and SARS-CoV-2 in individuals 50 years of age and older.

mCOMBRIAX is an injectable suspension for IM administration as a single 31.7 µg dose.

In September 2023, the World Health Organization (WHO) issued a recommendation stating that "inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as possible".

In March 2024, the Emergency Task Force (ETF) issued a statement stating that "antigens of the B/Yamagata lineage should be removed from the live attenuated influenza vaccines ideally for the 2024/2025 influenza season".

2.4. Inspection issues

GMP inspection(s)

No inspection required.

GLP inspection(s)

No inspection required.

GCP inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

Development and manufacture of mCOMBRIAX (termed mRNA-1083 in the dossier) is based on the LNP platform that is also used for the authorised vaccines Spikevax (mRNA-1273) and mRESVIA (mRNA-1345). In addition, mRNA-1283, a candidate 2nd generation SARS-CoV-2 vaccine that is recently authorised mNEXSPIKE (mRNA-1283), is also based on this platform. Of note, the SARS-CoV-2 specific mRNA construct is the same for mRNA-1083 and mRNA-1283.

mRNA-1083 finished product (FP) is a dispersion of four monovalent LNPs in Tris buffer and sucrose in water for injections. The LNPs are formed by a mixture of four different lipids: 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) and encapsulate the specific mRNA. The mRNAs encode for the N-terminal domain (NTD) and receptor-binding domain (RBD) of the spike glycoprotein of the SARS-CoV-2 virus linked to an influenza haemagglutinin transmembrane domain or for full-length haemagglutinin (HA) of seasonal influenza strains (HA subtypes H1, H3, and B/Victoria lineage) in accordance with WHO recommendations, respectively.

Finished Product is supplied as sterile dispersion for intramuscular injection in a 1-mL pre-filled syringe (PFS) containing a single dose of 31.7 µg mRNA in 0.32 mL (pack size 1 or 10 pre-filled syringes). The device parts of the PFS constitute an integral medical device.

3.2. Active Substance (RNA-Influenza and RNA-SARS-CoV-2)

3.2.1. General Information

The active substances contained within mRNA-1083 are RNA-101-BF41, RNA-101-BF34, RNA-101-BF35 and RNA-101-B815 and encode hemagglutinin surface glycoproteins (HA) derived from the three seasonal Influenza strains A/H1N1(pdm09), Influenza A/H3N2, and Influenza B/Victoria, and the linked N-terminal domain and receptor-binding domain of the spike glycoprotein of the SARS-CoV-2 Omicron XBB.1.5 subvariant, respectively. The receptor binding domain (RBD) is connected by a short soluble linker SGGGS to a transmembrane polypeptide from influenza hemagglutinin. The sequence elements

(5′ cap, the 5′ untranslated region (UTR), the Open Reading Frame (ORF), the 3′ UTR (containing unique Identification and Ratio (IDR) sequences) are described in the dossier.

For RNA-101-BF35, mutations had to be introduced since wild-type influenza B/Victoria and B/Yamagata lineage strains without these mutations failed to demonstrate non-inferiority (Study mRNA-1010 P301, see clinical part of the dossier). Given the evident impact of the mRNA sequence on protein stability and immunogenicity/efficacy, the Applicant will perform in silico analysis on future B strains to demonstrate that the introduced mutations are still applicable. Furthermore, protein expression will be confirmed for each new Influenza A or B strain using the in vitro protein expression assay (IVRPE) to further support annual strain updates. The importance to confirm immunogenicity in a suitable animal model and antigenic relatedness to the recommended wild-type influenza strains or recommended Influenza candidate vaccine virus (CVV) strains has been highlighted to the applicant, which may be addressed post-approval.

3.2.2. Manufacture, process controls and characterisation

Manufacture:

The same manufacturing process is applied for manufacture of all mRNAs contained within mRNA-1083 finished product.

All sites involved in manufacturing of the RNA active substance comply with GMP requirements.

. The active substance manufacturing process is the same for all antigens and includes the following steps: in vitro transcription (IVT), IVT tangential flow filtration (TFF), chromatography, final TFF and clarification bioburden reduction filtration). The mRNA-1083 is frozen and stored. A flow chart including material inputs and in-process controls/critical process parameters is included in the dossier.

The starting materials in the manufacture of RNA are well described. Nucleotides are considered as critical starting materials and supplied from approved, qualified suppliers. The information on single-use consumables and the process step where these are used has been provided. Compendial and non-compendial raw materials are listed in the dossier. Reference to the respective compendia is provided. In-house specifications are provided for all non-compendial raw materials.

Process validation was performed at commercial scale at the intended commercial site ModernaTX Norwood. All PPQ release testing and (C)IPCs results met the predefined acceptance criteria for SARS-CoV-2 and seasonal influenza PPQs. Step and Cycle yields were monitored for chromatography, final TFF, clarification and overall process (i.e. total yield). For the PPQ of seasonal influenza mRNA manufacturing overall eight deviations were recorded and for SARS-CoV-2 mRNA manufacturing three deviations were recorded. All deviations were considered not to have an impact on the product or PPQ conclusion.

Commercial scale qualification of resin lifetime for the RNA process is being performed concurrently to confirm resin lifetime.

A new membrane is used in the TFF unit operation for each RNA lot. Cleanliness and functionality of the membranes prior use is ensured by routinely monitoring the normalized water permeability (NWP) value.

Qualification of all process hold times for SARS-CoV-2 and seasonal influenza RNA-101-B815/BF41/BF35 and BF34 were performed with PPQ.

mRNA active substance is transported from the manufacturer (ModernaTX) for manufacturing of LNP, as needed. Operational Qualification (OQ) and Performance Qualification (PQ) confirm suitability of the shipping system to maintain the required temperature range

Characterisation

The structure, physicochemical and functional properties of the active substances within mRNA-1083 were studied on registration lots of mRNAs for SARS-CoV-2 and seasonal influenza, using a variety of relevant techniques. The ability of the mRNA to be translated and correct molecular weight of the translated protein were confirmed. Furthermore, degradation pathways were evaluated in forced degradation studies, performed with one representative RNA lot which was forward processed to FP used in clinical studies.

Product-related variants considered to be functional include high molecular weight species. Protein expression has been confirmed for these species. Cap1 sequence variants (Cap1-A and Cap1+G) may result from the RNA manufacturing process and are also considered to be functionally active.

Product-related impurities are either controlled at active substance release or via characterization assay as indicated in the dossier.

Clearance of process-related impurities has been investigated. Levels of low molecular weight impurities are well below the Safety Concern Threshold (SCT). The applicant committed to explore orthogonal methods for characterization of DNA content and size and to provide supporting characterization data within 18 months of market approval.

Manufacturing development, Process controls:

Critical Quality Attributes (CQAs)

CQAs were defined based on risk assessments, process and product characterization knowledge from mRNAs encoding for each of the seasonal influenza membrane-bound hemagglutinin (HA) (A/H1N1, A/H3N2, and B/Victoria) as well as prior knowledge from other mRNA vaccine products, including Spikevax (mRNA-1273). CQAs are controlled as part of mRNA-1083 release specifications.

Process characterization

Process risk assessment was performed using Failure Modes and Effects Analysis (FMEA) to identify potential CPPs and CIPCs and to inform characterization studies.

Scale Down Models

Process characterization studies were performed using scale-down models (SDM) for IVT reaction and chromatography steps. Tabular comparisons of manufacturing scale and SDM process parameters for IVT reaction are included in the dossier. Equivalence of SDM to commercial scale has been evaluated

Resin Lifetime

resin lifetime studies were performed using the qualified SDM and CQAs and column performance were evaluated.

Manufacturing process changes

A summary of manufacturing process changes from development through PPQ has been provided. The following processes have been applied: Version A (mRNA-1083-P101), Version B (mRNA-1083-P301) used for clinical lots, and commercial scale process (mRNA-1083 to be licensed). A major change from Version A to Version B, is the introduction of a unit operation to provide control of intermediate concentrations and facilitate greater control of chromatography loading. Furthermore, IVT was

optimized for improved mRNA purity. Setpoints were further optimized for the commercial process to optimize process performance and enable scaling of the RNA process to the final commercial scale

Comparability

Comparability assessments for RNAs of mRNA-1083 have been performed considering results from release, in-process control, extended characterization and stability testing.

3.2.3.Specification

Specifications

The list of quality attributes proposed for release testing includes appearance, identity, total RNA content, purity/product-related impurities, % Total Cap 1, % PolyA tailed RNA/% tailless RNA, pH, bacterial endotoxin and bioburden. The same quality attributes are tested for stability with the exception of identity and bioburden.

The specifications for the active substance have been established in accordance with ICH Q6B and Q11 and considering process and product characterization knowledge from mRNA-1083, prior knowledge from other mRNA vaccine products, including Spikevax™ (mRNA-1273) and compendial requirements. A rationale for establishment and justification of specifications has been provided for each quality attribute. Development, supportive, clinical and PPQ batches were considered for defining acceptance criteria as well as data from historical mRNA-1273 batches where applicable. When statistical analysis was performed and results fit a normal distribution, 5-sigma limits were used for the acceptance criteria. Acceptance criteria are identical for release and stability testing except for identity and bioburden (only tested at release).

Analytical Methods

Brief descriptions have been provided for all analytical methods.

QC release testing is performed at ModernaTX Norwood. Summaries of analytical method validations have been provided for all in-house methods. Detailed validation reports in line with ICH guidelines have been provided. Compendial methods have been verified.

Batch Analysis

Batch analysis data are presented for all strains to be included in mRNA-1083. All batches were manufactured at the intended commercial manufacturing site.

Reference Material

For SARS-CoV-2 and seasonal mRNA an in-house primary reference material (PRM) has been prepared from PPQ Lots. Both PRMs have been appropriately qualified by release and extended characterization testing and are representative of commercial production and clinical materials. Aliquots of the same lots are currently in use as working reference material (WRM), respectively. Qualification of future WRMs will be performed against the PRM according to the provided protocol including release and extended characterization testing. Requalification will be performed annually, and a respective protocol is available in the dossier.

Container Closure System

RNA is stored frozen in gamma irradiated, single-use storage bags. Respective specifications are indicated in the dossier.

3.2.4. Stability

The data support the shelf-life for storage of mRNA-1083 at the intended storage condition.

3.3. Finished Medicinal Product – LNP Intermediate

3.3.1. Description of the product and Pharmaceutical Development

. Except for the specific mRNA, the composition of the LNP is identical to the composition of LNP used for manufacture of Spikevax.

The LNPs contain mRNA encoding for the glycoprotein hemagglutinin (HA) of one of the three seasonal influenza virus strains (H1, H3, and B/Victoria lineage) and the N-terminal domain and receptor-binding domain of the spike glycoprotein of the SARS-CoV-2 virus [linked to an influenza virus haemagglutinin (HA) transmembrane domain], respectively. The mRNA is encapsulated in a lipid mixture SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octanoate, cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), and PEG2000-DMG (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000) to protect the mRNA against degradation (mainly hydrolysis) in aqueous solution and enable cellular uptake and cytosolic location of the mRNA. The LNPs are formulated in Tris/acetate buffer at neutral pH supplemented with sucrose as cryoprotectant. No excipients of human or animal origin or novel excipients are used.

As acetate buffer is introduced during manufacture. Initially a Major objection was raised on the composition of FP. The Applicant's justification for defining acetate to be a residual process-related buffer and a residue of the manufacturing process, is acceptable.

The Applicant followed an enhanced development approach as described in ICH Q8; risk assessment tools were systematically used to direct process development and identify Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Critical In-Process Controls (CIPCs). A design space is not claimed.

The physicochemical, structural, and biological properties of the LNPs were characterised.

Degradation pathways of LNP were investigated in forced degradation studies using a representative LNP. Generally, *in vitro* relative protein expression and mRNA purity were mainly impacted under these stress conditions.

The manufacturing process for mRNA-1083 LNP was developed using prior knowledge from Spikevax, mNEXSPIKE and mRESVIA. The process control strategy was established based on prior knowledge and mRNA-1083 specific process characterisation studies. Univariate and multivariate design of experiments (DOE) studies in small-scale models and Monte Carlo simulations were used.

The process changes and adaptations implemented during development are described in 3.2.P.2.3. The genealogy of the development, clinical, and PPQ batches manufactured at ModernaTX Norwood for development purposes, clinical studies, process validation, stability studies, and for comparability studies is provided.

Comparability studies that included results of release, characterisation, and stability testing were performed in accordance with ICH Q5E to demonstrate comparability of LNP originating from Process B (clinical batches including primary stability batches) or the intended commercial process. In addition, development batches originating from small-scale development processes and results for mRNA-1273 LNPs were included. Comparability of LNPs manufactured according to Process A could not be

evaluated due to the design of Process A. However, comparability of FP manufactured with LNP originating from the different process versions has been evaluated and was acceptable.

Microbiological quality of LNPs is ensured by process design, in-process controls (bioburden, endotoxin, filter integrity testing) and release/stability testing (bioburden, endotoxin).

Stability studies and extractables/leachables (E/L) assessments are provided to demonstrate suitability of the container closure.

3.3.2. Manufacture of the product and process controls

The manufacturing process for mRNA-1083 LNPs and associated controls resemble those used to manufacture mRNA-1273 LNP for Spikevax. Process characterisation and validation studies were performed to support process parameter classifications and acceptable ranges as well as hold times.

Process performance qualification (PPQ) encompassed manufacture of consecutive LNP batches at commercial scale at the intended commercial site. All process parameters and in-process controls complied. Hold times are supported by hold time studies. The risk associated with extractables/leachables (E/L) for consumables has been addressed. Shipping validation was performed to demonstrate that the intended shipping process is suitable and under control.

LNP Intermediate specification

The Applicant established release and end of shelf-life (EOSL) specifications for mRNA-1083 LNPs (Influenza, SARS-CoV-2) based on process understanding and CQAs, safety concerns per regulations, clinical experience, toxicology studies, process capability, and manufacturing history. In addition, compendial requirements and guidelines were considered by the Applicant.

Release and stability data for sufficient mRNA-1083 LNP batches including development batches, clinical batches used in Study P301 (Process B), supportive Process B batches, and PPQ batches (commercial process) are used to support the proposed specification limits. The LNP batches comprise LNPs with RNA encoding HA of different seasonal influenza H1, H3, B/Victoria, or B/Yamagata strains as well as for different SARS-CoV-2 variants. For mRNA-1273 LNP, a large historical data set covering various SARS-CoV-2 variants and manufacturing sites is presented.

For the in-house analytical procedures method descriptions including system suitability, assay, and sample acceptance criteria are provided; compendial methods are referenced**.**

The analytical methods have been validated in accordance with ICH Q2 (in-house methods) or verified (compendial methods). Validation summaries are provided. The capability of stability-indicating methods has been investigated during method validation and in forced degradation studies.

Batch analyses data are presented for the Influenza and the SARS-CoV-2 LNP PPQ batches, and phase 3 clinical batches manufactured at ModernaTX Norwood. All batches comply with the release specifications valid at time of release and also meet the proposed acceptance criteria for commercial LNPs.

RNA fragments and lipid adducts, and lipid impurities are formed during LNP manufacture; they are controlled at LNP release. To limit formation of adducts, the synthesis has been optimised to reduce the presence of adduct-forming impurities.

A two-tiered system for LNP reference materials with primary reference materials and working reference materials has been established. Season-specific reference materials are used. Protocols for (re)qualification are provided.

Stability of the LNP product

A shelf-life in the container closure described for mRNA-1083 LNPs and supported by the data detailed below.

Stability studies were performed in accordance with ICH Q1A and Q5C at long-term conditions and accelerated conditions. Development batches were additionally placed on stability at accelerated conditions. The shelf-life claim is based on a statistical evaluation of stability data that was performed in accordance with ICH Q1E.

Stability data are presented for primary LNP stability batches (PSBs) that were manufactured using Process B and used in Phase 3 studies and the LNP PPQ batches. In addition, stability data for development batches is used to support the shelf-life claim. The LNPs included in the studies target different seasonal influenza virus strains and SARS-CoV-2 variants. The Applicant concludes that all batches are representative for commercial LNP. The LNP batches are stored in representative containers at long-term conditions for up to 36 months (PPQ batches), 24 or 12 months (PSBs), or for up to 48 or 36 months (development batches). The studies at long-term conditions are ongoing. Storage studies at accelerated conditions are completed. It

The analytical procedures are the same as used for release testing and include stability indicating methods. For the studies with the development batches a reduced testing design was chosen.

Currently, for the PPQ batches, PSBs and development batches stability data covering storage at long-term conditions. The studies conducted at accelerated conditions are completed.

At long-term conditions, except several Out-of-Specification (OOS) and Out-of-Trend (OOT) results for pH (were attributed to sample handling, i.e. shipping on dry ice) and two isolated OOT IVRPE results (some variability is noted for IVRPE), all available results comply with the acceptance criteria valid at time of testing and the proposed commercial acceptance criteria (if tested). No general relevant trend is observed for any CQA; however, for several CQAs (minor trends that differ between individual batches are noted. Statistical analysis shows that even for the worst-case batches all specifications would be met after storage at long-term conditions.

When stored at accelerated or stress conditions, CQA trends were observed. Like for the long-term studies, some batch-to-batch variability is evident for some CQAs.

Freeze/thaw stability was investigated and demonstrated.

A post-approval stability protocol and commitment is provided.

3.4. Finished Medicinal Product

3.4.1. Description of the product and Pharmaceutical Development

Finished mRNA-1083 finished product (FP) is a dispersion of LNPs in Tris buffer supplemented with sucrose. The LNPs are formed by a mixture of four different lipids which encapsulate the specific mRNA. The mRNAs encode for the N-terminal domain (NTD) and receptor-binding domain (RBD) of the spike glycoprotein of the SARS-CoV-2 virus linked to an influenza haemagglutinin transmembrane domain or for full-length haemagglutinin (HA) of seasonal influenza strains (HA subtypes H1, H3, and B/Victoria lineage) in accordance with WHO recommendations, respectively.

Finished Product is supplied as sterile dispersion for intramuscular injection in a single-use 1-mL pre-filled syringe (PFS) containing a single dose of 31.7 µg mRNA in 0.32 mL (0.10 mg/mL). The device parts of the PFS constitutes an integral medical device; a Notified body opinion confirming compliance has been provided. The syringe is made of a cyclic olefin copolymer and is closed with a halobutyl rubber tip-cap and a coated halobutyl rubber plunger. Silicone oil is used as lubricant. The components are compliant to the relevant Ph. Eur. monographs. Syringe with tip cap and plunger stopper are sterilised by X-ray or gamma irradiation, respectively.

The LNPs protect the mRNA against degradation and enable cellular uptake and cytosolic location of mRNA. The selection and molar ratio of the lipid excipients as well as of the buffer system is based on prior knowledge from EU-authorised mRNA-1273 (Spikevax), mRNA-1283 (mNEXSPIKE) and mRNA-1345 (mRESVIA). The same excipients (compendial and non-compendial) as used to manufacture the above EU-authorised products are used for mRNA-1083 DP. No novel excipients or excipients of human or animal origin are used.

Table 3 Finished Product Composition: mRNA-1083

Component		**Grade**	**Function**
Total RNA		Custom	-
RNA for Influenza A/H1N1	RNA-101-BF41	-	Contains mRNA encoding glycoprotein HA of the seasonal influenza virus strains
RNA for Influenza A/H3N2	RNA-101-BF34		
RNA for Influenza B/Victoria	RNA-101-BF35		
RNA for SARS-CoV-2	RNA-101-B815		Contains mRNA encoding the linked NTD-RBD of the spike glycoprotein of the SARS-CoV-2 virus
Total Lipids	SM-102	Custom, Non-compendial	Individual lipids make up the lipid components of the LNP
	Cholesterol	NF, Ph. Eur., JP	
	DSPC	Non-compendial	
	PEG2000-DMG	Custom, Non-compendial	
Tris		USP, Ph. Eur., JP	Buffer components in Tris buffer
Tris-HCl		Non-compendial	
Sucrose		USP, Ph. Eur., JP	Cryoprotection
Water for injection		USP, Ph. Eur.	Diluent

Abbreviations: DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; HA = hemagglutinin; JP = Japanese Pharmacopeia; LNP = lipid nanoparticle; NF = United States National Formulary; NTD-RBD = N-terminal domain-receptor binding domain; PEG2000-DMG = 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000; Ph. Eur. = European Pharmacopoeia; RNA = ribonucleic acid; SM-102 = heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octanoate; USP = United States Pharmacopeia.

During development the concentration of mRNA was changed from 0.2 mg/mL (Phase 1) to 0.1 mg/mL (Phase 3); in the Phase 1 studies, product was diluted to evaluate different dose levels. For Phase 3, the mRNA concentration was lowered to 0.1 mg/mL. Consequently, lipid content as well as sodium acetate content differed throughout the development stages. The formulation of the Phase 3 material and the commercial product is identical.

Developmental stability studies were conducted at long-term and accelerated conditions to evaluate suitability of the formulation. In addition, stability studies were performed to assess a potential impact of the change in valency of influenza components and of the container closure, photostability, and stability during transportation. Results of an ICH Q1B-compliant photostability study reveal that FP is sensitive to light exposure and hence, must be stored protected from light. Results from a simulated transport study demonstrate that FP is stable when shipped frozen or at 2 – 8°C under conditions per ASTM D4169 Distribution Cycle 13, Assurance Level II.

The product is manufactured without overage. An overfill is included to ensure delivery of the full 0.32 mL dose to the vaccinee.

The Applicant followed an enhanced development approach as described in ICH Q8; risk assessment tools and prior knowledge were systematically used to direct process development and identify Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Critical In-Process Controls (CIPCs). A design space is not claimed. Prior knowledge and mRNA-1083 specific process characterisation studies that included general and site-specific characterisation studies were used to establish the process control strategy. The risk associated with E/L leaching from consumables has been assessed; a risk assessment for potential nitrosamine impurities has been provided. In addition, elemental impurities were satisfactorily assessed and controlled.

The process changes and adaptations implemented during development are sufficiently described and justified. Initially, a small-scale clinical process (Process A,) was used at Moderna Norwood to manufacture clinical trial material for Studies mRNA-1083-P101 (Phase 1). For manufacture of material for mRNA-1083-P301 (Phase 3), a conventional aseptic Process B (was established at Moderna Norwood. For commercial supply, the process was transferred to the intended commercial manufacturer and upscaled. The mRNAs were adapted in accordance with the WHO recommendations for influenza strains and the circulating SARS-CoV-2 variant. Process A is an integrated small-scale with no separate release of RNA and FP intermediates. With introduction of Process B, steps for thawing and pooling of LNP and a clarification/bioburden reduction filtration prior to sterile filtration were implemented. The commercial process and Process B have a very similar process flow (some equipment and scale specific adaptations). For the commercial process two options, i.e. direct forward processing after visual inspection (Process flow 1) or optional interim storage of frozen unlabelled FP after visual inspection (Process flow 2) were introduced. In addition, development lots including the primary stability lots (PSLs) were manufactured in a laboratory-scale process at Moderna Norwood to support the stability claim. The genealogy of the lots used for development purposes, clinical studies, process validation, stability studies, and for comparability studies is provided.

A comparability study that included results of release and stability testing was performed in accordance with ICH Q5E to demonstrate comparability of FP lots used to supply clinical studies, FP manufactured

via the intended commercial process, and the PSLs manufactured with a development-scale process. With a few exemptions, all release results complied with their respective comparability criteria. Stability profiles of the unlabelled FP PPQ lots, the five primary stability lots (all in PFS), and development lots under accelerated conditions were compared Clinical lots were not included as they were not stored at accelerated conditions. Overall, PSLs and PPQ lots exhibit a comparable stability profile at accelerated conditions; regarding Total Lipid Impurities the results are inconclusive. The stability profile of the Development lots and of the PSLs appears not comparable and hence, the Development lots were not used for shelf-life analysis.

Microbiological quality of LNPs is ensured by process design, in-process controls (bioburden, endotoxin, filter integrity testing) and release/stability testing (bioburden, endotoxin).

Suitability of the container closure system was investigated in terms of compatibility, product protection, syringe functionality, and material safety.

3.4.2. Manufacture of the product and process controls

The batch formula for minimum and maximum batch size is provided.

Upon controlled thawing, the LNPs are pooled and subsequently diluted to the target concentration of 0.10 mg/mL. After clarification/bioburden reduction filtration, the diluted LNPs are sterile filtered and aseptically filled into syringes. The PFS are 100% visually inspected and may be directly forward processed (Process flow 2) to assembly, labelling and packaging steps. Otherwise (Process flow 1 – main flow) the unlabelled PFS are frozen in a controlled process and stored. Upon thawing, the PFS are assembled, labelled, and packaged. Finally, the PFS are frozen in a controlled process for long-term storage at -40°C to -15°C. Reprocessing is not allowed at any stage of the FP manufacturing process. Process parameter classifications and their acceptable ranges, in-process control and their acceptance criteria as well as hold times are described.

Process performance qualification encompassed manufacture of consecutive mRNA-1083 FP lots at commercial scale at the intended commercial site. Each of the unlabelled drug product (UDP) PPQ lots was further processed into labelled FP (LDP) lots, that were manufactured according to Process flow 1 with interim storage, or directly onward processed to LDP with no interim storage (Process flow 2).

Beside routine in-process and release testing, additional testing was performed to qualify hold times, demonstrate homogeneity/consistency along the process, and to confirm absence of stopper movement during interim storage, assembly, labelling, packaging and final freezing.

All CPPs and reported other PPs were within their acceptable range. All results of CIPCs and other IPCs as well as all release tests complied with their acceptance criteria (and the proposed commercial specifications). Results of the in-process and release tests are consistent across the PPQ lots.

A prior knowledge validation approach was chosen for validation of the sterile filter. Media fill data are provided. The shipping process has been validated by thermal monitoring studies and simulated transportation studies.

3.4.3. Product specification

The Applicant established release and end of shelf-life (EOSL) specifications for mRNA-1083 FP based on clinical experience, compendial requirements and guidelines, manufacturing process capability and product knowledge, and prior knowledge from other mRNA vaccines, particularly mRNA-1273, for attributes that are sequence agnostic). In addition, stability data and analytical method performance were taken into consideration. Consequently, the specifications largely resemble those for the EU-

authorised Spikevax, mNEXSPIKE and mRESVIA with most of the analytical procedures being the same.

The finished product specification contains appropriate tests for appearance, identification, RNA and lipid content and purity, potency, particle size / polydispersity, physicochemical and microbiological properties and device performance parameters.

Induction of an immune response by mRNA-1083 FP requires uptake of the LNPs into antigen-presenting cells, release of mRNA into the cytoplasm, protein translation and processing, and antigen presentation on the cell surface. This mechanism of action depends on several quality attributes of mRNA-1083 FP, These attributes as well as the ratio of the four different mRNAs are controlled via the FP specification. In addition, functional and biological activity are controlled

For attributes showing relevant trends over time, the proposed release acceptance criterion was set using the confidence limit of the determined rate of change to ensure safety and efficacy of FP throughout its shelf-life. For qualitative attributes and attributes showing no practically relevant trend at recommended conditions, release and shelf-life acceptance criteria are identical.

Release and shelf-life acceptance criteria were established based on clinical experience, compendial and guideline requirements, manufacturing process capability and product knowledge, stability data, and prior knowledge from other mRNA vaccines. For sequence agnostic attributes, specifications were largely based on prior knowledge from mRNA-1273. Taking into account that mRNA-1083 and mRNA-1273 have the same mechanism of action and that both products are manufactured using similar manufacturing processes and control strategies, this approach is acceptable. For attributes showing relevant trends over time, the proposed release acceptance criterion was set using the confidence limit of the determined rate of change during storage to ensure safety and efficacy of FP throughout its shelf-life. The proposed acceptance criteria are agreeable. In response to an initially raised Major objection, the Applicant provided additional clinical data which support the proposed release and EOSL acceptance criteria for mRNA purity. As discussed in a recent EMA Scientific Advice (EMA/SA/0000267466) regarding the appropriateness of the proposed multi-attribute approach, including the semi-quantitative IVRPE functionality test to guarantee product potency and functionality at the end of its shelf-life. Further characterisation of the changes observed under refrigerated conditions and evaluation of their potential clinical relevance is requested post approval, an agreeable EOSL specification for IVRPE has been proposed. The currently proposed release specification for IVRPE will be maintained until additional commercial FP data are available.

Release and stability data for mRNA-1083 FP lots including development lots, clinical, and PPQ lots (Process flow 1 or 2) are used to justify the proposed specification limits. The batches/lots were manufactured according to Process A, B, or the commercial process using Process flow 1 or 2 and include mRNA encoding for different SARS-CoV-2 variants and Influenza H1/H3/B-Victoria/B-Yamagata HA subtypes for different seasons. For mRNA-1273 DP, a large historical data set (covering various variants and manufacturing sites is presented.

For the in-house analytical procedures, method descriptions including system suitability, assay, and sample acceptance criteria are provided; compendial methods are referenced.

The analytical procedures are the same as those used for release testing and include stability indicating methods. The CQAs appearance, RNA content, mRNA purity, RNA fragments and lipid adducts, particle size and polydispersity, %encapsulation, lipid content and lipid impurities, cell free translation (CFT), IVRPE, pH, bacterial endotoxin, particulate matter, BL/GF, deliverable volume, and container closure integrity (CCI) are tested for the PPQ lots. The testing frequency and analytical programme were reduced for studies with PSLs and development lots.

The analytical methods have been validated in accordance with ICH Q2 (in-house methods) or verified (compendial methods). Validation summaries are provided for initial validations and subsequent method transfers. The capability of stability-indicating methods to detect product deterioration has been investigated during method validation and in forced degradation studies.

The presented validation/verification data demonstrate that the analytical methods are suitable for their intended use. The original validation/verification reports have been provided upon request. Full validation data of the CCI test method performed at the future intended commercial manufacturing site will be provided. Supplementary IVRPE method validation data covering an expanded assay range for IVRPE should be submitted before release of any mRNA-1083 to the EU market.

Batch analyses data are presented for the PPQ lots, clinical lots including Phase 1, Phase 3 lots, and one supportive lot. The batches/lots were manufactured according to Process A, B, or the commercial process using Process flow 1 or 2 and include mRNA for different Influenza strains and SARS-CoV-2 variants. All lots comply with the release specifications valid at time of release and also meet the proposed acceptance criteria for commercial product (IVRPE was not performed for clinical lots).

Except leachables originating from processing equipment or container closure and particulate matter (controlled at FP release) that might form during manufacture, no new impurities are generated or introduced during FP manufacture.

A two-tiered system for FP reference materials with primary reference materials and working reference materials has been established. Season-specific reference materials are used. A protocol for (re-) qualification of reference materials is provided.

3.4.4.Stability of the product

A shelf-life of 12 months at long-term conditions of -40°C to -15°C including 30 days at 2 – 8°C and up to 24 hours at room temperature (up to 25°C) when stored in the container closure described under 3.2.P.7 is proposed and supported by the data detailed below.

The stability claim is primarily based on data for primary stability lots (PSLs) that were manufactured using a development scale process representative for the commercial process. The PSLs have the same composition, strength, and fill volume (except one lot) as commercial product, and are stored in the commercial container closure. Based on the comparability exercise and the process comparison presented under 3.2.P.2.3 *Comparability* and 3.2.P.2.3 *Manufacturing history*, the Applicant claims that the PSLs are representative for the PPQ lots. In addition, results for the PPQ lots were taken into account.

The stability studies follow ICH Q1A and ICH Q5C.

In-use stability studies have been performed to support the proposed handling for administration. An acceptable protocol for annual stability testing is available.

Photostability was investigated in line with ICH Q1B; mRNA-1083 FP was shown to be light sensitive and thus, must be stored protected from light. In-use stability has been demonstrated satisfactorily.

A shelf-life of 12 months at long-term conditions of -40°C to -15°C including 30 days at 2 – 8°C and up to 24 hours at room temperature (up to 25°C) when stored in the container closure as described in the Summary of Product Characteristics, is acceptable.

3.5. Adventitious agents

There are no raw materials of animal or human origin used in the manufacture of RNA, LNP and FP. Certain starting materials used in the RNA process are produced in *E. coli*. including plasmids and enzymes, however, these materials are animal free in manufacturing process and final product.

Furthermore, adequate controls for starting materials, raw materials, consumable, equipment, as well as specifications for in-process controls and release tests for microbial control are in place to ensure safety with respect to adventitious agents.

3.6. Discussion on chemical, pharmaceutical and biological aspects

Active substance:

The active substances contained within mRNA-1083 are RNA-101-BF41, RNA-101-BF34, RNA-101-BF35 and RNA-101-B815 and encode hemagglutinin surface glycoproteins (HA) derived from the three seasonal Influenza strains A/H1N1(pdm09), Influenza A/H3N2, and Influenza B/Victoria, and the linked N-terminal domain and receptor-binding domain of the spike glycoprotein of the SARS-CoV-2 Omicron XBB.1.5 subvariant, respectively. Structural identity and characterisation of the active substances are described in sufficient detail.

For RNA-101-BF35mutationshad to be introduced since wild-type influenza B/Victoria and B/Yamagata lineage strains without these mutations failed to demonstrate non-inferiority (Study mRNA-1010 P301, see clinical part of the dossier). Given the evident impact of the mRNA sequence on protein stability and immunogenicity/efficacy, the Applicant will perform in silico analysis on future B strains to demonstrate that the introduced mutations are still applicable. Furthermore, protein expression will be confirmed for each new Influenza A or B strain using the in vitro protein expression assay (IVRPE) to further support annual strain updates. The importance to confirm immunogenicity in a suitable animal model and antigenic relatedness to the recommended wild-type influenza strains or recommended Influenza candidate vaccine virus (CVV) strains has been highlighted to the applicant, which may be addressed post-approval.

The manufacturing process, control and validation of for commercial production of the four mRNAs contained within mRNA -1083 is based on substantial experience from already authorized mRNA vaccine constructs and satisfactory.

FP intermediate:

The finished product manufacturing process contains mRNA-1083 LNP which is essentially the same as in the previously authorized products. The mRNA-1083 LNP intermediate consists of and the mRNA active substance.

The control of critical steps and intermediates is sufficiently outlined in the dossier.

The provided information regarding the finished product intermediate LNP is sufficient.

Finished product

mRNA-1083 FP 31.7 µg PFS is a preservative-free, sterile dispersion for intramuscular injection containing LNPs. The LNPs contain mRNA (RNA-101-BF41, -BF34, or -BF35) encoding full-length haemagglutinin (H1, H3, or B/Victoria lineage, respectively) of seasonal influenza virus strains or mRNA (RNA-101-B815) encoding the N-terminal domain and receptor-binding domain of the spike glycoprotein of the SARS-CoV-2 virus (Omicron XBB.1.5) linked to an influenza haemagglutinin transmembrane domain.

A major objection was raised on the composition of FP. The Applicant's justification for defining acetate to be a residual process-related buffer and a residue of the manufacturing process, is acceptable. A commitment has been provided to align the classification of acetate and to exclude it from the list of excipients, as for previously authorized products via post-approval variation applications in a timely manner.

Development history and comparability study in accordance with ICH Q5E demonstrated comparability of FP lots used to supply clinical studies, PPQ lots, and the primary stability lots (PSLs) manufactured with a development-scale process (additional development lots were included in the comparability study as well). The mRNA-1083 FP manufacturing process was developed using prior knowledge from previously authorized products. The process and validation are adequately described and assessment and control of potential impurities also satisfactorily controlled.

Microbiological quality of the product is ensured by appropriate process design, in-process controls and release/stability testing.

The same excipients are used for EU-authorised products from the Applicant.

The container closure system is sufficiently described. Suitability of the container closure system in terms of functionality, product protection, compatibility, and safety has been demonstrated. A Notified body opinion has been provided confirming compliance of the device parts of the PFS with GSPRs.

According to the PIP (EMEA-003521-PIP01-23), no quality studies specific to paediatrics are warranted. As remarked by the applicant, it cannot be excluded that lower strength pharmaceutical forms might be needed but this would not be part of the PIP. This approach is in line with the one agreed in the PIP of the two components mRNA-1010 and mRNA-1283.

3.7. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

3.8. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. Stability data for LDP PPQ lots manufactured according to Process flow 1 that have undergone an interim storage period of 3 months at the UDP stage should be provided in a subsequent post-approval variation submission The corresponding stability studies should foresee LDP storage for 11 months at -25ºC to - 15ºC, followed by storage for 30 days at 2°C to 8°C and 24 hours at ambient light conditions and 25°C.
2. Envisaging potential future annual strain updates, the applicant will perform in silico analysis (B strains) and confirm protein expression using the in vitro protein expression assay (IVRPE). To further support annual strain updates, the applicant should evaluate immunogenicity of HA antigens in a suitable animal model as well. Generated antisera should be tested for their activity towards the recommended wild type influenza strains or recommended influenza candidate vaccine virus strains. Comparison to data from strains that were actually tested in clinical trials is recommended. Small scale monovalent vaccine formulations (LNP containing only one single HA mRNA) may be used for these characterisation studies. It is also strongly

recommended to evaluate whether the HA antigens expressed by the mRNA (e.g. by analysing cells with membrane-associated expression of HA, after transfection of cells with the mRNA vaccine, possibly with monovalent formulations) are sufficiently recognised by antisera against the recommended influenza strains (available from WHO collaborating centres or Essential regulatory laboratories).

3. The Applicant should provide full method validation data for the CCI test method at the intended commercial manufacturing site in a post-approval variation.
4. The release specification for IVRPE should be further evaluated upon availability of data from 30 additional commercial scale data lots and submit any updates to the control strategy in a postapproval variation.
5. The applicant should explore orthogonal methods for characterization of DNA content and size and provide supporting characterization data within 18 months of market approval.
6. The applicant should implement an optimized method to quantify PolyA tailed RNA. The anticipated variation submission is planned for December 2026. A method validation report, method description, and bridging study summary should be provided at that time.
7. Supplementary method validation data covering IVRPE should be submitted before release of any mRNA-1083 to the EU market.
8. The lipid changes observed upon storage under refrigerated conditions should be further investigated.

4. Non-clinical aspects

4.1. Introduction

The applicant submitted a complete non-clinical data package summary in Module 2 and complete study reports in Module 4. The non-clinical data package consists of pharmacodynamics studies with the seasonal influenza vaccine mRNA-1010, SARS-CoV-2 mRNA vaccine mRNA-1283, pharmacokinetics studies with data of the applicant's mRNA-based platform, and toxicity data with mRNA-1010, mRNA-1283 and applicant's mRNA-based platform.

4.2. Analytical methods

The methods used to quantify mRNA, SM-102, and/or expressed proteins in the non-GLP PK studies supporting the development of mRNA-1083 are summarized in the table below.

Additionally, identification of SM-102 lipid metabolites was performed in vitro in Sprague Dawley rat, cynomolgus monkey, and human hepatocytes (Report NCS-BA-2022-010) and in vivo in Sprague Dawley rat urine, bile, and plasma (Report QV-0236-DA-RE-RPT-01) using HRMS methods. In vitro identification of PEG2000-DMG metabolites in Sprague Dawley rat, cynomolgus monkey, and human serum was performed using HRMS methods (Report NCS-BMA-2023-06).

Table 4 Analytical Methods Used in Non-GLP PK Studies

Analyte	Analytical Method	Species	Matrix	Assay Rigor	LLOQ	Report Number
NPI-Luc mRNA	bDNA singleplex	Rats	Serum, tissues	Qualified	0.125 ng/mL	2308-582 Amendment 1
SM-102	LC-MS/MS	Rats	Plasma, tissues	Qualified	0.500 ng/mL	2308-582 Amendment 1 20456513 Amendment 1
			Plasma, bile, urine	Fit for purpose	0.2 ng/mL	QV-0236-DA-RE-RPT-01
NPI-Luc protein	ECL	Rats	Tissue	Qualified	200 ng/g	2308-582 Amendment 1
mRNA from mRNA-1273	RT-qPCR	Rats	Serum	Qualified	0.850 pg/mL	20456513 Amendment 1
			Tissues	Qualified	0.850 pg/g	20456513 Amendment 1
SARS-CoV-2 S protein	Ligand-binding assay	Rats	Serum	Qualified	4.57 ng/mL	20456513 Amendment 1
			Tissues	Qualified	91.4 ng/g	20456513 Amendment 1
Anti-SARS-CoV-2 S protein IgG antibody	ELISA	Rats	Serum	Qualified	0.059 AU/mL	20456513 Amendment 1
mRNAs from mRNA 1647 (gB, gH, gL, UL128, UL130, and UL131A)	bDNA multiplex	Rats	Plasma, tissues	Fit for purpose	0.01 ng/mL (gH, gL, UL128, and UL131A)[a] 0.05 ng/mL (gB and UL130)[a]	5002121 Amendment 2

Abbreviations: bDNA = branched DNA; ECL = electrochemiluminescence; LC-MS/MS = liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantification; Luc = luciferase; mRNA = messenger RNA; NPI = nascent peptide imaging; RT-qPCR = reverse transcriptase-quantitative polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: For the calculation of tissue-to-plasma/serum ratios, where tissue concentration is in ng/g and plasma/serum concentration is in ng/mL, the assumption is made that 1 g of tissue is equivalent to 1 mL of plasma/serum.

[a] The LLOQ values used for pharmacokinetic reporting reflect the standard range in neat plasma, while the calibration range in Section 2.6.5.2 reflects the range after minimum required dilution (100-fold).

4.3. Pharmacology

4.3.1. Pharmacodynamics

Primary pharmacodynamics

In vivo immunogenicity

The applicant conducted three non-GLP compliant studies in female BALB/c mice to investigate the immunogenicity of a multi-component mRNA vaccine (mRNA-1083) with different ratios of influenza virus to SARS-CoV-2 including 5:1. In two studies, mRNA-1083 compositions (quadrivalent NH2022/2023 influenza virus strains with bivalent SARS-CoV-2 original Wuhan-Hu-1 and Omicron BA.4/BA.5, as used in the mRNA-1083-P101 clinical study, or monovalent SARS-CoV-2 Omicron XBB.1.5) were comparatively assessed with their corresponding component vaccine (e.g. influenza or SARS-CoV-2), whereas the scope of the third study was to investigate two dose levels of each mRNA-1083 composition (NH2023/2024 influenza strains and the NTD-RBD of the SARS-CoV-2 Omicron XBB.1.5 S protein, which was evaluated in the Phase 3 mRNA-1083-P301 clinical study).

In general, summing up the data of all three studies, immunogenicity of each component in the multicomponent mRNA-1083 vaccine was not significantly influenced, which was confirmed by comparable IgG antibody binding (ELISA), influenza HAI and SARS-CoV-2 nAbs (haemagglutination inhibition (HAI) and SARS-CoV-2 pseudovirus-neutralisation assays) between mRNA-1083 and its individual component vaccines. Boosting with the same vaccine generally increased the antibody response. Additionally, a dose-response in IgG titres could be determined (for mRNA-1083 composition as used in the Phase 3 mRNA-1083-P301 clinical trial), and comparable CD4+ and CD8+ T cell responses (T cell analyses by intracellular cytokine staining and flow cytometry) were observed (with mRNA-1083 composition as used in the mRNA-1083-P101 clinical study). The CD4+ (Th1-biased) and CD8+ T cell responses in mice were supported by an additional study with mRNA-1083 (influenza HAs from the NH24/25 season and SARS-CoV-2 JN.1 strain) in BALB/c mice.

In vivo immunogenicity and protective efficacy (challenge studies)

Two non-GLP compliant in vivo immunogenicity and protective efficacy studies with quadrivalent mRNA-1010 [WHO-recommended Southern Hemisphere (SH) 2021 influenza virus strains], comparatively assessed to an adjuvanted influenza vaccine [(FLUAD, 2020/21 Northern Hemisphere (NH) composition)], in female BALB/c OlaHSD mice (immunised once) and Mustela putorius furo ferrets (boosted) were submitted with this marketing authorisation application (MAA). Mice were intranasally challenged with antigenically mismatched challenge viruses (H3N2 A/Hong Kong/1/1968 or H1N1pdm09 A/Netherlands/602/2009 with 50 or 10 years of drift, respectively), while ferrets were challenged intranasally and intrathecally with H1N1pdm09 A/Victoria/2570/2019 virus.

All vaccinated animals showed high HAI-titers against all vaccine-matched seasonal influenza virus strains (at least 1:40; which were comparable to FLUAD for the three consistent strains). mRNA-1010 was immunogenic against the respective H1N1 challenge viruses in mice and ferrets, as confirmed by relevant HAI titres and/or high VN titres, respectively. In mice, immunisation with mRNA-1010 and FLUAD similarly and effectively protected against the H1N1 challenge virus, whereas mRNA-1010 appeared to be superior in protecting against morbidity, reduction in body weight loss and clinical symptoms after challenge with H3N2 virus even without response in HAI and VN titres to this highly mismatched challenge virus. In ferrets, assessment of levels of viral RNA by TaqMan PCR (including viral genomic material from non-infectious virus) from nose swabs, throat swabs and nasal turbinates showed comparable viral loads between mRNA-1010, FLUAD and placebo treated ferrets, but reduced PCR titres in the lungs of mRNA-1010 and FLUAD vaccinated animals compared to the placebo group. Data obtained from a virus titration assay on MDCK cells, measuring levels of infectious (replication competent) virus, revealed that mRNA-1010 and FLUAD both reduced viral loads in the throat, nose and nasal turbinate, while in the lungs, no virus at all was detectable, when compared to animals treated with placebo. Furthermore, gross pathological and histopathological analysis revealed that vaccinated ferrets show reduced pulmonary and probably nasal pathology after infection with influenza virus A H1N1, since the most severe changes were observed in placebo-treated animals.

Stewart-Jones et al. (2023) described the protective effect against virus challenge with WA1/2020 D614G or B.1.1.529 (BA.1; Omicron), administered by focus forming units via the intranasal route, after previous IM vaccination with either mRNA-1283 or mRNA-1273 (5 or 0.1 µg in the high- or low-dose groups, respectively) as a 2-dose primary series in female K18-hACE2 C57BL/6 J mice. An immune response was observed for both mRNA vaccines, showing comparable nAb titres and significantly reduced viral burden in lungs, nasal turbinates and nasal washes. Overall, higher nAb titres were associated with lower N copies after virus challenge in mRNA-1283 vaccinated mice, which was most pronounced in the lungs. Taken together, mRNA-1283 (RBD/NTD vaccine) was shown not to be inferiorly immunogenic compared to mRNA-1273 (full-length protein vaccine).

Secondary pharmacodynamics

No secondary pharmacology studies have been conducted.

Safety pharmacology

No safety pharmacology studies have been conducted.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted.

4.3.2. Pharmacokinetics

In this MAA submission the non-clinical pharmacokinetics module was filed with platform studies of similar mRNA vaccine products developed by the applicant (e.g. mRNA 1273 and mRNA-1647 in SD rats) or surrogate products (e.g. NPI-Luc mRNA in the SD rat) that relied on the same LNP formulation (including the same lipid excipient constitution). Similarly, previously submitted studies in other applications with the lipid excipients SM-102 and PEG2000-DMG were submitted.

The platform data submitted by the applicant indicate that the mRNA load in the administered LNPs after intramuscular administration to SD rats mainly partitions to and is mainly measured in the spleen, the injection site, the draining lymph nodes (e.g. axillary, inguinal, popliteal lymph nodes), where did not persist more than 1-3 days, and to a lesser extent in other organs (e.g. the liver, bone marrow, lung etc.). Exposure was generally independent of sex. There were no apparent changes in exposure or kinetics after the first or second dose. A similar distribution pattern was demonstrated for SM-102 after administration of mRNA-containing LNPs. The half-life of systemic SM-102 was only 2.95 hours in serum and 8.44 hours in plasma, and in tissues was maximally 60.5 hours. Similar half-life values were measured for the mRNA fraction of the studied vaccine candidates.

In vitro incubation of SM-102 LNPs with rat-, cynomolgus monkey-, and human hepatocytes resulted in identical ester-hydrolyzed and β-oxidized metabolites without human-specific metabolites. IV infusion of SM-102 LNPs (with NTFIX mRNA) in rats resulted in 12 metabolites in addition to the unchanged parent SM-102 (i.e 9 metabolites in plasma, 5 in urine, and 12 in bile). Metabolism in rats occurs primarily by hydrolysis of the ester groups followed by β-oxidation of the resulting aliphatic acidic linkers. In general, the study demonstrated rapid clearance of SM-102 and the elimination of SM-102 and its metabolites via the kidney and liver.

In vitro metabolism of PEG2000-DMG in rat-, cynomolgus monkey- and human serum resulted in identical metabolites, PEG-glycerol and PEG-MMG isomers formed by ester hydrolysis without human-specific metabolites.

Finally, the applicant also studied the elimination kinetics of SM-102 and its metabolites in the rat and demonstrated renal and hepatobiliary excretion. Excretion was almost complete, demonstrating a low potential for accumulation upon intramuscular administration.

4.4. Toxicology

4.4.1. Single-dose toxicity

No single-dose toxicity studies were conducted. Toleration after a single IM dose of the mRNA

vaccines encapsulated by SM-102–containing LNPs was assessed in repeat-dose toxicity studies.

4.4.2. Repeat-dose toxicity

The applicant submitted an extensive repeated dose toxicity program, consisting of nine studies conducted in Sprague Dawley rats. Only study 20462549 was conducted with mRNA-1083.2 (although a different formulation was used compared to the final clinical formulation mRNA-1083). The other studies were carried out with other mRNA-vaccine products that are, however, also based on the same LNP technology as applied in mRNA-1083.

In the GLP repeated dose toxicity 20462549, mRNA-1083.2 was administered via intramuscular injection every 4 weeks to male and female Sprague Dawley rats. No clinical signs or injection site issues were observed at the highest dose (36 µg/dose). However, at this dose, some female rats exhibited moderate to marked multifocal liver necrosis and increased liver weights. Increased hepatocellular/hepatobiliary parameters were also observed in clinical chemistry (AST, ALP, ALT, GGT, total bilirubin). Other findings included increased spleen and kidney weights in females, and inflammation site reactions at the injection site.

Microscopic examination revealed liver changes such as increased mononuclear cell infiltrates and increased cellularity of the sinusoidal lining at doses of 20 µg and higher. Spleen findings included decreased cellularity of the marginal zone and periarteriolar lymphoid sheaths. Injection site inflammation was generally consistent with an inflammatory or acute phase response commonly seen after IM vaccine administration.

After a 2-week recovery period, most of the observed findings showed complete reversibility, while others only partially resolved. However, all findings showed lesser magnitude compared to the non-recovery necropsy group sacrificed after four weeks at the end of the main study. The non-completely resolved parameters included clinical pathology changes, such as higher neutrophils and globulin concentrations. Increases in reticulocytes and red blood cell distribution were concluded to be a compensatory erythropoietic activity by the applicant.

Antibody analyses showed strong responses against SARS-CoV-2 and influenza strains. Due to liver toxicity in some females at 36 µg/dose, the NOAEL (No Observed Adverse Effect Level) was established at 20 µg/dose.

In one of the two non-GLP compliant repeat-dose rat studies, mRNA-1010 was intramuscularly administered at 0, 30, 60, 100 µg/dose; 2 doses were administered every 3 weeks.

The administration of repeat doses of 30, 60, and 100 µg mRNA-1010 via intramuscular bolus injection on Days 1 and 22 in Sprague Dawley rats was well tolerated. Findings related to mRNA-1010 were limited to transient oedema and erythema at the injection site. Minimal to moderate changes in clinical chemistry and haematology parameters were observed on Day 23 (24 hours after the second dose), consistent with an inflammatory and/or immune response and signs of reduced erythropoiesis. Strong binding antibody responses against matching influenza virus haemagglutinins (HAs) were produced and were generally dose-independent, although small increases were noted with higher doses of mRNA-1010. The highest dose of 100 µg resulted in the highest measurable antibody levels for all four antigens.

Another non-GLP compliant RDT mRNA-1283-specific study only revealed test-article related findings that are expectable for an mRNA-based vaccine candidate and are related with the administration procedure and a local and systemic inflammation reaction towards the administered LNP, mRNA and the expressed protein antigen (mRNA-1283 was intramuscularly administered at 0, 30, 60, 100 µg/dose; 2 doses were administered every 3 weeks).

Specifically, oedema at the injection site with or without hindlimb impairment, increased in neutrophil and eosinophil counts, decreased in platelet and lymphocyte counts, signs of slightly diminished erythropoiesis (decreases in reticulocyte, mild increases in mean corpuscular volume, mild decreases in mean corpuscular haemoglobin contents, and mild increases in red blood cell distribution width, extramedullary erythropoiesis in the spleen), decreased in total protein, albumin and albumin to globulin ratio, and mild sporadic increases in triglyceride levels were reported.

Additional, supportive data conducted with other mRNA-based vaccines formulated in SM-102-containing LNPs encoding for various antigens (otherwise referred to as aggregated SM-102 platform toxicity data), were submitted. The aggregated SM-102 platform toxicity data were comprised of 6 GLP-compliant repeat-dose toxicity studies using 5 different mRNA vaccines, encoding unique antigens formulated similarly in SM-102-containing LNPs, each with 3 dose levels (ranging from 8.9 to 150 µg/dose) plus vehicle control for up to 4 administrations (once every 2 weeks) followed by a 2-week recovery period (using 2 vaccines against ZIKV: mRNA-1706 and mRNA-1893; 1 vaccine against hMPV and PIV3: mRNA-1653; and 2 vaccines against CMV: mRNA-1647 and mRNA-1443). Across these studies, there was consistency in the target organs (which included injection sites [and adjacent connective tissue around sciatic nerve], lymph nodes, bone marrow, spleen, liver, and/or adrenal glands) and similarities in clinical pathology and systemic biomarker changes that were indicative of a local and/or systemic inflammatory or immune response as expected with an IM-administered vaccine), e.g. macro- and microscopical findings on liver, spleen, as well as changes in chemical parameters (e.g., ALT, AST, GGT, triglyceride) were associated with the mode of action of immunogenicity of antigens administered, completely resolved or at least showed a clear tendency of recovery two weeks post last dose.

4.4.3. Genotoxicity

The conducted genotoxicity studies were already submitted for the initial marketing authorisation of Spikevax and mRESVIA.

An Ames test for SM-102 was conducted in compliance with GLP. SM-102 was tested for its genotoxic potential in study 9601567 in a bacterial reverse mutation test in *Salmonella typhimurium* and *Escherichia coli*. Results did not indicate any evidence of genotoxic activity in this in vitro mutagenicity assay.

PEG2000-DMG (Sunbright GM-020) was tested for its genotoxic potential in GLP-compliant study 9601035 in a bacterial reverse mutation test in *Salmonella typhimurium* and *Escherichia coli*. Results did not indicate any evidence of genotoxic activity in this in vitro mutagenicity assay.

SM-102 did not show any evidence of genotoxic activity in the conducted GLP-compliant in vitro mammalian cell micronucleus test in human peripheral blood lymphocytes (Study 9601568).

PEG2000-DMG did not show any evidence of genotoxic activity in the conducted GLP-compliant in vitro mammalian cell micronucleus test in human peripheral blood lymphocytes (Study 3601036).

A GLP-compliant in vivo erythrocyte micronucleus study in rat was performed with mRNA-1706 in SM-102-containing lipid nanoparticles using IV administration. In this study statistically significant increases in micronucleated erythrocytes were reported in both sexes. A strong increase in MIE was observed 48 hours after the final administration in the highest dose group in male rats (mRNA-1706: 4.0/5.2 mg/kg; SM-102: 54.1 mg/kg). No clear dose-response relationship was reported.

The administered mRNA/SM-102 concentrations in the genotoxicity study were much higher than the actual concentrations in the clinical setting (>27mg/kg SM-102). The vaccine will be administered two times only, and a low dose containing around 1 mg SM-102 per dose will be administered at the

proposed posology. Moreover, a different route of administration was used in the micronucleus study compared to the intended clinical route (IV vs. IM), and thus significantly lower systemic exposure to the individual excipients can be expected in the clinical setting.

NPI luciferase mRNA in SM-102-containing LNPs was determined to be negative (non-clastogenic) after a single IV dose of 0.32/6.0, 1.07/20, or 3.21/60 mg/kg NPI luciferase mRNA/SM-102 in Sprague Dawley rats. A statistically significant decrease in %PCEs (polychromatic erythrocyte) was observed in the low dose 0.32/6.0 mg/kg NPI luciferase mRNA/SM-102 group males at the 48-hour time point. This effect did not show dose dependency and was not observed after 24 hours (when even a slight increase was observed at this dose in males). Increases in cytokines IL-6, MCP-1, MIP-1α, and IP-10 were observed in this study 6 hours after IV administration of 1.07/20 mg/kg and 3.21/60 mg/kg NPI luciferase mRNA/SM-102, respectively. To mention, this study was conducted as an exploratory study and not in compliance with GLP.

4.4.4. Carcinogenicity

No dedicated carcinogenicity studies were conducted.

4.4.5. Developmental and reproductive toxicity

The applicant conducted two GLP-compliant combined peri/postnatal developmental and reproductive toxicity studies (Study 20323624 and Study 20346748) in rats. mRNA-1010 and mRNA-1283, respectively, were intramuscularly injected in these studies.

In cohort 1 of these studies, F0 females were assigned to Caesarean section on GD 21, whereas in cohort 2 of this study, females were allowed to naturally deliver their litters and were then euthanised after completion of the 21-Day postpartum period. F1 pups assigned were euthanised on Day 13 or 21 postpartum. Four doses of mRNA-1283 at 80 µg/dose were administered during the premating period (28 and 14 days prior to cohabitation) and on GD 1 and 13.

Similarly as in the repeat-dose rat toxicity studies also in these two studies, test-article related maternal effects pertaining to a local and systemic inflammatory response towards the administered LNPs, mRNA and especially the expressed protein antigen were observed (e.g. swollen hindlimbs). Specifically, administration of mRNA-1283 was associated with injection site reactions (skin scabs and flaking) including limited use and swelling of the respective hindlimbs.

Importantly, though, administration of both, mRNA-1010 and mRNA-1283, respectively, within these studies did not impact the number and length of oestrous cycles or mating, fertility, or pregnancy indices. Also, no macroscopic findings or effects on any ovarian, uterine, or litter parameters were noted. Additionally, no correlation of mRNA administration and incidence of foetal external, visceral or skeletal malformations or variations was found. mRNA administration did not impact natural delivery, maternal/litter interactions, or F1 preweaning parameter (e.g. viability, clinical observations, body weights, and pup macroscopic necropsy findings), including reflex and physical development. To conclude, administration of mRNA-1010/-1283 did not impact the reproductive performance of the F0 generation and the development (pre- and post-partum) of the F1 generation.

IgG titres against the expressed antigens were detected in the F0 generation (and in their milk) as well as in the F1 generation in utero and post-partum.

4.4.6. Toxicokinetics and exposure margins

Safety margins were calculated by the applicant the following way:

- Safety margins are calculated based on the proposed marketed human dose of 31.7 µg/dose of mRNA-1083 and assume a conservative human body weight estimate of 60 kg (0.53 µg/kg).
- Using the NOAEL from the GLP repeat-dose toxicity study in rats with mRNA-1083.2 (20 µg/dose) and assuming a rat body weight estimate of 0.3 kg, there is a 126-fold safety margin compared to the human dose.
- Regarding the NOAEL for female reproduction and peri/post-natal development in rats (100 or 80 µg/dose, or 333.3 or 266.7 µg/kg based on a 0.3 kg rat), the safety margin is 500-600 fold compared to the human dose.

4.4.7. Local tolerance

Local tolerance investigations were evaluated in the rat repeat-dose toxicity and DART studies.

4.4.8. Ecotoxicity/environmental risk assessment

The applicant did not conduct Environmental Risk Assessment (ERA) studies on mRNA-1083. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. This justification is sufficient and in compliance with EMA guideline EMEA/CHMP/SWP/4447/00 Corr 2. mRNA-1083 is not expected to pose a risk to the environment.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

All non-clinical studies have been conducted with vaccines containing four influenza antigens (quadrivalent, QIV) instead of three antigens (trivalent, TIV) as proposed for the current mCOMBRIAX product. This was discussed during the presubmission meeting and can be agreed with.

Pharmacology

The applicant has conducted three immunogenicity studies in mice with the mRNA-1083. In two of these studies, immunogenicity of this combined influenza/SARS-CoV-2 vaccine was compared to the immunogenicity of the single vaccines against influenza (mRNA-1010) and SARS-CoV-2 (mRNA-1283). In addition, two studies to evaluate the protection of mRNA-1010 against influenza virus challenge have been conducted in mice and ferrets. Furthermore, the applicant has provided data from a publication in which the protective effect of mRNA-1283 against SARS-CoV-2 virus challenge was assessed.

Overall, data of the non-GLP compliant immunogenicity studies in mice with the combination vaccine mRNA-1083 are acceptable and support the proposed indication. Immunogenic response was confirmed by determination of appropriate IgG antibody binding, influenza HAI and SARS-CoV-2 nAb titres, as well as CD4+ and CD8+ T cell responses. Cellular immunogenicity was not determined for mRNA-1083 containing SARS-CoV-2 XBB.1.5 Omicron subvariant, however, it is likely that CD4+ and CD8+ T cell responses are induced with the used variant of mRNA-1083, considering the similarity (at least for influenza) with the antigens used in mRNA-1083 in these studies. Antibody subclasses IgG1

and IgG2a, and their ratio as an indicator for Th1 and/or Th2 T-cell responses, were not determined in any of the submitted non-clinical immunogenicity studies. During the evaluation, the applicant submitted a study with mRNA-1083 (influenza HAs from the NH24/25 season and SARS-CoV-2 JN.1 strain) in BALB/c mice, again revealing CD4+ (Th1-biased) and CD8+ T cell responses. These findings in mice are coherent with data obtained in humans, as supported by literature (Ananworanich et al., 2025; Fierro et al., 2025). Immunogenicity and protective efficacy of quadrivalent mRNA-1010 (SH2021 influenza virus strains) was demonstrated by reduction of morbidity, body weight loss, clinical symptoms or viral load in relevant animal models (mice and ferrets) in challenge studies conducted by the applicant, while the immunogenic and protective effects of monovalent mRNA-1283 (COVID-19 vaccine encoding NTD-RBD of the SARS-CoV-2 S protein of the original Wuhan-Hu-1 strain) and monovalent mRNA-1273 (Spikevax, the Applicant's authorised full-length protein vaccine against SARS-CoV-2) in mice were described by literature data (Stewart-Jones et al., 2023). The final study report in *Mustela putorius furo* ferrets contained data from the assessment of levels of viral RNA by TaqMan PCR, while the interim report solely contained data obtained from a virus titration assay on MDCK cells. As assumed by the applicant, the differences between the results obtained by virus titration and TaqMan PCR (reduced viral loads in the throat, nose and nasal turbinate and no virus in the lungs in vaccinated animals versus comparable viral loads between vaccinated and placebo treated ferrets with only reduced PCR titres in the lungs of vaccinated animals, respectively) might be due to the presence of non-infectious virus particles in addition to infectious virus, as measured by TaqMan PCR. This is a plausible explanation.

Secondary pharmacology, safety pharmacology and pharmacodynamic drug interaction studies were not conducted with mRNA-1083 and submitted with this marketing authorisation application, which is in accordance with applicable guidelines and therefore acceptable.

It was noted that all studies in mice and ferrets have been conducted in adult females only and therefore, gender (and age) differences in immunogenic responses cannot be deduced from presented studies. It is well-known that there can be sex differences in the immune response to certain vaccines. Nevertheless, since immunogenicity data from animals cannot be directly translated (quantitatively) to humans, the non-clinical studies in females are considered sufficient to indicate that mRNA-1083 is immunogenic (i.e. proof-of-concept), and will likely also be in humans. Furthermore, non-clinical toxicology studies were conducted in both sexes, with (expectable) more severe effects in female rats, which is discussed and addressed in the toxicology part of the discussion. PD studies in animals cannot be used to determine actual efficacy, only to indicate whether the vaccine is immunogenic and whether protection may be expected. The level of immunogenicity and protection against viral infection induced by this vaccine should therefore come from clinical studies.

The target mass ratio in the drug product (DP) of the mRNA-based multi-component vaccine against influenza virus and SARS-CoV-2 is 3.75:1, containing mRNA against influenza strains A/H1N1, A/H3N2, and B/Victoria-lineage (1:1:1) and SARS-CoV-2 XBB.1.5 Omicron subvariant. In non-clinical pharmacology studies, various combinations of mRNA-1083 vaccines (differing in influenza and SARS-CoV-2 virus strains) with a higher influenza to SARS-CoV-2 ratio of at least 5:1 were used, and some of these combinations were investigated in clinical Phase 1/2 or Phase 3 trials (with clinical batches) as well.

No animal challenge studies were conducted with the combination vaccine mRNA-1083, which would have contributed to add more valuable information regarding the efficacy of a combined influenza and SARS-CoV-2 vaccine. Nevertheless, considering the similarity of the immunogenic response induced by the multi-component mRNA-1083 vaccine and the individual influenza (mRNA-1010) and SARS-CoV-2 (mRNA-1283) vaccines, it is very likely that the protection conferred by the combination vaccine will also be comparable. Proof for protection of the mRNA-1083 vaccine should come from

clinical studies.

Pharmacokinetics

The non-clinical pharmacokinetics of LNP-technology based mRNA-vaccines and its lipid excipients has already been sufficiently characterised in earlier platform studies of similar mRNA-based vaccine candidates. It is hence agreed that no new pharmacokinetics studies specific to mRNA-1083 are warranted for this specific MAA.

The applicant is using a platform approach of SM-102 containing LNPs to assess the pharmacokinetic aspects of mRNA-1083, which is acceptable. The used analytical methods were previously assessed as part of the initial MAA (or variation) applications of Spikevax, mRESVIA and/or mNEXSPIKE, and are considered adequate.

The distribution studies were conducted with different test products (mRNA-1647, NPI-Luc mRNA or mRNA-1273), all based on the same SM-102 LNP/mRNA platform as used for mRNA-1083 and were previously assessed as part of the initial MAA (or variation) applications of Spikevax, mRESVIA and/or mNEXSPIKE.

In general, these studies demonstrated that distribution of the SM-102 lipid and mRNA was high at the injection site, lymph nodes and spleen. Distribution was generally low and transient to other tissues, and did not persist more than 1-3 days in tissues other than the injection site, lymph nodes and spleen. Exposure was generally independent of sex. There were no apparent changes in exposure or kinetics after the first or second dose. In conclusion, these studies support the platform approach.

The metabolism studies of SM-102 and PEG2000 DMG were previously assessed as part of the initial MAA (or variation) applications of Spikevax, mRESVIA and/or mNEXSPIKE.

Additionally, the applicant conducted studies that demonstrate that SM-102 and PEG2000-DMG are both readily metabolised via hydrolytic and oxidative pathways, and that no human-specific metabolites are produced that would warrant further classification in in vitro and in vivo (rat) studies.

No absorption- or pharmacokinetic drug interaction studies were conducted. This is acceptable.

Altogether, it can be concluded that the submitted platform studies are relevant and valid for the evaluation of the (non-clinical) pharmacokinetics of mRNA-1083 (identical LNP formulation but varying mRNA content) and demonstrate that intramuscular administration of mRNA-1083 does not pose a relevant concern to vaccinees. No concerns were identified during the review of the submitted data.

Toxicology

Pivotal toxicity studies have been conducted in compliance with GLP. This is overall acceptable and in accordance with applicable guidelines.

The current understanding of toxicology of mRNA-vaccines based on the LNP-technology is driven by the assumption that the toxicity profile is almost entirely defined by the LNP-construct and only to a much lesser extent by the biologic activity of the expressed antigens of the mRNA vaccine.

In general, the study design appears adequate. A suitable animal model was used and animal numbers per sex per group were sufficient. The dose levels and dosing schedule are acceptable.

In the pivotal toxicity study using mRNA-1083.2, hepatic alterations and corresponding changes in clinical chemistry (statistically significant increases in ALT, AST, ALP, bilirubin) were frequently observed at highest tested dose of 36 µg/dose. NOAEL was accordingly set at 20 µg/dose. Hence, it appears that the administered mRNA-1083.2 induced a certain extent of hepatotoxicity in rats at the highest tested dose. According to the summaries of other LNP-based vaccines provided, although

reversible liver alterations as well as similar transient changes in clinical chemistry were observed, adverse findings in the study using mRNA-1083.2 were more severe than in the other GLP-compliant submitted LNP-technology based studies. The NOAEL in these supportive studies was always the highest dose administered, although much higher overall doses up to 150 µg/dose had been administered. It is acknowledged that the overall safety margins calculated on the µg/kg basis are still high with the NOAEL of 20 µg/dose. To mention, these adversities together with other non-adverse findings (e.g., increased organ weights of spleen, kidney, liver, decreases in mean lymphocyte counts) appeared to be sex-specific (only seen in female rats), with female rats receiving a relatively higher dose per kilogram due to lower body weight, which may explain their increased sensitivity. mRNA and lipid concentrations in the liver were reported to be low or undetectable, indicating that liver effects were likely secondary to immune responses rather than direct exposure.

The GLP toxicity study used mRNA-1083.2 and included two additional mRNA sequences. The applicant however reiterates that these sequences encoded the same antigen classes as the proposed product and that differences in strain variants would not affect antigen structure, cellular behaviour, or immune function. The lipid nanoparticle composition, mRNA backbone, untranslated regions, and manufacturing processes are consistent across both formulations. The RNA doses in the toxicity study furthermore exceeded those of the commercial product, ensuring conservative testing conditions.

Finally and foremost, across clinical studies with mRNA-1083, involving doses from 15 to 82 µg and a range of RNA ratios (including 5:1) of, no cases of drug-related adverse liver injury or acute hepatic events were reported, even at the highest tested dose of 82 µg. This suggests that the liver toxicity observed in rats at 36 µg does not translate to humans.

The repeated dose toxicity study with mRNA-1010 and mRNA-1283 were not conducted in GLP-compliance, thus regarded of minor value only. These aspects – in principle – render these two platform-specific studies inadequate for evaluating the repeated dose toxicity of mRNA-1083 to the extent recommended in relevant guidance on non-clinical development of vaccine products. However, the pivotal study using mRNA-1083.2 and all other submitted LNP-platform studies were conducted in compliance with GLP.

These supportive studies were already submitted in previous MAA submission for LNP-technology based vaccines developed by Moderna Biotech Spain S.L., were thoroughly assessed/regarded acceptable at that point in time, and regarded supportive of mRNA platform-technology based vaccines.

Generally stated, those studies using the same LNP platform technology with other mRNA sequences are generally supportive and overall show low toxicity for the used mRNA platform technology, thus supporting the nonclinical and further clinical development programme of mRNA-1083. Adverse findings within those studies were mostly directly or indirectly related with the administration procedure (injection site findings), but especially with a local and systemic inflammatory response towards the administered LNP, mRNA and the expressed protein antigen. Such findings are commonly seen with vaccine administration and are thus expected and deemed non-adverse. Other findings, e.g. macro- and microscopical findings on liver, spleen, as well as changes in chemical parameters (e.g., ALT, AST, GGT, triglyceride) were associated with the mode of action of immunogenicity of antigens administered, completely resolved or at least showed a clear tendency of recovery two weeks post last dose, and thus, were overall regarded to be non-adverse. In all of these six supportive LNP-technology-based repeat dose toxicity studies, the respective highest administered dose was determined as the NOAEL (ranging from 89 to 150 µg/dose).

All reported findings in the two non-GLP RDT studies are directly or indirectly related with the administration procedure (injection site findings), but especially with a local and systemic inflammatory response towards the administered LNP, mRNA and the expressed protein antigen.

These are expectable findings. A NOAEL was not specified by the applicant for these studies. No concerns were however identified.

In accordance with currently effective recommendations on the nonclinical development of vaccines, generally, no dedicated genotoxicity studies need to be performed for vaccine medicinal products. They may be nevertheless required for particular vaccine components such as novel adjuvants and additives. mRNA-1083 contains natural nucleosides. However, with regard to lipid nanoparticles, especially excipient SM-102 and PEG2000-DMG, used within the final vaccine formulation, the applicant submitted genotoxicity data to evaluate the genotoxic potential of the excipient as well as the final vaccine formulation. The other lipid components contained in the final formulation, i.e. DSPC and cholesterol, were not separately tested but are contained in the formulation tested in the in vivo genotoxicity studies, which is acceptable. DSPC and cholesterol do not raise any concern in terms of genotoxic potential.

With regard to positive findings observed in in vivo micronucleus assays, ICH S2(R1) states that in this case 'all the toxicological data should be evaluated to determine whether a non-genotoxic effect could be the cause or a contributing factor'. In the toxicological studies conducted in rat, various non-genotoxic effects that could impact on the increase of micronucleated erythrocytes in this species were observed: i.e., hyperthermia, disturbance of erythropoiesis (lower reticulocyte count, higher red blood cell distribution width), increase and inflammation of the spleen (which could affect clearance of micronucleated cells from the blood).

Considering the equivocal results obtained at high concentrations when evaluating both in vivo genotoxicity studies together, it is acknowledged that administration of mRNA-1083 in humans occurs twice only and via intramuscular route, rather than intravenous injection as used in the genotoxicity rat studies, and at lower mg/kg body weight, compared to animal tests. Assuming, thus, a very limited systemic exposure to SM-102 in the human setting, genotoxicity risk in humans is regarded negligible.

To mention, the submitted studies on genotoxicity were already submitted and discussed with EMA during other MAAs dealing with mRNA-vaccines based on the very same LNP-platform. Thus, the actual assessment was aligned with those previous assessments where potential issues on genotoxicity were satisfactorily clarified by the applicant. No additional concerns on genotoxicity were identified in the course of this MAA.

The applicant conducted two separate GLP compliant combined developmental and peri-/postnatal reproductive toxicity studies for the two mRNA sequences mRNA-1010 (containing 4 mRNA sequences encoding the HAs of the WHO-recommended NH2021/2022 influenza strains H1Nlpdm09 A/Wisconsin/588/2019, H3N2 A/Cambodia/e0826360/2020, B/Washington/02/2019 (B/Victoria-lineage), and B/Phuket/3073/2013 (B/Yamagata-lineage) combined at a target mass ratio of 1:1:1:1) and mRNA-1283 (containing 1 mRNA sequence encoding the NTD and RBD of the SARS-CoV-2 S protein of the original strain (Wuhan-Hu-1)).

These two DART studies were submitted as agreed during the corresponding pre-submission meeting, although it is acknowledged that the proposed indication does not include women of childbearing potential (WOCBP).

The final vaccine formulation for mRNA-1083 contains both mRNAs, 1010 and 1283, in a ratio 3.75:1 at a final combined human target dose of 31.7 µg/dose. Thus, the overall safety margin appears acceptable with regard to the mRNA concentrations used in the two DART studies conducted (100 and 80 µg/dose corresponding to safety margins of around 500-600 fold compared to the human dose.

According to current state of knowledge, toxicity profile of mRNA platform vaccines is only minimally

determined by the packed mRNA, however, rather corresponds to the LNP-composition / formulation. Thus, the applicant's approach to not conduct DART studies with the final vaccine formulation for mRNA-1083 but rather to show non-adversity of the two separate components, mRNA-1010 and mRNA-1283, appears reasonable and is regarded acceptable, considering the large individual safety margins provided for each component. Although, combination of both mRNAs, mRNA-1010 and mRNA-1283, (within one vaccine formulation but within different LNP packages) is generally not expected to (negatively) impact the overall DART profile of the final vaccine formulation, it has to be highlighted that the acceptance of the submitted DART data is also based on the fact that the targeted population does not include WOCBP, which renders these data of supportive value for the overall benefit/risk only.

Thus, without any significant adversities identified in studies 20323624 and 20346748, provided DART data supports the MAA of mRNA-1083.

The nonclinical data is adequately reflected in the SmPC.

The Applicant provided sufficient justification for not conducting dedicated ERA studies. This is acknowledged and in line with regulatory guidelines on the non-clinical development of vaccine candidates. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, mRNA-1083 is not expected to pose a risk to the environment.

4.5.2. Conclusions

The nonclinical testing of mCOMBRIAX is overall adequate.

The provided non-clinical pharmacology data indicate that the mRNA-1083 vaccine is immunogenic in mice and confers protection against infection with influenza and SARS-CoV-2 viruses in mice and ferrets. Therefore, the pharmacology studies provide a proof-of-concept for the use of this vaccine in humans.

The submitted non-clinical PK data demonstrates adequate characterisation of the SM-102 based mRNA platform, and is sufficient to support the authorisation of mCOMBRIAX.

In general, the toxicity study program was sufficient and compliant with WHO guidelines and it does not indicate any other effects besides those that can be expected for a vaccine.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 2.4).

5.1.2.Tabular overview of clinical trials

Table 5: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 1/2 Dose finding study					
mRNA-1083-P101	Phase 1/2, randomised, stratified, observer-blind, active-control safety, reactogenicity, and immunogenicity study. Cohort B only: Randomisation stratification by age (⩾18 to <50 and ⩾50 to <65 years) and by influenza vaccine status in the most recent season.	Cohort A: mRNA-1083.1 30 µg mRNA-1083.1 60 µg mRNA-1083.2 27.5 µg mRNA-1083.2 55 µg mRNA-1083.2 82 µg mRNA-1083.3 52.5 µg mRNA-1010.4 50 µg mRNA-1283.222 10 µg mRNA-1273.222 50 µg mRNA-1010 50 µg Fluarix Fluzone HD Cohort B: mRNA-1083.1 15 µg mRNA-1083.1 30 µg mRNA-1083.1 60 µg mRNA-1083.2 27.5 µg mRNA-1083.2 55 µg mRNA-1083.2 82 µg mRNA-1083.3 52.5 µg mRNA-1010.4 50 µg mRNA-1283.222 10 µg mRNA-1273.222 50 µg mRNA-1010 50 µg Fluarix	Cohort A Healthy adults ⩾65 to <80 years of age Cohort B Healthy adults ⩾18 to <65years of age	Primary Objective: • To evaluate the safety and reactogenicity of study intervention administration across study treatment groups. Secondary Objectives: • To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment groups at Day 29. • To evaluate the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment groups at all evaluable humoral immunogenicity timepoints. Exploratory Objective: • To assess the occurrence of clinical influenza and COVID-19 in study participants. • To evaluate the cellular immune responses against influenza and SARS-CoV-2 in a subset of participants.	Cohort A: mRNA-1083.1 30 µg (51) mRNA-1083.1 60 µg (33) mRNA-1083.2 27.5 µg (54) mRNA-1083.2 55 µg (54) 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) Cohort B: mRNA-1083.1 15 µg (55) mRNA-1083.1 30 µg (56) mRNA-1083.1 60 µg (37) mRNA-1083.2 27.5 µg (55) mRNA-1083.2 55 µg (55) 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 50 µg (55) Fluarix (52)
Phase 3 confirmatory study					
mRNA-1083-P301	Phase 3, randomised, stratified, observer-blind, active-control safety, reactogenicity, and immunogenicity	Cohort A Single IM injection: mRNA-1083 40 µg + placebo Fluzone HD + Spikevax	Cohort A Healthy adults ⩾65 years	Primary Objectives: • To evaluate the humoral immune responses of mRNA-1083 for noninferiority relative to active comparators against vaccine-matched	Cohort A Single IM injection: mRNA-1083 40 µg + placebo (2011) Fluzone HD +

	study. Cohort A only: Randomisation stratification by age (65 to <75 and ⩾75 years).	Cohort B Single IM injection: mRNA-1083 40 µg + placebo Fluarix + Spikevax	Cohort B Healthy adults ⩾50 to <65years	strains for influenza and SARS-CoV-2 at Day 29. • To evaluate the safety and reactogenicity of study injections across study intervention groups. Secondary Objectives: • To further evaluate the humoral immune response of mRNA-1083 for superiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29. • To evaluate the humoral immune responses to vaccine matched strains for influenza and SARS-CoV-2 across study intervention groups at Day 29. • To evaluate the humoral immune responses for influenza across study intervention groups at Day 29 using the MN assay. Exploratory Objective: • To evaluate the humoral immune responses SARS-CoV-2 prevalent variant of interest across study intervention groups	Spikevax (2006) Cohort B Single IM injection: mRNA-1083 40 µg + placebo (1993) Fluarix + Spikevax (2005)

RD = randomised; DB = double blind; PC = placebo controlled; SA = single arm; OL =open label; yrs = years; SC = sub-cutaneous; Q4W = every 4 weeks; Q2W = every 2 weeks

5.2. Clinical pharmacology

5.2.1. Methods

HAI- Haemagglutination assay

HAI assays have been developed to quantify anti-HA binding Abs for influenza viruses. For the Study P101, the HAI assay was qualified by Moderna for virus strains (A/Darwin/11/2021 [A/H3N2], A/Delaware/55/2019 [A/H1N1], B/Phuket/3073/2013 [B/Yamagata], and B/Singapore/WUH4618/2021 [B/Victoria].

For Study P301, the HAI assay was qualified and validated by Q2 Solutions to accurately detect and quantify anti-HA bAbs in test sera against live influenza strains A/Wisconsin/67/2022, A/Darwin/11/2021, B/Connecticut/01/2021 and B/Phuket/3073/2013.

ELISA-based Microneutralisation Test

The applicant developed an ELISA-based Microneutralisation Test for the detection and quantification of influenza-specific neutralising antibodies. The tested seasonal influenza virus strains are: A/Wisconsin/67/2022 (H1N1), A/Darwin/6/2021 (H3N2), B/Connecticut/01/2021 (B Victoria) and B/Phuket/3073/2013 (B Yamagata) for the single cycle assay.

For the multicycle assay the following strains were assessed: A/Wisconsin/67/2022, A/Darwin/11/2021 (H3N2) and B/Austria/1359417/2021 (B Victoria).

Pseudotyped Virus Neutralisation Assay

A cell-based microneutralisation assay for the detection and quantification of nAb titres (spike variants: D614G, BA.4/BA.5, XBB.1.5 and JN.1) against SARS-CoV-2 strains in human serum was presented. The SARS CoV-2 MN Seasonal Variant assay, specifically for Omicron XBB.1.5 was partially validated by PPD Laboratory Services, Virginia, US, and used in Phase I-III clinical analysis. Validation parameters addressed were precision/ruggedness, relative accuracy and dilutional linearity.

For Study P301, PsVNA assays were validated by PPD Laboratories or qualified fit-for-purpose by The Duke Vaccine Immunogenicity Programs. The PPD Laboratories method is intended to evaluate a new variant of concern each season and outlines the validation of the Omicron XBB.1.5 variant. The Duke University PsVNA assays were validated for several SARS-CoV-2 variants and these validation efforts formed the basis of the qualified fit-for-purpose PsVNA assay assessing Omicron variant, XBB.1.5, and FLiRT variant, and JN.1.

5.2.2. Pharmacokinetics

No pharmacokinetic studies have been conducted for mCOMBRIAX.

5.2.3. Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/05 Rev. 1). As immunogenicity data of this vaccine are used to support the authorisation of this vaccine, immunogenicity data are included under the clinical efficacy section.

In this section the mechanism of action and the respective assays applied to determine the immunogenicity data are discussed.

Mechanism of action

After delivery into cells, the mRNA serves as a template for the synthesis of the intended proteins. In the case of mRNA-1083, the expressed, membrane bound HA proteins of the encoded influenza strains and cell surface-anchored NTD-RBD subdomains of the encoded SARS-CoV-2 Spike protein are recognized by immune cells as a foreign antigen, eliciting immune responses, which contribute to protection against influenza and COVID-19.

5.2.4. Overall discussion and conclusions on clinical pharmacology

Discussion

The bioanalytical methods used to support the clinical development of mRNA-1083 were for the influenza strains the HAI assay to evaluate anti-HA antibody levels and the microneutralisation assay to detect neutralising capacity against influenza strains. For SARS-CoV-2 the PsVNA is used to assess specific neutralising antibodies and ECLIA to examine binding IgG antibodies. These methods have been qualified or validated, and considered fit for purpose, including the Correlate of Protection analysis.

From a clinical perspective, it remains open in how far HAI titres are a surrogate for protection in light of the vaccine technology.

The applicant did not perform clinical trials to investigate the pharmacokinetic features of mRNA-1083. This is in line with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) and acceptable, since no new delivery system is employed, and the vaccine does not contain novel adjuvants or excipients.

Conclusions

No pharmacokinetics studies have been conducted for mRNA-1083 or the component vaccines mRNA-1010 and mRNA-1283. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current Guidelines on clinical evaluation of vaccines.

During the clinical development a variety of assays have been used to assess HA-specific (neutralising) antibodies against influenza as well as binding and neutralising antibodies against SARS-CoV-2. All assays used to determine humoral immunogenicity for influenza in the phase 3 studies for mRNA-1083 as well as for the Correlate of Protection analyses were validated. The assays used for evaluation of immunogenicity for SARS-CoV-2 in the phase 3 studies for mRNA-1083 were validated or qualified fit for purpose.

5.3. Clinical efficacy

5.3.1. Dose response study

Study mRNA-1083-P101

mRNA-1083-P101 is a 2-Part Phase 1/2 clinical study aimed to generate safety, reactogenicity, and immunogenicity data of a multi-component influenza and SARS-CoV-2 vaccine in adults ≥18 to <80 years of age. The study duration was up to 7 months, including the Screening period for each participant.

Study mRNA-1083-P101 is a 2-part study:

Part 1 of the study was a Phase 1/2, randomised, stratified, observer-blind, active-control study that evaluated the safety, reactogenicity, and immunogenicity of multiple mRNA-1083 compositions and dose levels compared to age-appropriate authorised influenza (Fluarix and/or Fluzone HD) and authorised SARS-CoV-2 (mRNA-1273.222 [thereafter referred to as mRNA-1273]) vaccine comparators, to the individual influenza (mRNA-1010.4 [optimised mRNA-1010]) and SARS-CoV-2 (mRNA-1283.222 [thereafter referred to as mRNA-1283]) components of mRNA-1083, as well as to the experimental influenza comparator mRNA-1010. The purpose of Part 1 was to generate sufficient safety, reactogenicity, and immunogenicity data to enable selection of an mRNA-1083 vaccine composition and dose level to evaluate in a subsequent Phase 3 clinical study in adults.

Part 1 included adults ≥18 to <80 years of age that were enrolled in 2 age cohorts: Cohort A included participants ≥65 to <80 years of age, and Cohort B included participants ≥18 to <65 years of age.

Part 2 of the study has the purpose to generate safety and immunogenicity data for additional mRNA-1083 compositions and dose levels in adults aged ≥18 to <50 years. Enrollment for Part 2 started in May 2024 and results for Part 2 have not been submitted.

Part 1 main criteria for inclusion and exclusion:

Part 1 of the study enrolled healthy adults ≥18 to <80 years of age at the time of consent with a body mass index of 18 kg/m2 to 35 kg/m2 (inclusive) at the Screening Visit. Female participants of

childbearing potential were required to have a negative pregnancy test at screening and to practice adequate contraception ≥28 days before study injection and through 90 days thereafter. All participants were to be fully vaccinated for the COVID-19 primary series according to the locally authorised or approved regimen, and their last COVID-19 vaccine (primary series or booster) was to be administered ≥120 days prior to Day 1.

Study interventions, dose, and mode of administration:

The study interventions and group assignments for Part 1 are outlined in the table below.

Table 6 Study interventions and group assignments for Part 1

Cohort A: (≥65 to <80 years), n=50/group, 600 total	**Cohort B: (≥18 to <65 years), n=52/group, 624 total**	**Intervention**	**Total mRNA Dose (µg)[a]**	**Component mRNA Dose (µg)[b]**		**Intervention Type**
				SARS-CoV-2	**Flu**	
NA	B1	mRNA-1083.1	15	2.5	12.5	IP
A2	B2	mRNA-1083.1	30	5	25	IP
A3	B3	mRNA-1083.1	60	10	50	IP
A4	B4	mRNA-1083.2	27.5	2.5	25	IP
A5	B5	mRNA-1083.2	55	5	50	IP
A6	B6	mRNA-1083.2	82	7.5	74.5	IP
A7	B7	mRNA-1083.3	52.5	2.5	50	IP
A8	B8	mRNA-1010.4 [c]	50	-	50	Non-IP experimental comparator
A9	B9	mRNA-1283.222 [d]	10	10	-	Non-IP experimental comparator
A10	B10	mRNA-1273.222 [d]	50	50	-	Non-IP authorized comparator
A11	B11	mRNA-1010	50	-	50	Non-IP experimental comparator
A12	B12	Fluarix	-	-	-	Authorised vaccine comparator
A13	NA	Fluzone HD	-	-	-	Authorised vaccine comparator

Abbreviations: HD = high dose; IP = investigational product; mRNA = messenger ribonucleic acid; NA = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Total mRNA dose is rounded to the nearest 0.5 µg.
b. Component mRNA dose was calculated based on the mass ratio of total influenza RNA to total SARS-CoV-2 RNA.
c. Optimized version of mRNA-1010.
d. mRNA-1273.222 and mRNA-1283.222 are referred to as mRNA-1273 and mRNA-1283, respectively, in this report.

The components of the mRNA vaccines used in Part 1 are shown in the table below.

Table 7: Components of the mRNA vaccines

Vaccine	mRNA Encoding Influenza HA				mRNA Encoding SARS-CoV-2 Spike				Influenza to SARS-CoV-2 mRNA ratio[a]
	H1N1	H3N2	B/ Yamagata	B/ Victoria	Wuhan-Hu-1 NTD-RBD	BA.4/BA.5 NTD-RBD	Wuhan-Hu-1 full length	BA.4/BA.5 full length	
mRNA-1083.1	✓	✓	✓[b]	✓[b]	✓	✓			5:1
mRNA-1083.2	✓	✓	✓[b]	✓[b]	✓	✓			10:1
mRNA-1083.3	✓	✓	✓[b]	✓[b]	✓	✓			20:1
mRNA-1010.4[c]	✓	✓	✓[b]	✓[b]					NA
mRNA-1283.222[d]					✓	✓			NA
mRNA-1273.222[d]							✓	✓	NA
mRNA-1010	✓	✓	✓	✓					NA

Abbreviations: HA = hemagglutinin; mRNA = messenger ribonucleic acid; NA = not applicable; NTD = N-terminal domain; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
[a] The ratio of the combined RNA mass of the 4 influenza mRNAs to the combined RNA mass of the 2 SARS - CoV-2 mRNAs.
[b] Encoded influenza B proteins HAs contained mutations.
[c] Optimized version of mRNA-1010.
[d] mRNA-1273.222 and mRNA-1283.222 are referred to as mRNA-1273 and mRNA-1283, respectively, in this report.

Objectives and Endpoints

The primary objective of the study was to evaluate the safety and reactogenicity of study intervention administration across study treatment groups.

Secondary objectives were the evaluation of the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment groups at Day 29 and the evaluation of the humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment groups at all evaluable humoral immunogenicity timepoints.

Immunogenicity Analyses

Immunogenicity analyses were descriptive only and were based on the Per Protocol Set.

Disposition of participants

A total of 596 participants received study injection in Cohort A and 620 in Cohort B (307 participants in the ≥50 to <65 years group and 313 participants in the ≥18 to <50 years group). In Cohort A, 52 to 54 participants were randomised in each study intervention group, except for mRNA-1083.1 60 µg (N=33) and mRNA-1083.2 82 µg (N=33). In Cohort B, 52 to 56 participants were randomised in each study intervention group, except for mRNA-1083.1 60 µg (N=37) and mRNA-1083.2 82 µg (N=38). The number of participants was unequal among the groups because of a temporary pause in enrollment at the recommendation of the Independent Safety Review Team.

Demographic and Other Baseline Characteristics

Cohort A: Among participants ≥65 to <80 years in the mRNA-1083 30-µg group, median age was 69.0 years, 90.2% (46/51) were White, 15.7% (8/51) were Hispanic or Latino, and 52.9% (27/51) were female. The proportion of participants who had received an influenza vaccine in the most recent season was 66.7% (34/51), and the proportion of participants who had received a bivalent COVID-19 vaccine was 51.0% (26/51). Participants in the mRNA-1083 60 µg group had a median age of 70.0 years, 84.8% (28/33) were White, 12.1% (4/33) were Hispanic or Latino, and 48.5% (16/33) were

female. The proportion of participants who had received an influenza vaccine in the most recent season was 66.7% (22/33), and the proportion of participants who had received a bivalent COVID-19 vaccine was 60.6% (20/33). Participants in the Fluarix group had a median age of 70.5 years, 88.9% (48/54) were White, 7.4% (4/54) were Hispanic or Latino, and 59.3% (32/54) were female. The proportion of participants who had received an influenza vaccine in the most recent season was 72.2% (39/54), and the proportion of participants who had received a bivalent COVID-19 vaccine was 50.0% (27/54). Participants in the Fluzone HD group had a median age of 68.0 years, 88.7% (47/53) were White, 7.5% (4/53) were Hispanic or Latino, and 56.6% (30/53) were female. The proportion of participants who had received an influenza vaccine in the most recent season was 69.8% (37/53), and the proportion of participants who had received a bivalent COVID-19 vaccine was 54.7% (29/53). Participants in the mRNA-1273 group had a median age of 70.0 years, 81.5% (44/54) were White, 7.4% (4/54) were Hispanic or Latino, and 61.1% (33/54) were female. The proportion of participants who had received an influenza vaccine in the most recent season was 68.5% (37/54), and the proportion of participants who had received a bivalent COVID-19 vaccine was 68.5% (37/54).

Cohort B: Among participants ⩾50 to <65 years who received mRNA-1083 30 µg, the median age was 56.5 years, 42.9% (12/28) were female, 71.4% (20/28) were White, and 7.1% (2/28) were Hispanic or Latino. The proportion of participants who had received an influenza vaccine in the most recent season was 42.9% (12/28), and the proportion of participants who had received a bivalent COVID-19 vaccine was 39.3% (11/28). In the mRNA-1083 60 µg group, the median age was 58.0 years, 31.3% (5/16) were female, 87.5% (14/16) were White, and 12.5% (2/16) were Hispanic or Latino. The proportion of participants who had received an influenza vaccine in the most recent season was 43.8% (7/16) and the proportion of participants who had received a bivalent COVID-19 vaccine was 37.5% (6/16). In the Fluarix group, the median age was 59.0 years, 50.0% (13/26) were female, 76.9% (20/26) were White, 19.2% (5/26) were Hispanic or Latino, 50.0% (13/26) had received an influenza vaccine in the most recent season, and 38.5% (10/26) had received a bivalent COVID-19 vaccine. In the mRNA-1273 group, the median age was 59.0 years, 55.6% (15/27) were female, 85.2% (23/27) were White, 11.1% (3/27) were Hispanic or Latino, 48.1% (13/27) had received an influenza vaccine in the most recent season, and 40.7% (11/27) had received a bivalent COVID-19 vaccine.

Exposure

Overall, the median duration of follow up was approximately 170 days across the different age groups analysed.

Immunogenicity Results

Influenza antibody response

Cohort A (Participants ≥65 to <80 Years)

An overview of the Day 1 GMT, Day 29 GMT, GMFR, SCR and D181 GMT for the influenza haemagglutination inhibition antibody responses for each of the four influenza strains for the ≥65 to <80 years group are provided in the tables below.

Table 8: Influenza Hemagglutination Inhibition Antibody Responses - Cohort A: ⩾65 to <80 Years (Per Protocol Set)

Influenza A Strains

Values (95% CI)	Fluarix (N=51)	Fluzone HD (N=50)	mRNA-1010 50 µg (N=50)	mRNA-1010.4 50 µg (N=45)	mRNA-1083.1 30 µg (N=50)	mRNA-1083.1 60 µg (N=30)	mRNA-1083.2 27.5 µg (N=53)	mRNA-1083.2 55 µg (N=51)	mRNA-1083.2 82 µg (N=31)	mRNA-1083.3 52.5 µg (N=50)
Influenza A/H1N1 (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**49.7**	**47.5**	**55.0**	**55.7**	**58.2**	**41.4**	**55.1**	**53.1**	**39.1**	**57.7**
(95% CI) [a]	(40.4, 61.1)	(36.9, 61.2)	(42.3, 71.6)	(43.3, 71.6)	(46.3, 73.1)	(29.0, 59.2)	(41.1, 73.9)	(39.5, 71.3)	(29.7, 51.6)	(46.1, 72.4)
Day 29 GMT	**78.4**	**85.7**	**108.5**	**149.3**	**95.8**	**104.3**	**106.0**	**139.5**	**82.7**	**129.1**
(95% CI) [a]	(60.9, 100.8)	(62.9, 116.8)	(84.0, 140.1)	(107.5, 207.3)	(74.8, 122.8)	(69.4, 156.8)	(81.5, 137.9)	(99.9, 194.9)	(56.3, 121.3)	(99.9, 166.8)
GMFR	**1.6**	**1.8**	**2.0**	**2.7**	**1.6**	**2.5**	**1.9**	**2.6**	**2.1**	**2.2**
(95% CI) [a]	(1.2, 2.0)	(1.5, 2.2)	(1.7, 2.3)	(2.0, 3.6)	(1.4, 2.0)	(1.8, 3.6)	(1.5, 2.4)	(2.1, 3.4)	(1.6, 2.8)	(1.7, 2.9)
SCR % [b]	**11.8**	**14.0**	**18.4**	**28.9**	**12.0**	**33.3**	**20.8**	**34.0**	**19.4**	**18.0**
(95% CI) [c]	(4.4, 23.9)	(5.8, 26.7)	(8.8, 32.0)	(16.4, 44.3)	(4.5, 24.3)	(17.3, 52.8)	(10.8, 34.1)	(20.9, 49.3)	(7.5, 37.5)	(8.6, 31.4)
Day 181 GMT	**104.5**	**104.7**	**99.3**	**148.1**	**104.3**	**145.6**	**127.3**	**135.3**	**104.2**	**140.2**
(95% CI) [a]	(80.1, 136.3)	(74.8, 146.7)	(74.0, 133.3)	(99.2, 221.1)	77.6, 140.3	(104.1, 203.7)	(96.2, 168.5)	(102.4, 178.7)	(73.7, 147.2)	(108.9, 180.5)
Influenza A/H3N2 (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**34.4**	**34.1**	**38.9**	**30.7**	**43.1**	**31.7**	**29.0**	**37.6**	**39.6**	**32.1**
(95% CI) [a]	(25.5, 46.6)	(26.5, 43.9)	(29.3, 51.5)	(23.0, 41.0)	(33.9, 54.9)	(22.4, 44.8)	(21.4, 39.5)	(27.4, 51.5)	(28.3, 55.2)	(24.0, 43.0)
Day 29 GMT	**61.8**	**67.7**	**88.3**	**113.2**	**90.7**	**119.8**	**64.8**	**103.4**	**94.6**	**100.6**
(95% CI) [a]	(45.6, 83.8)	(48.9, 93.8)	(65.7, 118.6)	(77.6, 165.0)	(65.6, 125.2)	(74.9, 191.7)	(47.8, 87.9)	(78.1, 136.9)	(63.8, 140.2)	(75.5, 134.1)
GMFR	**1.8**	**2.0**	**2.3**	**3.7**	**2.1**	**3.8**	**2.2**	**2.8**	**2.4**	**3.1**
(95% CI) [a]	(1.4, 2.3)	(1.6, 2.5)	(1.8, 2.8)	(2.8, 4.8)	(1.7, 2.6)	(2.5, 5.6)	(1.8, 2.8)	(2.1, 3.6)	(1.7, 3.4)	(2.4, 3.9)
SCR % [b]	**15.7**	**22.0**	**22.4**	**55.6**	**26.0**	**43.3**	**22.6**	**38.0**	**25.8**	**44.9**
(95% CI) [c]	(7.0, 28.6)	(11.5, 36.0)	(11.8, 36.6)	(40.0, 70.4)	(14.6, 40.3)	(25.5, 62.6)	(12.3, 36.2)	(24.7, 52.8)	(11.9, 44.6)	(30.7, 59.8)
Day 181 GMT	**85.1**	**87.2**	**116.9**	**146.7**	**129.8**	**196.4**	**91.5**	**114.2**	**107.2**	**117.9**
(95% CI) [a]	(64.2, 112.9)	(63.2, 120.3)	(80.0, 170.7)	(99.3, 216.9)	(96.2, 175.2)	(125.1, 308.5)	(71.5, 117.0)	(81.4, 160.2)	(72.5, 158.5)	(87.1, 159.6)

Influenza B Strains

Values (95% CI)	Fluarix (N=51)	Fluzone HD (N=50)	mRNA-1010 50 µg (N=50)	mRNA-1010.4 50 µg (N=45)	mRNA-1083.1 30 µg (N=50)	mRNA-1083.1 60 µg (N=30)	mRNA-1083.2 27.5 µg (N=53)	mRNA-1083.2 55 µg (N=51)	mRNA-1083.2 82 µg (N=31)	mRNA-1083.3 52.5 µg (N=50)
Influenza B/Victoria (LLOQ: 10, ULOQ: 320)										
Day 1 GMT	**55.4**	**49.2**	**46.7**	**46.8**	**73.1**	**52.2**	**72.5**	**55.0**	**46.8**	**69.6**
(95% CI) [a]	(41.3, 74.3)	(35.8, 67.8)	(34.0, 64.2)	(34.5, 63.4)	(56.4, 94.7)	(36.7, 74.3)	(56.2, 93.7)	(41.3, 73.0)	(32.5, 67.3)	(52.3, 92.8)
Day 29 GMT	**100.7**	**106.3**	**88.3**	**151.5**	**141.2**	**128.5**	**148.0**	**155.5**	**152.9**	**172.7**
(95% CI) [a]	(70.1, 144.8)	(72.7, 155.3)	(65.3, 119.4)	(120.5, 190.5)	107.9, 184.9	(82.0, 201.3)	(115.3, 189.9)	(121.1, 199.6)	.06.7, 219.1)	(131.9, 226.0)
GMFR	**1.8**	**2.2**	**1.9**	**3.3**	**1.9**	**2.5**	**2.0**	**2.9**	**3.3**	**2.5**
(95% CI) [a]	(1.3, 2.5)	(1.6, 2.9)	(1.5, 2.4)	(2.4, 4.6)	(1.6, 2.4)	(1.6, 3.7)	(1.7, 2.4)	(2.2, 3.8)	(2.3, 4.7)	(1.9, 3.3)
SCR % [b]	**21.6**	**18.0**	**22.4**	**48.8**	**16.0**	**23.3**	**24.5**	**36.2**	**41.9**	**28.0**
(95% CI) [c]	(11.3, 35.3)	(8.6, 31.4)	(11.8, 36.6)	(33.3, 64.5)	(7.2, 29.1)	(9.9, 42.3)	(13.8, 38.3)	(22.7, 51.5)	(24.5, 60.9)	(16.2, 42.5)
Day 181 GMT	**167.2**	**128.2**	**95.1**	**139.9**	**140.6**	**178.8**	**174.5**	**142.5**	**183.7**	**185.7**
(95% CI) [a]	113.6, 246.2	(86.3, 190.6)	(68.6, 131.9)	(108.0, 181.1)	106.9, 184.8	110.4, 289.4	136.2, 223.6	101.1, 200.9	122.6, 275.4	136.2, 253.1
Influenza B/Yamagata (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**49.0**	**56.5**	**62.9**	**52.7**	**80.6**	**63.5**	**74.5**	**56.5**	**48.4**	**90.6**
(95% CI	(36.9, 65.2)	(43.0, 74.3)	(46.5, 85.0)	(39.7, 70.0)	(65.0, 99.9)	(45.3, 88.9)	(57.2, 96.9)	(42.8, 74.7)	(33.1, 70.7)	(68.8, 119.4)
Day 29 GMT	**75.2**	**110.0**	**100.4**	**108.1**	**110.8**	**101.9**	**112.3**	**98.7**	**80.0**	**145.2**

Values (95% CI)	Fluarix (N=51)	Fluzone HD (N=50)	mRNA-1010 50 µg (N=50)	mRNA-1010.4 50 µg (N=45)	mRNA-1083.1 30 µg (N=50)	mRNA-1083.1 60 µg (N=30)	mRNA-1083.2 27.5 µg (N=53)	mRNA-1083.2 55 µg (N=51)	mRNA-1083.2 82 µg (N=31)	mRNA-1083.3 52.5 µg (N=50)
(95% CI	(56.2, 100.7)	(83.3, 145.3)	(75.9, 132.8)	(82.3, 141.9)	(86.9, 141.3)	(69.0, 150.4)	(83.3, 151.5)	(75.9, 128.1)	(56.5, 113.3)	(109.5, 192.7)
GMFR	**1.5**	**1.9**	**1.6**	**2.0**	**1.4**	**1.6**	**1.5**	**1.8**	**1.7**	**1.6**
(95% CI	(1.2, 1.9)	(1.5, 2.6)	(1.3, 1.9)	(1.6, 2.6)	(1.2, 1.6)	(1.2, 2.1)	(1.2, 1.8)	(1.5, 2.2)	(1.2, 2.2)	(1.3, 1.9)
SCR % [t]	**9.8**	**18.0**	**12.2**	**28.9**	**2.0**	**13.3**	**7.5**	**16.7**	**16.1**	**6.0**
(95% CI	(3.3, 21.4)	(8.6, 31.4)	(4.6, 24.8)	(16.4, 44.3)	(<0.1, 10.6)	(3.8, 30.7)	(2.1, 18.2)	(7.5, 30.2)	(5.5, 33.7)	(1.3, 16.5)
Day 181 GMT	**94.8**	**112.0**	**84.5**	**98.9**	**109.6**	**109.6**	**98.9**	**98.1**	**87.3**	**121.9**
(95% CI	(65.4, 137.4)	(78.2, 160.5)	(56.5, 126.4)	(68.6, 142.5)	(80.9, 148.4)	(71.7, 167.6)	(74.0, 132.3)	(68.4, 140.9)	(53.2, 143.1)	(87.6, 169.6)

Abbreviations: CI = confidence interval; GM = geometric mean; GMFR = geometric mean fold rise; GMT = geometric mean titre; HAI = haemagglutination inhibition; HD = high dose; LLOQ = lower limit of quantification; SCR = seroresponse rate; ULOQ = upper limit of quantification.

a. 95% CI was calculated based on the t-distribution of the log-transformed values for GM titre and GM fold rise values, respectively, then back transformed to the original scale for presentation.

b. Seroconversion at a participant level was defined as a preinjection HAI titre <1:10 and a postinjection HAI titre ≥1:40 or a preinjection HAI titre ≥ 1:10 and a minimum 4-fold rise in postinjection HAI antibody titre.

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

Source: Table 14.2.1.1.

Cohort B (Participants ≥18 to <65 Years)

An overview of the Day 1 GMT, Day 29 GMT, GMFR, SCR and D181 GMT for the influenza hemagglutination inhibition antibody responses for each of the four influenza strains for Cohort B (≥50 to <65 and ≥18 to <50 years) are provided in the tables below.

Table 9: Influenza Hemagglutination Inhibition Antibody Responses - Cohort B: ⩾50 to <65 Years (Per Protocol Set)

Influenza A Strains

Values (95% CI)	Fluarix (N=25)	mRNA-1010 50 µg (N=24)	mRNA-1010.4 50 µg (N=27)	mRNA-1083.1 15 µg (N=24)	mRNA-1083.1 30 µg (N=27)	mRNA-1083.1 60 µg (N=16)	mRNA-1083.2 27.5 µg (N=24)	mRNA-1083.2 55 µg (N=26)	mRNA-1083.2 82 µg (N=16)	mRNA-1083.3 52.5 µg (N=27)
Influenza A/H1N1 (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**48.6**	**62.0**	**47.3**	**43.6**	**59.6**	**54.2**	**67.2**	**58.1**	**71.8**	**79.9**
(95% CI) [a]	(36.1, 65.5)	(40.2, 95.4)	(37.3, 59.9)	(28.9, 65.7)	(41.9, 84.8)	(34.1, 86.0)	(43.3, 104.2)	(44.5, 75.7)	(46.0, 112.2)	(57.7, 110.6)
Day 29 GMT	**100.0**	**111.4**	**128.6**	**104.9**	**107.5**	**131.7**	**187.6**	**119.3**	**150.0**	**172.9**
(95% CI) [a]	(72.1, 138.7)	(69.7, 178.0)	(86.7, 190.6)	(71.0, 155.2)	(72.6, 159.2)	(85.5, 202.8)	(127.3, 276.6)	(88.8, 160.4)	(87.8, 256.3)	(127.2, 235.0)
GMFR	**2.1**	**1.8**	**2.7**	**2.4**	**1.8**	**2.4**	**2.8**	**2.1**	**2.1**	**2.2**
(95% CI) [a]	(1.5, 2.8)	(1.3, 2.4)	(1.9, 3.9)	(1.4, 4.0)	(1.3, 2.4)	(1.7, 3.6)	(2.0, 3.9)	(1.5, 2.9)	(1.1, 4.0)	(1.7, 2.8)
SCR % [b]	**24.0**	**17.4**	**40.7**	**21.7**	**11.1**	**25.0**	**41.7**	**23.1**	**12.5**	**22.2**
(95% CI) [c]	(9.4, 45.1)	(5.0, 38.8)	(22.4, 61.2)	(7.5, 43.7)	(2.4, 29.2)	(7.3, 52.4)	(22.1, 63.4)	(9.0, 43.6)	(1.6, 38.3)	(8.6, 42.3)
Day 181 GMT	**100.7**	**103.3**	**157.7**	**124.9**	**136.7**	**125.6**	**167.8**	**105.5**	**123.4**	**162.4**
(95% CI) [a]	(69.7, 145.6)	(74.8, 142.8)	(111.0, 224.2)	(81.6, 191.4)	(92.0, 203.1)	(92.2, 171.1)	(107.0, 263.3)	(78.7, 141.3)	(72.5, 210.1)	(106.1, 248.6)
Influenza A/H3N2 (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**28.7**	**57.5**	**47.9**	**30.8**	**31.3**	**38.3**	**33.6**	**57.3**	**47.6**	**38.4**
(95% CI) [a]	(20.3, 40.6)	(38.6, 85.5)	(32.1, 71.5)	(22.1, 43.0)	(24.5, 40.1)	(21.8, 67.3)	(24.0, 47.1)	(34.4, 95.5)	(35.4, 63.9)	(27.1, 54.5)
Day 29 GMT	**71.7**	**116.7**	**122.2**	**85.0**	**71.3**	**91.1**	**97.9**	**113.0**	**120.7**	**98.2**
(95% CI) [a]	(46.1, 111.6)	(73.3, 185.7)	(80.4, 185.8)	(56.5, 127.8)	(45.7, 111.2)	(57.7, 143.8)	(58.8, 163.2)	(69.7, 183.4)	(75.9, 191.9)	(62.0, 155.5)
GMFR	**2.5**	**2.0**	**2.6**	**2.8**	**2.3**	**2.4**	**2.9**	**2.0**	**2.5**	**2.5**
(95% CI) [a]	(1.7, 3.6)	(1.5, 2.7)	(1.8, 3.7)	(1.7, 4.6)	(1.6, 3.2)	(1.7, 3.4)	(2.0, 4.3)	(1.2, 3.2)	(1.8, 3.6)	(1.8, 3.3)
SCR % [b]	**32.0**	**21.7**	**40.7**	**26.1**	**25.9**	**25.0**	**37.5**	**34.6**	**31.3**	**19.2**
(95% CI) [c]	(14.9, 53.5)	(7.5, 43.7)	(22.4, 61.2)	(10.2, 48.4)	(11.1, 46.3)	(7.3, 52.4)	(18.8, 59.4)	(17.2, 55.7)	(11.0, 58.7)	(6.6, 39.4)
Day 181 GMT	**71.3**	**121.8**	**142.6**	**97.6**	**81.3**	**121.3**	**111.5**	**133.7**	**123.4**	**111.6**

Values (95% CI)	Fluarix (N=25)	mRNA-1010 50 µg (N=24)	mRNA-1010.4 50 µg (N=27)	mRNA-1083.1 15 µg (N=24)	mRNA-1083.1 30 µg (N=27)	mRNA-1083.1 60 µg (N=16)	mRNA-1083.2 27.5 µg (N=24)	mRNA-1083.2 55 µg (N=26)	mRNA-1083.2 82 µg (N=16)	mRNA-1083.3 52.5 µg (N=27)
(95% CI) [a]	(49.2, 103.2)	(80.4, 184.4)	(76.8, 264.7)	(72.5, 131.4)	(50.6, 130.4)	(84.2, 174.8)	(62.3, 199.4)	(88.8, 201.2)	(70.2, 217.0)	(74.4, 167.5)

Influenza B Strains

Values (95% CI)	Fluarix (N=25)	mRNA-1010 50 µg (N=24)	mRNA-1010.4 50 µg (N=27)	mRNA-1083.1 15 µg (N=24)	mRNA-1083.1 30 µg (N=27)	mRNA-1083.1 60 µg (N=16)	mRNA-1083.2 27.5 µg (N=24)	mRNA-1083.2 55 µg (N=26)	mRNA-1083.2 82 µg (N=16)	mRNA-1083.3 52.5 µg (N=27)
Influenza B/Victoria (LLOQ: 10, ULOQ: 320)										
Day 1 GMT	**45.9**	**54.0**	**39.0**	**49.6**	**61.1**	**63.0**	**70.2**	**50.8**	**48.7**	**57.3**
(95% CI) [a]	(28.6, 73.8)	(32.6, 89.7)	(23.3, 65.2)	(31.6, 77.9)	(41.4, 90.1)	(31.8, 124.8)	(45.4, 108.6)	(34.8, 74.1)	(30.1, 78.8)	(38.9, 84.4)
Day 29 GMT	**104.2**	**87.6**	**125.4**	**116.6**	**135.4**	**150.1**	**127.0**	**153.8**	**123.4**	**132.0**
(95% CI) [a]	(67.7, 160.4)	(58.8, 130.3)	(79.4, 198.2)	(80.4, 169.3)	(93.4, 196.3)	(82.4, 273.4)	(87.4, 184.4)	(106.7, 221.6	(70.6, 215.6)	(87.9, 198.3)
GMFR	**2.3**	**1.6**	**3.2**	**2.5**	**2.2**	**2.4**	**1.8**	**3.0**	**2.5**	**2.4**
(95% CI) [a]	(1.5, 3.4)	(1.2, 2.2)	(2.2, 4.7)	(1.9, 3.2)	(1.6, 3.0)	(1.3, 4.2)	(1.2, 2.7)	(2.1, 4.5)	(1.6, 4.1)	(1.9, 3.0)
SCR % [b]	**32.0**	**8.7**	**40.7**	**17.4**	**22.2**	**31.3**	**20.8**	**38.5**	**37.5**	**26.9**
(95% CI) [c]	(14.9, 53.5)	(1.1, 28.0)	(22.4, 61.2)	(5.0, 38.8)	(8.6, 42.3)	(11.0, 58.7)	(7.1, 42.2)	(20.2, 59.4)	(15.2, 64.6)	(11.6, 47.8)
Day 181 GMT	**128.9**	**135.6**	**190.4**	**160.1**	**162.5**	**165.5**	**138.8**	**121.3**	**195.6**	**167.1**
(95% CI) [a]	(84.5, 196.6)	(78.0, 235.8)	(120.9, 299.9)	(104.2, 245.8)	(112.4, 235.1)	(70.3, 389.3)	(87.5, 220.2)	(91.4, 161.0)	(84.6, 452.3)	(109.4, 255.2)
Influenza B/Yamagata (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**67.7**	**91.6**	**87.5**	**88.5**	**122.1**	**75.0**	**74.4**	**76.9**	**85.3**	**77.9**
(95% CI) [a]	(47.8, 96.0)	(63.3, 132.5)	(61.4, 124.6)	(57.0, 137.6)	(80.3, 185.8)	(44.2, 127.1)	(48.9, 113.4)	(50.7, 116.5)	(48.3, 150.8)	(54.6, 111.3)
Day 29 GMT	**121.3**	**164.8**	**184.2**	**177.8**	**200.7**	**131.6**	**121.6**	**140.0**	**190.2**	**119.1**
(95% CI) [a]	(77.0, 191.1)	(113.5, 239.2)	(122.0, 278.1)	(103.9, 304.3)	(145.1, 277.4)	(59.1, 293.2)	(81.5, 181.4)	(94.9, 206.4)	(106.0, 341.2	(81.0, 175.1)
GMFR	**1.8**	**1.8**	**2.1**	**2.1**	**1.7**	**1.8**	**1.6**	**1.8**	**2.2**	**1.6**
(95% CI) [a]	(1.2, 2.7)	(1.4, 2.4)	(1.6, 2.8)	(1.4, 3.1)	(1.2, 2.5)	(1.2, 2.6)	(1.4, 1.9)	(1.5, 2.2)	(1.5, 3.3)	(1.3, 1.9)
SCR % [b]	**20.0**	**17.4**	**18.5**	**26.1**	**15.4**	**25.0**	**4.2**	**7.7**	**31.3**	**7.7**
(95% CI) [c]	(6.8, 40.7)	(5.0, 38.8)	(6.3, 38.1)	(10.2, 48.4)	(4.4, 34.9)	(7.3, 52.4)	(0.1, 21.1)	(0.9, 25.1)	(11.0, 58.7)	(0.9, 25.1)
Day 181 GMT	**71.2**	**89.1**	**103.7**	**84.1**	**122.4**	**60.6**	**122.4**	**73.6**	**82.3**	**58.2**
(95% CI) [a]	(48.6, 104.4)	(59.8, 132.8)	(65.0, 165.6)	(52.5, 134.7)	(82.6, 181.4)	(25.9, 141.7)	(66.7, 224.7)	(48.2, 112.5)	(41.4, 163.6)	(41.5, 81.8)

Abbreviations: CI = confidence interval; GM = geometric mean; GMFR = geometric mean fold rise; GMT = geometric mean titre; HAI = haemagglutination inhibition; LLOQ = lower limit of quantification; SCR = seroconversion rate; ULOQ = upper limit of quantification.

a. 95% CI was calculated based on the t-distribution of the log-transformed values for GM titre and GM fold rise values, respectively, then back transformed to the original scale for presentation.

b. Seroconversion at a participant level was defined as a preinjection HAI titre <1:10 and a postinjection HAI titre ≥1:40 or a preinjection HAI titre ≥1:10 and a minimum 4-fold rise in postinjection HAI antibody titre.

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

Source: Table 14.2.1.2.

Table 10: Influenza Haemagglutination Inhibition Antibody Responses - Cohort B: ⩾18 to <50 Years (Per Protocol Set)

Influenza A Strains

Values (95% CI)	Fluarix (N=25)	mRNA-1010 50 µg (N=24)	mRNA-1010.4 50 µg (N=25)	mRNA-1083.1 15 µg (N=27)	mRNA-1083.1 30 µg (N=26)	mRNA-1083.1 60 µg (N=20)	mRNA-1083.2 27.5 µg (N=26)	mRNA-1083.2 55 µg (N=26)	mRNA-1083.2 82 µg (N=22)	mRNA-1083.3 52.5 µg (N=24)
Influenza A/H1N1 (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**47.9**	**61.7**	**50.7**	**59.6**	**55.0**	**63.9**	**42.2**	**58.9**	**81.2**	**41.1**

Values (95% CI)	Fluarix (N=25)	mRNA-1010 50 µg (N=24)	mRNA-1010.4 50 µg (N=25)	mRNA-1083.1 15 µg (N=27)	mRNA-1083.1 30 µg (N=26)	mRNA-1083.1 60 µg (N=20)	mRNA-1083.2 27.5 µg (N=26)	mRNA-1083.2 55 µg (N=26)	mRNA-1083.2 82 µg (N=22)	mRNA-1083.3 52.5 µg (N=24)
(95% CI) [a]	(33.3, 69.1)	(42.9, 88.6)	(32.9, 77.9)	(38.8, 91.4)	(40.3, 75.2)	(42.2, 96.8)	(31.6, 56.2)	(40.7, 85.0)	(50.1, 131.7)	(27.3, 62.0)
Day 29 GMT	**130.0**	**187.5**	**149.4**	**148.1**	**136.3**	**139.3**	**168.7**	**171.0**	**241.8**	**128.8**
(95% CI) [a]	(71.9, 235.2)	(118.8, 296.1)	(90.2, 247.2)	(105.8, 207.4)	(85.0, 218.6)	(90.5, 214.5)	(113.2, 251.6)	(124.3, 235.3)	(148.1, 394.8)	(80.1, 207.0)
GMFR	**2.7**	**3.0**	**2.9**	**2.5**	**2.5**	**2.2**	**4.0**	**2.9**	**3.0**	**3.1**
(95% CI) [a]	(1.6, 4.5)	(2.0, 4.5)	(1.7, 5.2)	(1.6, 3.8)	(1.6, 3.8)	(1.5, 3.2)	(2.4, 6.6)	(1.8, 4.7)	(1.7, 5.2)	(2.0, 5.0)
SCR % [b]	**36.0**	**37.5**	**32.0**	**37.0**	**30.8**	**15.0**	**53.8**	**38.5**	**42.9**	**54.2**
(95% CI) [c]	(18.0, 57.5)	(18.8, 59.4)	(14.9, 53.5)	(19.4, 57.6)	(14.3, 51.8)	(3.2, 37.9)	(33.4, 73.4)	(20.2, 59.4)	(21.8, 66.0)	(32.8, 74.4)
Day 181 GMT	**142.5**	**185.7**	**197.0**	**143.9**	**160.0**	**183.9**	**185.6**	**169.9**	**186.3**	**160.0**
(95% CI) [a]	(87.6, 232.0)	(125.6, 274.6)	(140.4, 276.3)	(105.1, 197.1)	(107.9, 237.2)	(104.5, 323.6)	(133.6, 257.9)	(121.3, 238.0)	(125.1, 277.4)	(107.3, 238.4)
Influenza A/H3N2 (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**26.4**	**41.0**	**40.0**	**47.9**	**28.6**	**34.2**	**30.6**	**32.3**	**27.4**	**28.3**
(95% CI) [a]	(17.7, 39.3)	(23.8, 70.7)	(26.3, 60.8)	(32.0, 71.7)	(19.1, 42.8)	(22.7, 51.7)	(17.8, 52.7)	(21.9, 47.5)	(17.2, 43.6)	(18.3, 43.6)
Day 29 GMT	**58.1**	**106.8**	**113.2**	**127.0**	**74.8**	**117.2**	**136.3**	**101.6**	**77.4**	**127.0**
(95% CI) [a]	(33.4, 101.1)	(76.3, 149.4)	(62.4, 205.3)	(84.6, 190.6)	(45.4, 123.3)	(61.0, 225.0)	(88.8, 209.4)	(64.4, 160.4)	(46.0, 130.3)	(74.0, 217.9)
GMFR	**2.2**	**2.6**	**2.8**	**2.7**	**2.6**	**3.4**	**4.4**	**3.1**	**2.8**	**4.5**
(95% CI) [a]	(1.5, 3.2)	(1.7, 4.0)	(1.9, 4.1)	(1.8, 4.0)	(1.5, 4.6)	(2.3, 5.2)	(2.6, 7.5)	(1.9, 5.3)	(1.6, 5.0)	(3.0, 6.6)
SCR % [b]	**32.0**	**41.7**	**40.0**	**40.7**	**23.1**	**60.0**	**50.0**	**42.3**	**38.1**	**50.0**
(95% CI) [c]	(14.9, 53.5)	(22.1, 63.4)	(21.1, 61.3)	(22.4, 61.2)	(9.0, 43.6)	(36.1, 80.9)	(29.9, 70.1)	(23.4, 63.1)	(18.1, 61.6)	(29.1, 70.9)
Day 181 GMT	**99.2**	**102.5**	**136.9**	**167.4**	**128.4**	**171.4**	**131.3**	**160.0**	**103.7**	**165.4**
(95% CI) [a]	(70.7, 139.4)	(75.6, 138.9)	(80.4, 233.2)	(110.3, 254.1)	(80.6, 204.5)	(81.1, 362.1)	(97.2, 177.5)	(109.0, 234.7)	(64.8, 165.9)	(101.4, 269.5)

Influenza B Strains

Values (95% CI)	Fluarix (N=25)	mRNA-1010 50 µg (N=24)	mRNA-1010.4 50 µg (N=25)	mRNA-1083.1 15 µg (N=27)	mRNA-1083.1 30 µg (N=26)	mRNA-1083.1 60 µg (N=20)	mRNA-1083.2 27.5 µg (N=26)	mRNA-1083.2 55 µg (N=26)	mRNA-1083.2 82 µg (N=22)	mRNA-1083.3 52.5 µg (N=24)
Influenza B/Victoria (LLOQ: 10, ULOQ: 320)										
Day 1 GMT	**26.0**	**20.3**	**25.0**	**29.4**	**24.4**	**21.1**	**18.7**	**26.8**	**24.2**	**26.3**
(95% CI) [a]	(18.4, 36.7)	(13.6, 30.1)	(18.3, 34.0)	(21.0, 41.1)	(16.9, 35.2)	(15.0, 29.5)	(12.6, 27.7)	(18.5, 38.8)	(17.4, 33.5)	(15.9, 43.3)
Day 29 GMT	**66.8**	**40.6**	**54.2**	**53.8**	**68.1**	**58.6**	**47.5**	**83.2**	**72.5**	**63.5**
(95% CI) [a]	(37.6, 118.6)	(28.5, 57.7)	(33.8, 87.0)	(39.5, 73.2)	(40.7, 114.1)	(39.8, 86.3)	(29.8, 75.8)	(49.2, 140.8)	(47.3, 111.0)	(37.6, 107.1)
GMFR	**2.6**	**2.2**	**2.2**	**1.8**	**2.8**	**2.8**	**2.5**	**3.1**	**2.9**	**2.4**
(95% CI) [a]	(1.7, 4.0)	(1.6, 2.9)	(1.5, 3.1)	(1.4, 2.3)	(1.5, 5.1)	(1.9, 4.1)	(1.8, 3.6)	(2.2, 4.4)	(1.8, 4.7)	(1.7, 3.5)
SCR % [b]	**36.0**	**17.4**	**36.0**	**14.8**	**46.2**	**45.0**	**34.6**	**38.5**	**40.0**	**29.2**
(95% CI) [c]	(18.0, 57.5)	(5.0, 38.8)	(18.0, 57.5)	(4.2, 33.7)	(26.6, 66.6)	(23.1, 68.5)	(17.2, 55.7)	(20.2, 59.4)	(19.1, 63.9)	(12.6, 51.1)
Day 181 GMT	**80.0**	**51.2**	**63.9**	**86.3**	**98.2**	**51.5**	**52.1**	**70.9**	**60.4**	**71.3**
(95% CI) [a]	(54.4, 117.8)	(37.0, 70.8)	(41.8, 97.7)	(59.1, 125.9)	(68.7, 140.3)	(35.7, 74.4)	(41.2, 65.8)	(46.9, 107.2)	(42.5, 85.9)	(45.6, 111.5)
Influenza B/Yamagata (LLOQ: 10, ULOQ: 640)										
Day 1 GMT	**90.6**	**96.5**	**83.4**	**111.7**	**67.2**	**87.2**	**74.9**	**101.8**	**115.1**	**91.2**
(95% CI) [a]	(66.7, 123.1)	(68.9, 135.2)	(56.8, 122.5)	(72.1, 173.0)	(44.8, 100.7)	(60.8, 125.1)	(53.6, 104.5)	(70.9, 146.2)	(71.1, 186.4)	(54.0, 153.8)
Day 29 GMT	**188.9**	**167.1**	**169.0**	**191.4**	**157.8**	**157.2**	**192.8**	**235.5**	**299.6**	**207.7**
(95% CI) [a]	(114.9, 310.7)	(124.9, 223.4)	(102.3, 279.2)	(128.0, 286.0)	(108.3, 230.1)	(117.6, 210.2)	(134.1, 277.3)	(165.9, 334.4)	(197.7, 454.2)	(126.2, 341.6)
GMFR	**2.1**	**1.7**	**2.0**	**1.7**	**2.3**	**1.8**	**2.6**	**2.3**	**2.6**	**2.3**
(95% CI) [a]	(1.4, 3.1)	(1.4, 2.2)	(1.2, 3.3)	(1.3, 2.2)	(1.7, 3.3)	(1.3, 2.4)	(1.8, 3.7)	(1.8, 3.0)	(1.6, 4.2)	(1.5, 3.4)
SCR % [b]	**28.0**	**8.3**	**28.0**	**14.8**	**26.9**	**15.0**	**34.6**	**26.9**	**33.3**	**25.0**
(95% CI) [c]	(12.1, 49.4)	(1.0, 27.0)	(12.1, 49.4)	(4.2, 33.7)	(11.6, 47.8)	(3.2, 37.9)	(17.2, 55.7)	(11.6, 47.8)	(14.6, 57.0)	(9.8, 46.7)
Day 181 GMT	**113.1**	**94.3**	**146.7**	**196.3**	**120.4**	**87.7**	**102.5**	**125.7**	**140.4**	**142.6**

Values (95% CI)	Fluarix (N=25)	mRNA-1010 50 µg (N=24)	mRNA-1010.4 50 µg (N=25)	mRNA-1083.1 15 µg (N=27)	mRNA-1083.1 30 µg (N=26)	mRNA-1083.1 60 µg (N=20)	mRNA-1083.2 27.5 µg (N=26)	mRNA-1083.2 55 µg (N=26)	mRNA-1083.2 82 µg (N=22)	mRNA-1083.3 52.5 µg (N=24)
(95% CI) [a]	(73.6, 173.7)	(61.1, 145.6)	(99.0, 217.4)	(140.1, 275.2)	(77.6, 186.8)	(54.7, 140.7)	(67.5, 155.6)	(93.0, 169.9)	(89.3, 220.7)	(95.6, 212.7)

Abbreviations: CI = confidence interval; GM = geometric mean; GMFR = geometric mean fold rise; GMT = geometric mean titre; HAI = hemagglutination inhibition; LLOQ = lower limit of quantification; SCR = seroconversion rate; ULOQ = upper limit of quantification.

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

b. Seroconversion at a participant level was defined as a preinjection HAI titre <1:10 and a postinjection HAI titre ≥1:40 or a preinjection HAI titre ≥ 1:10 and a minimum 4-fold rise in postinjection HAI antibody titre.

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

Source: Table 14.2.1.2

SARS-CoV-2 antibody response

Cohort A (Participants ≥65 to <80 Years)

An overview of the Day 1 GMT, Day 29 GMT, GMFR, SRR and D181 GMT for the neutralising antibody levels for vaccine-matched SARS-CoV-2 strains measured by PsVNA assay for the ≥65 to <80 years group are provided in the table below.

Table 11: Summary of Neutralising Antibody Levels for Vaccine-Matched SARS-CoV-2 Strains Measured by PsVNA Assay - Cohort A: ⩾65 to <80 Years (Per Protocol Set)

Values (95% CI)	mRNA-1273.222 (50 µg) N=51	mRNA-1283.222 (10 µg) N=49	mRNA-1083.1 (30 µg) N=50	mRNA-1083.1 (60 µg) N=30	mRNA-1083.2 (27.5 µg) N=53	mRNA-1083.2 (55 µg) N=51	mRNA-1083.2 (82 µg) N=31	mRNA-1083.3 (52.5 µg) N=50
SARS-CoV-2 BA.4/5 (LLOQ: 53, ULOQ: 71376)								
Day 1 GMT	**618.0**	**547.1**	**616.9**	**585.9**	**646.6**	**536.3**	**1008.2**	**883.2**
(95% CI) [a]	(403.0, 947.9)	(352.8, 848.2)	(367.1, 1036.8)	(314.7, 1090.6)	(408.8, 1022.7)	(329.5, 872.7)	(616.1, 1649.7)	(584.9, 1333.6)
Day 29 GMT	**4536.9**	**5476.9**	**4636.7**	**5387.3**	**3706.0**	**3669.6**	**5647.8**	**4120.6**
(95% CI) [a]	(3147.0, 6540.8)	(3988.2, 7521.5)	(3098.6, 6938.3)	(3207.7, 9047.8)	(2656.8, 5169.4)	(2577.8, 5223.8)	(4227.0, 7546.2)	(3224.4, 5265.8)
GMFR	**7.3**	**10.0**	**7.5**	**9.6**	**5.7**	**6.8**	**5.6**	**4.7**
(95% CI) [a]	(5.0, 10.9)	(7.0, 14.2)	(5.0, 11.2)	(6.5, 14.4)	(4.1, 7.9)	(4.8, 9.7)	(3.7, 8.5)	(3.3, 6.7)
SRR % [b]	**62.7**	**69.4**	**68.0**	**75.9**	**59.6**	**62.7**	**58.1**	**44.0**
(95% CI) [c]	(48.1, 75.9)	(54.6, 81.7)	(53.3, 80.5)	(56.5, 89.7)	(45.1, 73.0)	(48.1, 75.9)	(39.1, 75.5)	(30.0, 58.7)
Day 181 GMT	**1500.1**	**2524.4**	**1793.9**	**1851.8**	**1461.3**	**1552.5**	**2185.7**	**1480.3**
(95% CI) [a]	(977.6, 2301.8)	(1588.3, 4012.3)	(1145.8, 2808.5)	(899.5, 3812.3)	(945.9, 2257.6)	(935.1, 2577.6)	(1425.4, 3351.4)	(980.2, 2235.6)
SARS-CoV-2 D614G (LLOQ: 74.1, ULOQ: 184317)								
Day 1 GMT	**2052.1**	**2176.0**	**2362.5**	**2578.4**	**2992.6**	**2091.1**	**3284.9**	**2909.8**
(95% CI) [a]	(1472.4, 2860.0)	(1546.4, 3062.0)	(1525.7, 3658.3)	(1482.4, 4484.8)	(2118.7, 4226.9)	(1408.0, 3105.7)	(2260.6, 4773.3)	(2255.8, 3753.4)
Day 29 GMT	**9943.4**	**12229.6**	**9275.7**	**10433.9**	**7678.3**	**8513.1**	**10057.5**	**8639.7**
(95% CI) [a]	(7910.9, 12498.1)	(9571.1, 15626.7)	(6926.0, 12422.7)	(7040.4, 15463.1)	(6034.4, 9770.0)	(6542.0, 11078.0)	(7712.1, 13116.1)	((7025.9, 10624.1)
GMFR	**4.8**	**5.6**	**4.2**	**4.0**	**2.5**	**4.1**	**3.1**	**3.0**
(95% CI) [a]	(3.6, 6.5)	(4.1, 7.7)	(2.9, 6.0)	(2.9, 5.6)	(1.9, 3.4)	(2.9, 5.7)	(2.2, 4.2)	(2.4, 3.7)
SRR % [b]	**43.1**	**57.1**	**37.5**	**56.7**	**21.2**	**43.1**	**25.8**	**32.0**
(95% CI) [c]	(29.3, 57.8)	(42.2, 71.2)	(24.0, 52.6)	(37.4, 74.5)	(11.1, 34.7)	(29.3, 57.8)	(11.9, 44.6)	(19.5, 46.7)
Day 181 GMT	**3583.2**	**5778.1**	**4006.2**	**3927.0**	**3317.4**	**3877.3**	**5622.0**	**3889.4**

(95% CI) [a]	(2756.2, 4658.4)	(4110.6, 8121.9)	(2759.3, 5816.7)	(2086.7, 7390.1)	(2397.5, 4590.2)	(2667.2, 5636.2)	(3718.2, 8500.5)	(2807.8, 5387.6)

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; LLOQ = lower limit of quantification; nAb = neutralising antibody; PsVNA = pseudovirus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; ULOQ = upper limit of quantification.

Antibody values reported as <LLOQ were replaced by 0.5 x LLOQ. Values >ULOQ were converted to the ULOQ if actual values were not available.

a. 95% CI was calculated based on the t-distribution of the log-transformed values for GMT and GMFR values, respectively, then back transformed to the original scale for presentation.

b. Seroresponse at a participant level was defined as an increase from <LLOQ to ≥4 x LLOQ if Baseline nAb level was <LLOQ, or ≥4-fold rise if Baseline nAb level was ≥LLOQ.

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

Source: Table 14.2.2.1

Cohort B (Participants ≥18 to <65 Years)

An overview of the Day 1 GMT, Day 29 GMT, GMFR, SRR and D181 GMT for the neutralising antibody levels for vaccine-matched SARS-CoV-2 strains measured by PsVNA assay for Cohort B (≥50 to <65 and ≥18 to <50 years) are provided in the tables below.

Table 12: Summary of Neutralising Antibody Levels for Vaccine-Matched SARS-CoV-2 Strains Measured by PsVNA Assay - Cohort B: ⩾50 to <65 Years (Per Protocol Set)

Values (95% CI)	**mRNA-1273.222 (50 µg) N=26**	**mRNA-1283.222 (10 µg) N=28**	**mRNA-1083.1 (15 µg) N=24**	**mRNA-1083.1 (30 µg) N=27**	**mRNA-1083.1 (60 µg) N=16**	**mRNA-1083.2 (27.5 µg) N=24**	**mRNA-1083.2 (55 µg) N=26**	**mRNA-1083.2 (82 µg) N=16**	**mRNA-1083.3 (52.5 µg) N=27**
SARS-CoV-2 BA.4/5 (LLOQ: 53, ULOQ: 71376)									
Day 1 GMT	**471.1**	**465.2**	**671.5**	**362.8**	**613.5**	**328.7**	**667.6**	**313.9**	**348.9**
(95% CI) [a]	(246.0, 902.2)	(251.1, 861.7)	(351.2, 1283.6)	(195.6, 673.0)	(230.5, 1632.9)	(161.4, 669.3)	(402.7, 1106.7)	(138.4, 712.1)	(187.7, 648.2)
Day 29 GMT	**2438.9**	**4780.8**	**4661.2**	**2333.0**	**4216.0**	**3055.6**	**4304.0**	**2832.4**	**2921.1**
(95% CI) [a]	(1542.0, 3857.4)	066.8, 7452.	(3164.9, 6864.8)	(1624.9, 3349.8)	(2374.2, 7486.5)	(1983.4, 4707.4)	(3033.8, 6105.9)	(1939.2, 4136.9)	(1847.7, 4618.1)
GMFR	**5.2**	**10.2**	**6.9**	**6.4**	**6.9**	**9.3**	**6.4**	**9.0**	**8.2**
(95% CI) [a]	(3.0, 8.9)	(6.0, 17.2)	(3.5, 13.7)	(3.9, 10.6)	(3.5, 13.4)	(5.2, 16.7)	(4.0, 10.4)	(3.8, 21.4)	(4.3, 15.7)
SRR % [b]	**50.0**	**74.1**	**45.8**	**55.6**	**56.3**	**70.8**	**61.5**	**56.3**	**76.9**
(95% CI) [c]	(29.9, 70.1)	(53.7, 88.9)	(25.6, 67.2)	(35.3, 74.5)	(29.9, 80.2)	(48.9, 87.4)	(40.6, 79.8)	(29.9, 80.2)	(56.4, 91.0)
Day 181 GMT	**1386.2**	**2179.0**	**1753.6**	**813.5**	**1348.7**	**1231.8**	**1566.5**	**991.3**	**970.6**
(95% CI) [a]	(870.0, 2208.4)	(1283.0, 3700.7)	(1095.5, 2807.0)	(521.6, 1268.7)	(442.0, 4115.2)	(660.2, 2298.4)	(1071.9, 2289.2)	(360.3, 2727.6)	(562.6, 1674.2)
SARS-CoV-2 D614G (LLOQ: 74.1, ULOQ: 184317)									
Day 1 GMT	**2011.5**	**2137.9**	**2695.5**	**1802.5**	**1997.4**	**1475.5**	**2919.5**	**1953.8**	**1232.9**
(95% CI) [a]	(1180.7, 3427.1)	243.7, 3675.	(1727.2, 4206.7)	(1127.5, 2881.7)	(1047.3, 3809.6)	(775.6, 2807.1)	(1878.3, 4537.9)	(1098.6, 3474.8)	(699.2, 2173.7)
Day 29 GMT	**7474.5**	**10278.8**	**9316.1**	**6556.5**	**7457.9**	**6623.7**	**8695.3**	**8463.1**	**6429.2**
(95% CI) [a]	(5579.0, 10014.2)	(7566.6, 13963.0)	(6685.2, 12982.2)	(4905.2, 8763.5)	(5011.1, 11099.2)	(4644.0, 9447.3)	(6536.3, 11567.4)	(6334.5, 11307.0)	(4221.8, 9790.6)
GMFR	**3.7**	**4.8**	**3.5**	**3.6**	**3.7**	**4.5**	**3.0**	**4.3**	**5.2**
(95% CI) [a]	(2.4, 5.7)	(3.1, 7.4)	(2.1, 5.6)	(2.3, 5.8)	(2.4, 5.9)	(2.7, 7.5)	(2.0, 4.4)	(2.4, 7.9)	(3.0, 9.1)
SRR % [b]	**30.8**	**42.9**	**29.2**	**37.0**	**43.8**	**41.7**	**30.8**	**43.8**	**46.2**
(95% CI) [c]	(14.3, 51.8)	(24.5, 62.8)	(12.6, 51.1)	(19.4, 57.6)	(19.8, 70.1)	(22.1, 63.4)	(14.3, 51.8)	(19.8, 70.1)	(26.6, 66.6)
Day 181 GMT	**4247.9**	**4344.3**	**3660.8**	**2613.5**	**3523.2**	**2525.7**	**3025.5**	**2569.9**	**1858.6**
(95% CI) [a]	(2820.0, 6398.7)	(2916.8, 6470.3)	(2519.9, 5318.2)	(1818.8, 3755.3)	(1369.2, 9066.0)	(1496.0, 4264.1)	(2089.0, 4381.7)	(1426.7, 4629.1)	(1073.1, 3218.8)

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; LLOQ = lower limit of quantification; nAb = neutralising antibody; PsVNA = pseudovirus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; ULOQ = upper limit of quantification.
Antibody values reported as <LLOQ were replaced by 0.5 x LLOQ. Values >ULOQ were converted to the ULOQ if actual values were not available.

a. 95% CI was calculated based on the t-distribution of the log-transformed values for GMT and GMFR values, respectively, then back transformed to the original scale for presentation.

b. Seroresponse at a participant level was defined as an increase from <LLOQ to ≥4 x LLOQ if Baseline nAb level was <LLOQ, or ≥4-fold rise if Baseline nAb level was ≥ LLOQ.

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

Source: Table 14.2.2.2.

Table 13: Summary of Neutralising Antibody Levels for Vaccine-Matched SARS-CoV-2 Strains Measured by PsVNA Assay - Cohort B: ⩾18 to <50 Years (Per Protocol Set)

Values (95% CI)	mRNA-1273.222 (50 µg) N=24	mRNA-1283.222 (10 µg) N=25	mRNA-1083.1 (15 µg) N=27	mRNA-1083.1 (30 µg) N=26	mRNA-1083.1 (60 µg) N=20	mRNA-1083.2 (27.5 µg) N=26	mRNA-1083.2 (55 µg) N=26	mRNA-1083.2 (82 µg) N=22	mRNA-1083.3 (52.5 µg) N=24
SARS-CoV-2 BA.4/5 (LLOQ: 53, ULOQ: 71376)									
Day 1									
GMT	**307.9**	**474.8**	**638.4**	**538.9**	**405.6**	**651.4**	**412.6**	**293.3**	**717.6**
(95% CI) [a]	(174.1, 544.6)	(229.8, 981.0)	(386.0, 1055.8)	(316.7, 917.0)	(209.7, 784.4)	(339.7, 1249.1)	(234.4, 726.2)	(172.9, 497.6)	(403.7, 1275.4)
Day 29									
GMT	**2867.2**	**4701.2**	**3501.1**	**4058.4**	**3171.1**	**3806.8**	**4480.3**	**3346.8**	**4152.6**
(95% CI) [a]	(1968.9, 4175.1)	105.0, 7117.	(2520.1, 4864.0)	(2632.3, 6257.1)	(2066.0, 4867.1)	(2502.4, 5791.1)	(3239.0, 6197.4)	(2199.2, 5093.2)	(2912.2, 5921.2)
GMFR	**9.3**	**11.9**	**5.5**	**7.5**	**7.8**	**5.8**	**10.9**	**11.4**	**5.8**
(95% CI) [a]	(5.4, 16.0)	(6.6, 21.2)	(3.5, 8.6)	(5.1, 11.2)	(4.4, 13.8)	(3.6, 9.4)	(6.5, 18.2)	(7.0, 18.5)	(3.5, 9.6)
SRR % [b]	**70.8**	**79.2**	**55.6**	**69.2**	**60.0**	**50.0**	**69.2**	**77.3**	**58.3**
(95% CI) [c]	(48.9, 87.4)	(57.8, 92.9)	(35.3, 74.5)	(48.2, 85.7)	(36.1, 80.9)	(29.9, 70.1)	(48.2, 85.7)	(54.6, 92.2)	(36.6, 77.9)
Day 181									
GMT	**1502.1**	**1777.1**	**1464.3**	**1844.6**	**1901.7**	**1632.4**	**2075.9**	**1083.1**	**1727.8**
(95% CI) [a]	(936.0, 2410.6)	(902.6, 3499.0)	(934.1, 2295.3)	(1094.2, 3109.6)	(1106.6, 3268.0)	(912.9, 2918.9)	(1220.2, 3531.6)	(581.0, 2019.1)	(1094.7, 2726.9)
SARS-CoV-2 D614G (LLOQ: 74.1, ULOQ: 184317)									
Day 1									
GMT	**1166.4**	**1410.0**	**2045.1**	**2216.5**	**1270.1**	**1673.0**	**1448.3**	**1086.8**	**1926.4**
(95% CI) [a]	(663.7, 2050.0)	772.2, 2574.7	(1448.5, 2887.4)	(1480.5, 3318.3)	(690.0, 2337.9)	(969.0, 2888.5)	(882.6, 2376.6)	(707.2, 1670.3)	(1184.9, 3131.9)
Day 29									
GMT	**6594.0**	**10203.4**	**6078.2**	**7773.0**	**5864.1**	**6846.9**	**7077.7**	**6607.1**	**7398.4**
(95% CI) [a]	(4502.3, 9657.6)	(7220.6, 14418.5)	(4851.0, 7615.9)	(5871.4, 10290.3)	(3716.1, 9253.5)	(4782.6, 9802.3)	(5382.4, 9306.9)	(4681.9, 9324.1)	(5045.4, 10848.8)
GMFR	**5.7**	**7.2**	**3.0**	**3.5**	**4.6**	**4.1**	**4.9**	**6.1**	**3.8**
(95% CI) [a]	(3.6, 8.8)	(3.8, 13.8)	(2.2, 4.1)	(2.6, 4.8)	(3.0, 7.2)	(2.6, 6.4)	(3.2, 7.4)	(4.2, 8.9)	(2.6, 5.7)
SRR % [b]	**54.2**	**60.0**	**37.0**	**42.3**	**40.0**	**42.3**	**65.4**	**68.2**	**37.5**
(95% CI) [c]	(32.8, 74.4)	(38.7, 78.9)	(19.4, 57.6)	(23.4, 63.1)	(19.1, 63.9)	(23.4, 63.1)	(44.3, 82.8)	(45.1, 86.1)	(18.8, 59.4)
Day 181									
GMT	**2557.5**	**4303.5**	**2988.5**	**3463.5**	**2169.6**	**2991.0**	**2778.3**	**1526.2**	**3174.5**
(95% CI) [a]	(1661.0, 3937.7)	(2781.3, 6658.7)	(2174.7, 4106.8)	(2387.4, 5024.6)	(1047.7, 4493.1)	(1940.0, 4611.4)	(1653.8, 4667.4)	(921.0, 2528.9)	(2044.9, 4928.1)

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; LLOQ = lower limit of quantification; nAb = neutralising antibody; PsVNA = pseudovirus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate; ULOQ = upper limit of quantification.
Antibody values reported as <LLOQ were replaced by 0.5 x LLOQ. Values >ULOQ were converted to the ULOQ if actual values were not available.

a. 95% CI was calculated based on the t-distribution of the log-transformed values for GMT and GMFR values, respectively, then back transformed to the original scale for presentation.

b. Seroresponse at a participant level was defined as an increase from <LLOQ to ≥4 x LLOQ if Baseline nAb level was < LLOQ, or ≥4-fold rise if Baseline nAb level was ≥ LLOQ.

c. 95% CI was calculated using the Clopper-Pearson method. Source: Table 14.2.2.2.

5.3.2. Main study

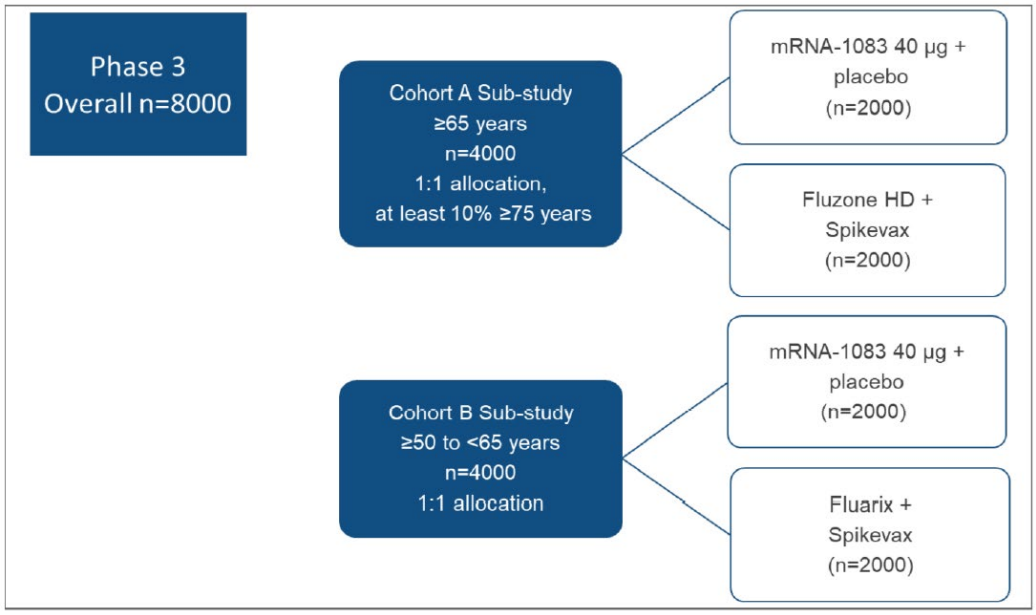
mRNA-1083-P301

A Phase 3, Randomised, Observer blind, Active control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1083 (SARS-CoV-2 and Influenza) Vaccine in Healthy Adult Participants, ≥50 Years of Age

Study design

Study mRNA-1083-P301 was a Phase 3, randomised, observer blind, active control study to evaluate the immunogenicity, reactogenicity, and safety of a single dose of mRNA-1083 multicomponent influenza and COVID-19 vaccine in healthy adults ≥50 years of age. Study P301 was conducted in 2 independent substudies: Cohort A (≥65 years) and Cohort B (≥50 to <65 years). Each substudy had its own active control group (Cohort A: Fluzone HD and Spikevax; Cohort B: Fluarix and Spikevax) and immunogenicity hypotheses.

Figure 1: Study schema



Treatment

The study interventions included mRNA-1083 40µg, placebo (commercially available 0.9% sodium chloride), and the active comparators Fluzone HD quadrivalent, Fluarix quadrivalent, and Spikevax (commercially available formulations). Each participant received 2 IM injections on Day 1 into deltoid muscle.

Table 14: Study Interventions

Cohort A Substudy (⩾65 years): n=4000		
Study intervention	mRNA-1083 + Placebo [a] n=2000	Fluzone HD + Spikevax [b] n=2000
Type of intervention	Experimental	Active comparator
Description	Participants received mRNA-1083 40 µg and Placebo, administered as 2 IM injections, 1 in each deltoid muscle on Day 1	Participants received Fluzone HD and Spikevax, administered as 2 IM injections, 1 in each deltoid muscle on Day 1
Cohort B Substudy (⩾50 to <65 years): n=4000		
Study intervention	mRNA-1083 + Placebo [a] n=2000	Fluarix +Spikevax [b] n=2000
Type of intervention	Experimental	Active comparator
Description	Participants received mRNA-1083 40 µg and Placebo, administered as 2 IM injections, 1 in each deltoid muscle on Day 1	Participants received Fluarix and Spikevax, administered as 2 IM injections, 1 in each deltoid muscle on Day 1

Abbreviations: HD = high dose; IM = intramuscular(ly).

a. 0.9% sodium chloride -commercially available material.

b. Commercially available formulations.

Each participant was to receive 2 injections on Day 1: mRNA-1083 and placebo or Fluzone HD and Spikevax in Cohort A or Fluarix and Spikevax in Cohort B. The first injection was administered in a blinded manner to the deltoid muscle in one arm. The second injection was administered in a blinded manner to the deltoid muscle in the contralateral arm.

Study Assessments

Blood samples for immunogenicity assessments were collected in all participants at planned timepoints.

The following analytes were measured:

- Influenza: Serum antibody levels as measured by HAI assay and, in a subset of randomly sampled participants, serum nAb levels as measured by MN assay.
- SARS-CoV-2: Serum nAb levels as measured by PsVNA specific to SARS-CoV-2 XBB.1.5 variant and, in a subset of randomly sample participants, cross-reactive serum nAb levels as measured by PsVNA to SARS-CoV-2 JN.1 variant.

Samples for humoral immunogenicity on Day 181 were collected for at least 800 participants of each cohort. These participants required a clinic visit on Day 181. Plasma and serum from humoral immunogenicity samples are stored for potential future use.

Randomisation and Blinding

All participants were randomised to the study intervention group using an interactive response technology.

Participants were randomised into age cohorts (≥65 years and ≥50 to <65 years) aligned with standard of care influenza vaccination to allow the comparison of mRNA-1083 with HD and standard dose vaccines separately. The population was also stratified by influenza vaccine status.

This study was designed as an observer-blind study.

Patient population

Inclusion criteria

Age

1. Healthy adults either ≥65 years of age (Cohort A) or 50 to <65 years of age (Cohort B) at the time of consent (Screening Visit).

Type of Participant and Disease Characteristics

2. Investigator assessment that participant understands and is willing and physically able to comply with protocol-mandated follow-up, including all procedures, and according to the Investigator's assessment, is in good general health.

Sex and Contraceptive/Barrier Requirements

3. Participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as postmenopausal or permanently sterilized. An follicle-stimulating hormone level may be measured at the discretion of the Investigator to confirm postmenopausal status.

4. Participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:

    - Has a negative pregnancy test at the Screening Visit and on the day of vaccine administration.
    - Has practiced adequate contraception, or has abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.
    - Has agreed to continue adequate contraception through 3 months following vaccine administration. Adequate contraception is defined as consistent and correct use of a local health authority approved contraceptive method in accordance with the product label.

Informed Consent

5. Capable of giving signed informed consent, for participation in this study, which includes compliance with the requirements and restrictions listed in the informed consent form and in the protocol, including all evaluations and procedures as specified in this protocol.

Other Inclusion Criteria

6. Fully vaccinated for COVID-19 primary series according to the locally authorised or approved regimen, and their last COVID-19 vaccine (primary series or booster) was ≥90 days prior to Day 1.

Main exclusion criteria

Medical Conditions

1. Acutely ill or febrile (temperature ≥38.0℃ [100.4°F]) 72 hours prior to or at the Screening Visit or Day 1. Participants meeting this criterion may be rescheduled within the 42-day Screening window and will retain their initially assigned participant number.

2. History of a diagnosis or condition that, in the judgment of the Investigator, is clinically unstable, or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a

diagnosis or condition requiring changes in management or medication ≤60 days prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.

- Asymptomatic conditions and conditions with no evidence of end organ involvement (e.g., mild hypertension, dyslipidemia) are not exclusionary, if they are being appropriately managed and are clinically stable (i.e., unlikely to result in symptomatic illness within the time course of this study). Illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them (e.g., immune modifying treatments), at the discretion of the Investigator.

3. Participants who have undergone surgical procedures within 14 days prior to Day 1 or are scheduled to undergo a surgical procedure within 28 days after study injection are also excluded. However, minor surgical procedures under local anesthesia (e.g., excision of skin lesion) or diagnostic procedures (e.g., colonoscopy) are allowed.
4. Reported history of congenital or acquired immunodeficiency (e.g., HIV), immunocompromising/immunosuppressive condition, asplenia, or recurrent severe infections. The following conditions are permitted at the discretion of the Investigator:
    - Certain immune-mediated conditions that are stable and well-controlled (e.g., alopecia areata, Hashimoto thyroiditis, type 1 diabetes mellitus, gout, primary ovarian insufficiency) as well as those that do not require systemic immunosuppressants per Exclusion Criterion 14 (e.g., asthma, psoriasis, or vitiligo), are permitted at the discretion of the Investigator.
5. Dermatologic conditions that could affect local solicited AR assessments (e.g., tattoos, psoriasis patches affecting skin over the deltoid areas).
6. 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.
7. Reported history of coagulopathy or bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
8. Diagnosis of malignancy within the previous 2 years (excluding nonmelanoma skin cancer).
9. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the Investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
10. Has a history of myocarditis or pericarditis or myopericarditis within 90 days prior to the Screening Visit. Participants who have not returned to Baseline clinical status after their convalescent period will also be excluded.
11. Has a history of Guillain-Barre syndrome.
12. Has a known history of SARS-CoV-2 infection within ≤90 days prior to Day 1.
13. Tested positive for influenza by local health authority-approved testing methods ≤150 days prior to Day 1.

Prior/Concomitant Therapy

14. Participant 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.

15. Received or plans to receive any vaccine authorized or approved by a local health agency ≤28 days prior to study injections or plans to receive a vaccine authorized or approved by a local health agency within 28 days after the study injections.
16. Received a seasonal influenza vaccine ≤150 days prior to Day 1.
17. Treated with antiviral therapies for influenza (e.g., Tamiflu) within 150 days prior to Day 1.
18. Treated with any other non-influenza antiviral therapies (including antivirals for treating individuals with HIV or in at-risk individuals as pre-exposure prophylaxis) within 14 days prior to Day 1 or plans to use antiviral therapies within 28 days of study injection.
19. 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.

For full exclusion criteria refer to the study protocol.

Objectives and estimands

Primary objective

The primary immunogenicity objective in both cohorts was to evaluate the humoral immune responses of mRNA-1083 for noninferiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.

Primary endpoints

- GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS-CoV-2.
- Influenza: Percentage of participants with seroconversion defined as a Day 29 post-injection level ≥ 1:40 if Baseline is <1:10 or a 4-fold or greater rise if Baseline is ≥1:10 in anti-HA antibodies measured by HAI assay.
- SARS-CoV-2: Percentage of participants with seroresponse defined as a Day 29 post-injection level ≥4-fold rise if Baseline is ≥LLOQ or ≥4×LLOQ if Baseline value is <LLOQ in the nAb values measured by PsVNA.

Estimand for the primary objective

No estimand definition according to the estimand framework was specified.

Statistical methods for estimation and sensitivity analysis on primary estimand

Table 15: Analysis sets

Analysis Sets	Description
Randomisation Set	The Randomisation Set consisted of all participants who were randomly assigned. Participants were included in the study intervention group to which they were randomised.
Full Analysis Set	The FAS consisted of all participants who were randomly assigned and received the study injection. Participants were analysed according to the study intervention group to which they were randomised.
Immunogenicity Set	The Immunogenicity Set consisted of all participants in the FAS who had baseline and Day 29 antibody assessment via HAI or PsVNA assay.

Analysis Sets	Description
	Participants were analysed according to the study intervention group to which they were randomised.
Per-Protocol Immunogenicity Set	The PPIS consisted of all participants in the FAS who complied with the timing of immunogenicity blood sample collections to have both Baseline and Day 29 assessments using a window of -7 to +14 days, had no major dosing error (see SAP Section 5 [Appendix 16.1.9]), had negative RT-PCR test for influenza and SARS-CoV-2 on Day 1, and had no major protocol deviations or conditions/medications that affected the immune response. The PPIS was used as the primary analysis set for analyses of immunogenicity in Cohort A or B unless otherwise specified. Participants were analysed according to the study intervention group to which they were randomised.
Per-Protocol Immunogenicity Set for Microneutralisation Assay	The PPIS for MN assay consisted of a subset of participants randomly sampled from the FAS to be tested for MN, who complied with the timing of immunogenicity blood sample collections to have both Baseline and Day 29 assessments using a window of -7 to +14 days, had no major dosing error, had negative RT-PCR test for influenza and SARS-CoV-2 on Day 1, and had no major protocol deviations or conditions/medications that affected the immune response. The PPIS for MN assay was used for MN related immunogenicity analyses in Cohort A or Cohort B for influenza unless otherwise specified. Participants were analysed according to the study intervention group to which they were randomised.
Safety Set	The Safety Set consisted of all participants who were randomly assigned and received the study injection. The Safety Set was used for all analyses of safety, except for the solicited ARs. Participants were included in the study intervention group to what they actually received.
Solicited Safety Set	The Solicited Safety Set consisted of all participants in the Safety Set who contributed any solicited AR data. The Solicited Safety Set was used for the analyses of solicited ARs, and participants were included in the study intervention group corresponding to what they actually received.

The primary analyses population for immunogenicity was the PPIS. Each of the 2 independent substudies, Cohort A (⩾65 years) and Cohort B (⩾50 to <65 years of age), had its own separate immunogenicity hypotheses, statistical analyses, and its own multiplicity control for overall Type I error rate (2-sided alpha of 5%) for the co-primary endpoints within the substudy. Each of the 2 substudies had the co-primary immunogenicity endpoints as described below. There were 6 statistical hypotheses for each substudy that were tested sequentially.

Co-primary Immunogenicity Hypotheses

Each of the primary immunogenicity endpoints was evaluated for NI of mRNA-1083 vs the active comparator (Fluzone HD + Spikevax for Cohort A, Fluarix + Spikevax for Cohort B) at a 2-sided alpha of 0.025 level. The first 2 null hypotheses H^1_0 and H^2_0 were tested simultaneously, as below.

The success criteria of NI on the 5 co-primary endpoints for GM level (titre for influenza and concentration for SARS-CoV-2) were met if H^1_0 was rejected at 2-sided 0.025 level. Similarly, the success criteria of NI on the 5 co primary endpoints for SCR or SRR were met if H^2_0 was rejected at 2-sided 0.025 level.

Five co-primary endpoints based on influenza and SARS-CoV-2 GM level at Day 29:

The null hypothesis H^1_0: for each of the 4 influenza strains (2 A strains: H1N1, H3N2, and 2 B strains:

Victoria, Yamagata) and 1 SARS-CoV-2 variant (XBB.1.5), the immunogenicity response to mRNA-1083, as measured by GM level at Day 29 using HAI assay for influenza and PsVNA for SARS-CoV-2, was inferior compared with that in participants who received the active comparator.

The NI in GM level in participants who received mRNA-1083 vs that of participants who received the active comparator was demonstrated by the lower bound of the 2-sided 97.5% CI of the GMR ruling out 0.667 (lower bound >0.667) using a NIM of 1.5. The GMR was defined as the ratio of the GM level of HAI or PsVNA in those participants receiving mRNA-1083 vs the GM level of those participants receiving the active comparator.

Five co-primary endpoints based on influenza SCR or SARS CoV-2 SRR at Day 29:

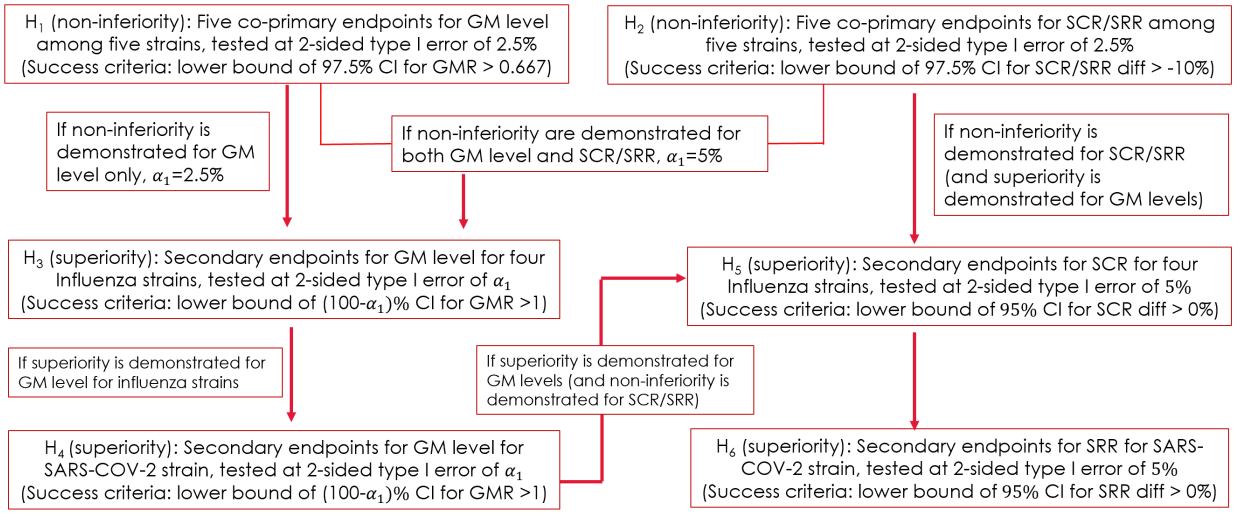
The null hypothesis H^2_0: for each of the 4 influenza strains and the SARS-CoV-2 variant, the immunogenicity response in participants who received mRNA-1083, as measured by Day 29 SCR using HAI assay (for influenza strains) or SRR using PsVNA (for SARS-CoV-2), was inferior compared with that in participants who received the active comparator.

The NI in SCR or SRR in participants who received mRNA-1083 vs that of participants who received the active comparator was demonstrated by the lower bound of the 2-sided 97.5% CI of the SCR or SRR difference at Day 29 ruling out -10% (lower bound >-10%) using a NIM of 10%.

No multiplicity adjustment was needed between the Cohort A and Cohort B substudies.

For each cohort, a 2-sided alpha of 0.05 would be fully spent as shown in the testing sequence for co-primary and secondary endpoints (see figure below). All other endpoints were not controlled for multiplicity and the analyses were descriptive in nature.

Figure 2: Hypotheses Testing Sequence for Co-primary and Secondary Endpoints



Abbreviations: CI = confidence interval; GM = geometric mean; GMR = geometric mean ratio; H = hypothesis; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SRR = seroresponse rate.

Sample Size

A total of 8000 participants were planned for enrollment in the study (4000 participants in Cohort A and 4000 participants in Cohort B).

A total of 2000 participants from each cohort were planned to be exposed to the study injection in the mRNA-1083 group. With this sample size, the study had approximately over 95% probability to observe at least 1 participant with an AE given a true underlying 0.1% AE rate among the total of 4000 participants in Cohort A and Cohort B combined.

In both Cohort A and Cohort B, with approximately 2000 participants (including an assumed approximate 15% drop-outs) receiving mRNA-1083 and 2000 participants receiving active comparator, this provided at least 95% overall power to demonstrate NI across the 5 co-primary immunogenicity endpoints for GM level at Day 29 between mRNA-1083 and active comparator in all the 4 influenza strains and 1 SARS-CoV-2 variant. The power evaluation assumed a 2-sided alpha of 0.025, approximately 15% dropout rate, true GMR of 0.85 (SD of antibody level in natural logarithm being 1.5) and a NIM of 1.5 for GMR in all the 4 influenza strains and 1 SARS-CoV-2 variant.

The study had at least 95% overall power to demonstrate NI across the 5 co-primary immunogenicity endpoints for SCR or SRR between mRNA-1083 and active comparator in all the 4 influenza strains and 1 SARS-CoV-2 variant. The power evaluation assumed a 2-sided alpha of 0.025, approximately 15% dropout rate, an underlying SCR or SRR of 68% in the mRNA-1083 group, an SCR or SRR of 70% in active comparator group (with a true SCR or SRR difference being -2%), and a NIM of 10% for the rate difference in the 2 influenza A strains and 1 SARS-CoV-2 variant; and assumed an underlying SCR of 58% in the mRNA-1083 group, a SCR of 60% in active comparator group (with a true SCR difference being -2%), and a NIM of 10% for the rate difference in the 2 influenza B strains.

Secondary objectives

Secondary immunogenicity objectives were:

To further evaluate the humoral immune response of mRNA-1083 for superiority relative to active comparators against vaccine matched strains for influenza and SARS-CoV-2 at Day 29.

To evaluate the humoral immune responses to vaccine matched strains for influenza and SARS-CoV-2 across study intervention groups at Day 29.

To evaluate the humoral immune responses for influenza across study intervention groups at Day 29 using the MN assay.

Secondary endpoints

- GM level at Day 29 by HAI assay for influenza and by PsVNA for SARS CoV-2.
- Influenza: Percentage of participants with seroconversion.
- SARS-CoV-2: Percentage of participants with seroresponse.
- GMFR at Day 29 compared to Day 1 by HAI assay for influenza and by PsVNA for SARS CoV-2.
- GM level at Day 29 and GMFR at Day 29 compared to Day 1 by MN assay for influenza in a subset of participants.

Estimands for the secondary objectives

No specific estimand was pre-specified in the protocol.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Secondary Immunogenicity Hypotheses

If the NI success criteria of the co-primary endpoints for GM level were met, the following hypotheses were tested sequentially to support secondary objectives:

The null hypothesis H^3_0: for each of the 4 influenza strains, the immunogenicity response as measured using the GM level at Day 29 for the HAI assay for influenza, of mRNA-1083 to the active comparator was not superior to the active comparator. The superiority in GM level in participants who received mRNA-1083 vs that of participants who received active comparator was demonstrated by the lower bound of the (100%- α1) CI of the GMR ruling out 1 (lower bound >1) for all 4 influenza

strains. It was tested at a 2-sided α1=5% level if NI was demonstrated for GM level (H^1_0 rejected) and SCR or SRR (H^2_0 rejected); and at a 2-sided α1=2.5% level if NI was only demonstrated for GM level (H^1_0 rejected).

If the superiority success criteria for GM levels at Day 29 using HAI assay for influenza were met (H^3_0rejected), the null hypothesis H^4_0 would be tested: for the SARS-CoV-2 variant, the immunogenicity response to mRNA-1083, as measured by GM level at Day 29 using PsVNA was not superior to that in participants who received the active comparator. The superiority in GM level in participants who received mRNA-1083 vs that of participants who received active comparator was demonstrated by the lower bound of the (100%- α1) CI of the GMR ruling out 1 (lower bound >1). The same level α1 would be passed to test hypothesis H^4_0.

If the superiority success criteria for GM levels at Day 29 using PsVNA for SARS-CoV-2 were met (H^4_0 rejected), and NI success criteria for SCR or SRR were met (H^2_0 rejected), the hypothesis H^5_0 would be tested. The null hypothesis H^5_0: for each of the 4 influenza strains, the immunogenicity response to mRNA-1083, as measured by D29 SCR using HAI assay (for influenza strains), was not superior to that in participants who received the active comparator. The superiority in SCR in participants who received mRNA-1083 vs that of participants who received active comparator was demonstrated by the lower bound of the 95% CI of the SCR difference ruling out 0% (lower bound >0%) for all 4 influenza strains.

If the superiority success criteria for SCR at Day 29 using HAI assay for influenza were met (H^5_0 rejected), the hypothesis H^6_0 would be tested. The null hypothesis H^6_0: for the SARS-CoV-2 variant, the immunogenicity response to mRNA-1083, as measured by Day 29 SRR using PsVNA (for SARS-CoV-2) was not superior to that in participants who received active comparator. The superiority in SRR in participants who received mRNA-1083 vs that of participants who received active comparator was demonstrated by the lower bound of the 95% CI of the SRR difference ruling out 0% (lower bound >0%).

Tertiary objectives

Exploratory immunogenicity objectives were:

To evaluate the humoral immune responses to vaccine matched strains for influenza and SARS-CoV-2 across study intervention groups at all evaluable humoral immunogenicity timepoints.

To evaluate the humoral immune responses to vaccine mismatched strains for influenza and SARS-CoV-2 across study intervention groups.

Exploratory endpoints

- GM level and GMFR at all evaluable timepoints compared to Day 1 by HAI for influenza and by PsVNA for SARS-CoV-2.
- Influenza: Percentage of participants with seroconversion.
- SARS-CoV-2: Percentage of participants with seroresponse.

Estimand for the tertiary objectives

No specific estimand was pre-specified in the protocol.

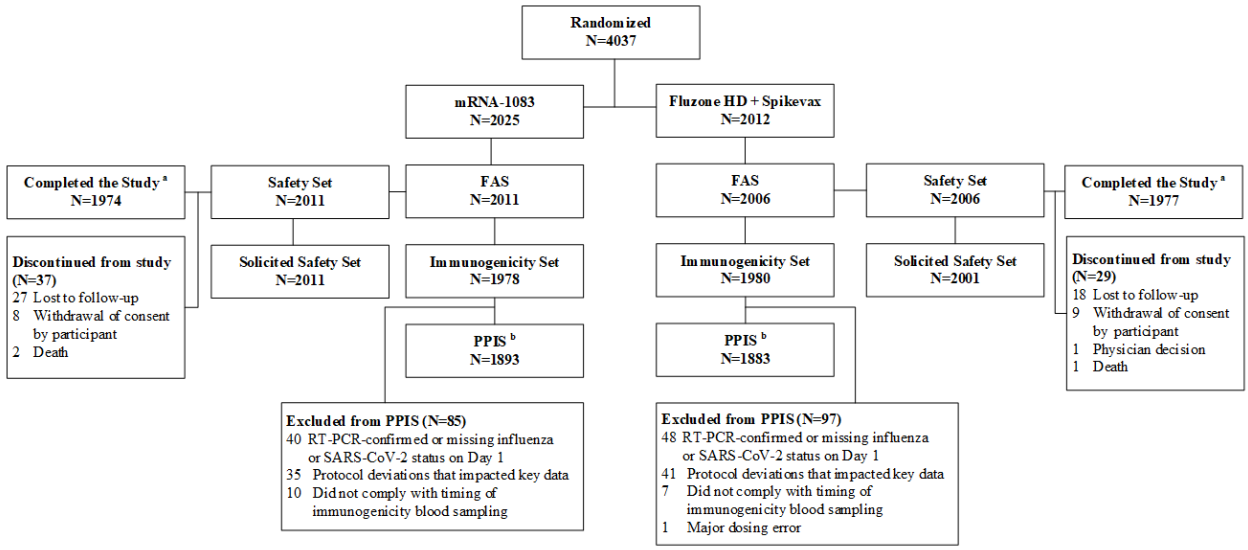
Results

Participant flow and numbers analysed

This study was conducted at 146 enrolling centres in the US. A total of 4037 participants were randomised in Cohort A and 4024 participants were randomised in Cohort B to receive study injections. Across the study, 4004 participants received mRNA-1083.

Screen failure was reported for 1472/9533 participants (15.4%) screened. The primary reasons for screen failure were eligibility criteria in 785/1472 participants (53.3%) and enrollment target already reached for the respective cohort in 643/1472 participants (43.7%).

Figure 3: Participant flow Cohort A



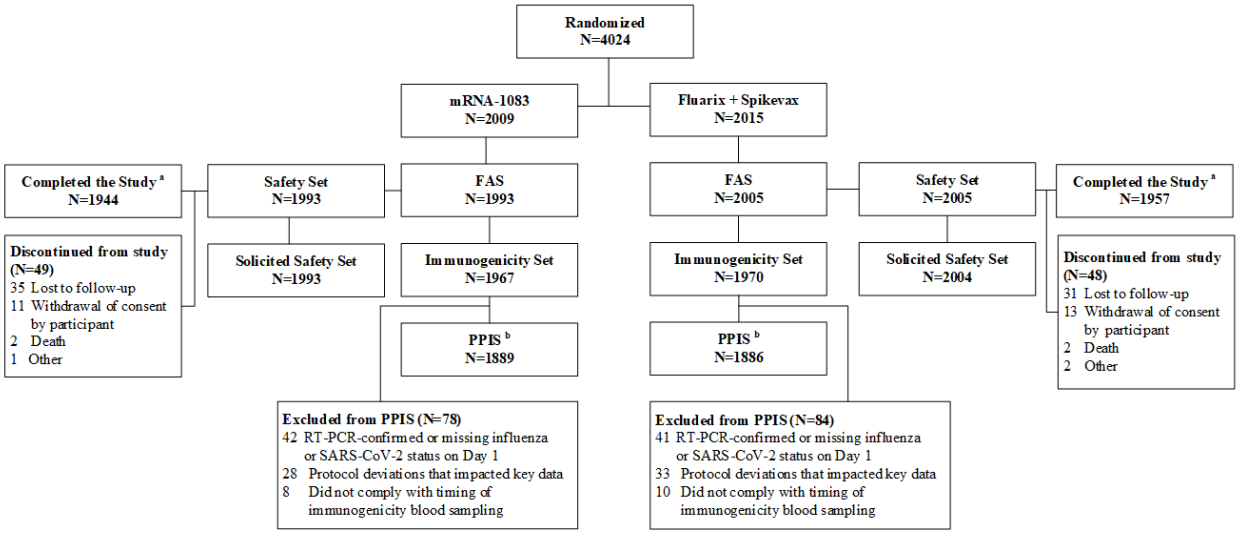
Abbreviations: FAS = full analysis set; PPIS = per-protocol immunogenicity set; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Analysis sets are defined in Section 4.1.3.

a. Participants were considered to have completed the study if they completed the final Day 181 visit.

b. The figure presents the PPIS based on the final database lock (01 Jul 2024). The PPIS from the Primary Analysis database lock (09 Apr 2024) consisted of 1886 participants in the mRNA-1083 group and 1883 participants in the Fluzone HD + Spikevax group.

A participant who had multiple reasons for exclusion from PPIS was counted only once based on the order of the reasons for exclusion listed.
Major dosing error was defined as wrong vaccination injected, or dose was outside of acceptable range.
Source: Table 14.1.1.2a, Table 14.1.3.1a, Table 14.1.3.4a (01 Jul 2024).

Figure 4: Participant flow Cohort B



Abbreviations: FAS = full analyses set; PPIS = per-protocol immunogenicity set; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Analysis sets are defined in Section 4.1.3.
a. Participants were considered to have completed the study if they completed the final Day 181 visit.
b. The figure presents the PPIS based on final database lock (01 Jul 2024). The PPIS from the Primary Analysis database lock (09 Apr 2024) consisted of 1890 participants in the mRNA-1083 group and 1884 participants in the Fluarix + Spikevax group.
A participant who had multiple reasons for exclusion from PPIS was counted only once based on the order of the reasons for exclusion listed.
Source: Table 14.1.1.2b, Table 14.1.3.1b, Table 14.1.3.4b (01 Jul 2024).

Deviations from study plan

The original protocol was dated 21 Sep 2023 and there was an amendment to the protocol dated 22 Mar 2024 (Protocol Amendment 1). This amendment added a new secondary objective and endpoint for both Cohort A and Cohort B to evaluate the humoral immune responses for influenza using microneutralisation assay at the Day 29.

Reporting of major protocol deviations was similar between groups (27.5% in the mRNA-1083 group and 27.7% in the Fluzone HD + Spikevax group) (Randomisation Set).

Primary Analysis - Day 91 Database Lock (09 Apr 2024) Analysis Sets:

The numbers and percentages of participants in each analysis set were similar between the mRNA-1083 and Fluzone HD + Spikevax groups for the Primary Analysis. Of the 3958 participants in the Immunogenicity Set, 92/1978 participants (4.7%) in the mRNA-1083 group and 97/1980 participants (4.9%) in the Fluzone HD + Spikevax group were excluded from the PPIS. The most common reasons for exclusion from the PPIS in both groups were positive or missing RT-PCR-confirmed influenza or SARS-CoV-2 results on Day 1 and major protocol deviations that impacted key data. One participant in the Fluzone HD + Spikevax group had a major dosing error (participant was administered Fluarix instead of Fluzone HD) and was excluded from the PPIS.

Baseline data

Table 16: Baseline data Cohort A

	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)
Race, 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)
Ethnicity, 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)
Unknown/Not reported	40 (2.0)	42 (2.1)	82 (2.0)
BMI (kg/m^2)			
n	2005	2001	4006
Mean (SD)	30.29 (6.209)	30.04 (6.091)	30.16 (6.151)
Median	29.40	29.20	29.30
Min, Max	13.3, 69.7	16.5, 57.8	13.3, 69.7
BMI group, n (%)[c]			
<30 kg/m^2	1083 (53.9)	1105 (55.1)	2188 (54.5)
≥30 kg/m^2	922 (45.8)	896 (44.7)	1818 (45.3)
Missing	6 (0.3)	5 (0.2)	11 (0.3)
Frailty status, n (%)[d]			
0-3: Fit	1465 (72.8)	1507 (75.1)	2972 (74.0)
4-5: Vulnerable	372 (18.5)	351 (17.5)	722 (18.0)
6 or More: Frailty	166 (8.3)	138 (6.9)	304 (7.6)
Missing	8 (0.4)	10 (0.5)	18 (0.4)
Influenza vaccination status since Sep 2022, n (%)[a]			
Received	1019 (50.7)	1016 (50.6)	2035 (50.7)
Not received	992 (49.3)	990 (49.4)	1982 (49.3)

	mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	Overall (N=4017) n (%)
COVID-19 vaccination status since Sep 2022, n (%)[e]			
Received	854 (42.5)	853 (42.5)	1707 (42.5)
Not received	1157 (57.5)	1153 (57.5)	2310 (57.5)
Number of COVID-19 vaccinations, n (%)[e]			
No dose	0	0	0
1-2 doses	480 (23.9)	487 (24.3)	967 (24.1)
3 doses	630 (31.3)	604 (30.1)	1234 (30.7)
4 doses	564 (28.0)	535 (26.7)	1099 (27.4)
≥5 doses	337 (16.8)	380 (18.9)	717 (17.8)
Baseline SARS-CoV-2 RT-PCR results via NP swab, n (%)[f]			
Positive	14 (0.7)	23 (1.1)	37 (0.9)
Negative	1973 (98.1)	1957 (97.6)	3930 (97.8)
Missing	24 (1.2)	26 (1.3)	50 (1.2)
Baseline influenza status, n (%)[g]			
Positive	4 (0.2)	1 (<0.1)	5 (0.1)
Negative	1983 (98.6)	1979 (98.7)	3962 (98.6)
Missing	24 (1.2)	26 (1.3)	50 (1.2)

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; Max = maximum; Min = minimum; NP = nasopharyngeal; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

BMI = (body weight in kilograms)/(height in meters)^2.

Baseline value for height, weight, BMI, and Edmonton Frail Scale total score was defined as the most recent nonmissing measurement (scheduled or unscheduled) collected on or before the injection of study injection.

Numbers were based on actual 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.
c. BMI ≥30 kg/m^2 was classified as obesity.
d. Frailty status was based on Edmonton Frail Scale.
e. Derived from concomitant medication data reporting prior COVID-19 vaccination before first injection of study injection.
f. For SARS-CoV-2 RT-PCR via NP swab result at baseline, participants were counted as positive if at least 1 positive result was observed on or before Day 1, counted as negative if all results were negative on or before Day 1, and counted as missing if all results were missing on or before Day 1.
g. Baseline Influenza Status: Positive if there was evidence of flu, defined as positive RT-PCR test result on or before Day 1. Negative was defined as negative RT-PCR test result on or before Day 1.

Table 17: Baseline data Cohort B

	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

	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)	Overall (N=3998) n (%)
Sex, n (%)			
Male	837 (42.0)	811 (40.4)	1648 (41.2)
Female	1156 (58.0)	1194 (59.6)	2350 (58.8)
Participants of childbearing potential, n (%)[b]			
Yes	95 (8.2)	101 (8.5)	196 (8.3)
No	1061 (91.8)	1093 (91.5)	2154 (91.7)
Reasons if "No", n (%)[c]			
Surgically sterile	384 (36.2)	384 (35.1)	768 (35.7)
Postmenopausal	677 (63.8)	708 (64.8)	1385 (64.3)
Other	0	1 (<0.1)	1 (<0.1)
Race, 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)
Ethnicity, 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)
Unknown/Not reported	25 (1.3)	21 (1.0)	46 (1.2)
BMI (kg/m^2)			
n	1987	2005	3992
Mean (SD)	31.11 (7.124)	31.62 (7.325)	31.36 (7.229)
Median	30.20	30.50	30.30
Min, Max	12.2, 96.7	14.9, 75.3	12.2, 96.7
BMI index group, n (%)[d]			
<30 kg/m^2	963 (48.3)	936 (46.7)	1899 (47.5)
≥30 kg/m^2	1024 (51.4)	1069 (53.3)	2093 (52.4)
Missing	6 (0.3)	0	6 (0.2)
Influenza vaccination status since Sep 2022, n (%)[a]			
Received	784 (39.3)	784 (39.1)	1568 (39.2)
Not received	1209 (60.7)	1221 (60.9)	2430 (60.8)
COVID-19 vaccination status since Sep 2022, n (%)[a]			
Received	631 (31.7)	611 (30.5)	1242 (31.1)
Not received	1362 (68.3)	1394 (69.5)	2756 (68.9)
Number of COVID-19 vaccinations, n (%)[e]			

	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)	Overall (N=3998) n (%)
No dose	1 (<0.1)	0	1 (<0.1)
1-2 doses	693 (34.8)	704 (35.1)	1397 (34.9)
3 doses	725 (36.4)	694 (34.6)	1419 (35.5)
4 doses	413 (20.7)	444 (22.1)	857 (21.4)
≥5 doses	161 (8.1)	163 (8.1)	324 (8.1)
Baseline SARS-CoV-2 RT-PCR results via NP swab, n (%)[f]			
Positive	21 (1.1)	22 (1.1)	43 (1.1)
Negative	1954 (98.0)	1962 (97.9)	3916 (97.9)
Missing	18 (0.9)	21 (1.0)	39 (1.0)
Baseline influenza status, n (%)[g]			
Positive	3 (0.2)	2 (<0.1)	5 (0.1)
Negative	1972 (98.9)	1982 (98.9)	3954 (98.9)
Missing	18 (0.9)	21 (1.0)	39 (1.0)

Outcomes and estimation

Primary immunogenicity analyses at 29 days after vaccination

The primary NI objective was evaluated in the PPIS by assessing the GM level and SCR/SRR of the mRNA-1083 group as compared with the Fluzone HD + Spikevax group by the HAI assay at Day 29 for the vaccine-matched influenza strains and by the PsVNA for the SARS-CoV-2 variant.

Cohort A (Participants ⩾65 years of age)

The primary immunogenicity hypothesis was met. NI of mRNA-1083 compared with Fluzone HD + Spikevax based on GMR and SCR (for influenza)/SRR (for SARS-CoV-2) differences was demonstrated for all 10 co-primary endpoints.

Table 18: Analysis of Anti-HA antibody levels for vaccine-matched seasonal influenza A and B Strains and analysis of neutralising antibody levels for vaccine-matched SARS-CoV-2 strain and geometric mean titre ratios on Day 29 - Cohort A (Per-Protocol Immunogenicity Set)

	mRNA-1083 40 µg + Placebo (N=1886)		Fluzone HD + Spikevax (N=1883)		mRNA-1083 40 µg + Placebo vs. Fluzone HD + Spikevax		
	n	GM Level [a] (95% CI)	n	GM Level [a] (95% CI)	GMR [a]	97.5% CI [b]	95% CI [c]
Influenza A/H1N1	1885	120.5 (116.0, 125.2)	1883	104.3 (100.4, 108.4)	1.155	1.086, 1.229	1.094, 1.220
Influenza A/H3N2	1885	114.7 (110.4, 119.1)	1883	107.9 (103.9, 112.1)	1.063	0.999, 1.130	1.007, 1.122
Influenza B/Victoria	1885	245.3 (237.8, 252.9)	1883	219.4 (212.8, 226.3)	1.118	1.063, 1.175	1.070, 1.167
Influenza B/Yamagata	1885	93.3 (91.1, 95.6)	1883	92.6 (90.4, 94.9)	1.007	0.969, 1.047	0.973, 1.042
SARS-CoV-2 Omicron XBB.1.5	1849	1396.7 (1326.6, 1470.5)	1859	851.1 (808.6, 895.9)	1.641	1.510, 1.783	1.526, 1.765

Abbreviations: CI = confidence interval; GM = geometric mean, estimated by geometric least squares mean; GMR = geometric mean ratio, estimated by the ratio of geometric least squares mean; HA = hemagglutinin; HAI =

hemagglutination inhibition; LLOQ = lower limit of quantification; nAb = neutralising antibody; PsVNA = pseudovirus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULOQ = upper limit of quantification.

Anti-HA antibody titres were measured by HAI assay and nAb levels were measured by PsVNA.

n = number of participants with nonmissing antibody data at Day 29.

Antibody values reported as below the LLOQ were replaced by 0.5× LLOQ. Values greater than the ULOQ were converted to the ULOQ.

The log-transformed GM levels were analysed using an analysis of covariance model with vaccination group as the fixed variable, adjusting for the randomisation stratification factors: age group (≥65 to <75 years and ≥75 years), influenza vaccine status since Sep 2022 (received seasonal flu vaccine, did not receive seasonal flu vaccine), and baseline antibody level. Coefficients for least squares means used the observed marginal distribution of the fixed variables, adjusting for any unbalanced distribution of participants across strata.

a. The model-based GM level and GMR, and its corresponding 95% CI and 97.5% CI were obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

b. The noninferiority in GM level in the mRNA-1083 40 µg + Placebo group compared with that of Fluzone HD + Spikevax group was demonstrated if the lower bound of the 97.5% CI of the GMR was >0.667.

c. The superiority in GM level in the mRNA-1083 40 µg + Placebo group compared with that of Fluzone HD + Spikevax group was demonstrated if the lower bound of the 95% CI of the GMR was >1.

Table 19: Seroconversion for vaccine-matched seasonal influenza A and B strains measured and seroresponse for vaccine-matched SARS-CoV-2 Strain on Day 29 - Cohort A (Per-Protocol Immunogenicity Set)

	mRNA-1083 40 µg + Placebo (N=1886)		Fluzone HD + Spikevax (N=1883)		mRNA-1083 40 µg + Placebo vs. Fluzone HD +Spikevax		
	n/N1	SCR/SRR (95% CI) [a] [b]	n/N1	SCR/SRR (95% CI) [a] [b]	SCR/SRR Difference n(%) [a]	97.5% CI [c] [d]	95% CI [c] [e]
Influenza A/H1N1	687/1885	36.4 (34.3, 38.7)	585/1883	31.1 (29.0, 33.2)	5.4	1.9, 8.8	2.4, 8.4
Influenza A/H3N2	729/1885	38.7 (36.5, 40.9)	652/1883	34.6 (32.5, 36.8)	4.0	0.5, 7.6	1.0, 7.1
Influenza B/Victoria	451/1885	23.9 (22.0, 25.9)	365/1883	19.4 (17.6, 21.2)	4.5	1.5, 7.5	1.9, 7.2
Influenza B/Yamagata	165/1885	8.8 (7.5, 10.1)	192/1883	10.2 (8.9, 11.7)	-1.4	-3.6, 0.7	-3.3, 0.4
SARS-CoV-2 Omicron XBB.1.5	1516/1841	82.3 (80.5, 84.1)	1290/1854	69.6 (67.4, 71.7)	12.8	9.6, 15.9	10.0, 15.5

Abbreviations: CI = confidence interval; HA = hemagglutinin; HAI = hemagglutination inhibition; LLOQ = lower limit of quantification; nAb = neutralising antibody; PsVNA = pseudovirus neutralisation assay; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SRR = seroresponse rate; ULOQ = upper limit of quantification.

n = number of participants experiencing a seroconversion or seroresponse and with nonmissing antibody data at baseline (Day 1) and at Day 29.

N1 = number of participants with nonmissing antibody data at baseline (Day 1) and at Day 29.

Anti-HA antibody titres were measured by HAI assay and nAb levels were measured by PsVNA.

Antibody values reported as below the LLOQ were replaced by 0.5× LLOQ. Values greater than the ULOQ were converted to the ULOQ.

a. Seroconversion was defined as a Day 29 postinjection level ≥1:40 if Baseline was <1:10 or a 4-fold or greater rise if Baseline was ≥1:10 in anti HA antibodies measured by the HAI assay. Seroresponse was defined as a Day 29 postinjection level ≥4-fold rise if Baseline was ≥LLOQ or ≥4×LLOQ if Baseline value was <LLOQ in the nAb values measured by PsVNA.

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

c. 95% CI and 97.5% CI were calculated using the Miettinen-Nurminen (score) method.

d. The noninferiority in SCR/SRR in the mRNA-1083 40 µg + Placebo group compared with that of Fluzone HD + Spikevax group was demonstrated if the lower bound of the 97.5% CI of the SCR/SRR difference was >-10%.

e. The superiority in SCR/SRR in the mRNA-1083 40 µg + Placebo group compared with that of Fluzone HD + Spikevax group was demonstrated if the lower bound of the 95% CI of the SCR/SRR difference was >0%.

Cohort B (Participants ⩾50 to <65 years of age)

The primary immunogenicity hypothesis was met. NI of mRNA-1083 compared with Fluarix + Spikevax based on GMR and SCR (for influenza)/SRR (for SARS-CoV-2) differences was demonstrated for all 10 co-primary endpoints.

Table 20: Analysis of Anti-HA antibody levels for vaccine-matched seasonal influenza A and B strains and analysis of neutralising antibody levels for vaccine-matched SARS-CoV-2 Strain and geometric mean titre ratios on Day 29 - Cohort B (Per-Protocol Immunogenicity Set)

	mRNA-1083 40 µg + Placebo (N=1890)		Fluarix + Spikevax (N=1884)		mRNA-1083 40 µg + Placebo vs. Fluarix + Spikevax		
	n	GM Level [a] (95% CI)	n	GM Level [a] (95% CI)	GMR [a]	97.5% CI [b]	95% CI [c]
Influenza A/H1N1	1889	137.7 (132.1, 143.5)	1883	97.3 (93.4, 101.5)	1.414	1.322, 1.513	1.333, 1.500
Influenza A/H3N2	1889	111.5 (107.5, 115.7)	1882	80.8 (77.9, 83.8)	1.380	1.300, 1.465	1.310, 1.454
Influenza B/Victoria	1889	224.9 (218.0, 232.0)	1883	185.0 (179.3, 190.8)	1.216	1.156, 1.278	1.163, 1.270
Influenza B/Yamagata	1889	101.7 (99.3, 104.3)	1882	88.1 (86.0, 90.3)	1.154	1.109, 1.201	1.115, 1.195
SARS-CoV-2 Omicron XBB.1.5	1854	1551.6 (1476.3, 1630.7)	1848	1186.1 (1128.5, 1246.7)	1.308	1.207, 1.418	1.219, 1.404

Table 21: Seroconversion for Vaccine-matched Seasonal Influenza A and B Strains and Seroresponse for Vaccine matched SARS-CoV-2 Strain on Day 29 - Cohort B (Per-Protocol Immunogenicity Set)

	mRNA-1083 40 µg + Placebo (N=1890)		Fluarix + Spikevax (N=1884)		mRNA-1083 40 µg + Placebo vs. Fluarix + Spikevax		
	n/N1	SCR/SRR (95% CI) [a] [b]	n/N1	SCR/SRR (95% CI) [a] [b]	SCR/SRR Difference n(%) [a]	97.5% CI [c] [d]	95% CI [c] [e]
Influenza A/H1N1	955/1888	50.6 (48.3, 52.9)	615/1882	32.7 (30.6, 34.8)	17.9	14.3, 21.4	14.8, 21.0
Influenza A/H3N2	792/1888	41.9 (39.7, 44.2)	515/1881	27.4 (25.4, 29.5)	14.6	11.1, 18.0	11.6, 17.6
Influenza B/Victoria	488/1888	25.8 (23.9, 27.9)	324/1882	17.2 (15.5, 19.0)	8.6	5.6, 11.6	6.0, 11.2
Influenza B/Yamagata	245/1888	13.0 (11.5, 14.6)	194/1881	10.3 (9.0, 11.8)	2.7	0.3, 5.0	0.6, 4.7
SARS-CoV-2 Omicron XBB.1.5	1566/1852	84.6 (82.8, 86.2)	1412/1846	76.5 (74.5, 78.4)	8.1	5.2, 11.0	5.5, 10.6

Secondary analyses

Secondary immunogenicity endpoints included a superiority analysis of the GMR and SCR/SRR differences at Day 29 by the HAI assay between the mRNA-1083 group and the Fluzone HD + Spikevax group for the 4 vaccine-matched influenza strains, and by PsVNA for the vaccine-matched

SARS-CoV-2 variant in the PPIS. Secondary immunogenicity endpoints also included GM at Day 29 and GMFR (Day 29 GMT/Day 1 [Baseline] GMT) by MN assay for influenza in a subset of randomly sampled participants.

Cohort A (Participants ⩾65 years of age)

Superiority analyses

The secondary objective of superiority was formally not achieved in Cohort A (subjects ⩾65 years of age) due to results with B/Yamagata.

Neutralising antibody responses for influenza

Table 22: Neutralising antibody levels measured by microneutralisation assay for vaccine-matched seasonal influenza A and B strains at Day 29 - Cohort A (Per-Protocol Immunogenicity Set for Microneutralisation Assay)

	mRNA-1083 40 µg + Placebo (N=146)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI) [b]	n[c]	GM Level (95% CI) [b]	Adjusted GM Level (95% CI) [d]	GMFR (95% CI) [b]
Influenza A/H1N1	146	138.4 (107.8, 177.7)	146	676.4 (528.8, 865.3)	674.4 (549.5, 827.7)	4.89 (3.92, 6.10)
Influenza A/H3N2	146	203.8 (176.9, 234.8)	146	587.6 (483.9, 713.6)	643.7 (542.8, 763.3)	2.88 (2.44, 3.41)
Influenza B/Victoria	146	884.0 (715.0, 1093.0)	146	2845.4 (2406.1, 3364.9)	2935.2 (2536.1, 3397.2)	3.22 (2.63, 3.94)
Influenza B/Yamagata	146	375.9 (297.0, 475.8)	146	1118.8 (910.4, 1374.9)	1159.7 (1000.5, 1344.3)	2.98 (2.56, 3.46)
	Fluzone HD + Spikevax (N=146)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI) [b]	n[c]	GM Level (95% CI) [b]	Adjusted GM Level (95% CI)[d]	GMFR (95% CI) [b]
Influenza A/H1N1	146	136.0 (106.9, 173.1)	146	635.9 (489.4, 826.4)	637.8 (519.7, 782.8)	4.68 (3.68, 5.94)
Influenza A/H3N2	146	272.1 (222.7, 332.6)	146	668.8 (538.9, 830.0)	610.6 (514.9, 724.0)	2.46 (2.01, 3.01)
Influenza B/Victoria	146	1018.7 (809.8, 1281.4)	146	3072.5 (2571.0, 3671.9)	2978.5 (2573.5, 3447.2)	3.02 (2.48, 3.67)
Influenza B/Yamagata	146	424.8 (345.7, 522.1)	146	1434.4 (1200.9, 1713.3)	1383.8 (1193.8, 1604.1)	3.38 (2.75, 4.15)

Abbreviations: CI = confidence interval; GM = geometric mean; GMFR = geometric mean fold rise; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification.

Antibody values reported as below the LLOQ were replaced by 0.5× LLOQ. Values greater than the ULOQ were converted to the ULOQ.

a. Number of participants with nonmissing baseline (Day 1) neutralising antibody data.

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

c. Number of participants with nonmissing neutralising antibody data at the corresponding visit.

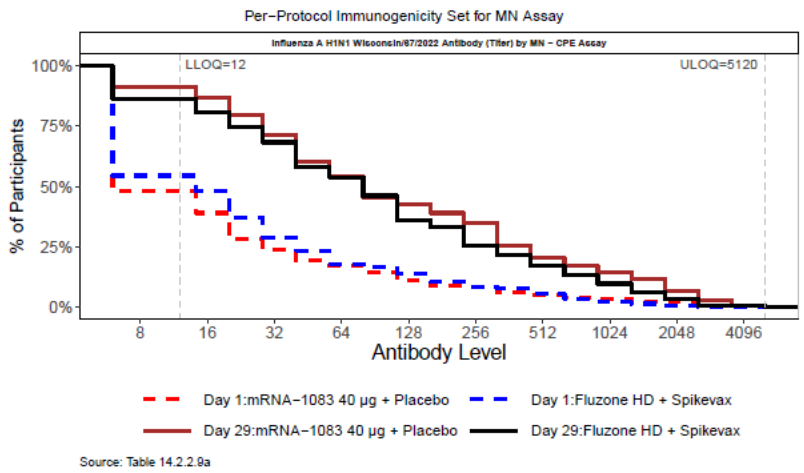
[d] The log-transformed antibody levels were analysed using an analysis of covariance model with vaccination group as the fixed variable, adjusting for the randomisation stratification factors: age group (≥65 to <75 years and ≥75 years), influenza vaccine status since Sep 2022 (received seasonal flu vaccine, did not receive seasonal flu vaccine), and baseline antibody level. Coefficients for least squares means used the observed marginal distribution of the fixed variables, adjusting for any unbalanced distribution of participants across strata. The model-based GM level and its corresponding 95% CI were obtained by transforming the least square mean estimate and its CI back to the original scale for presentation.

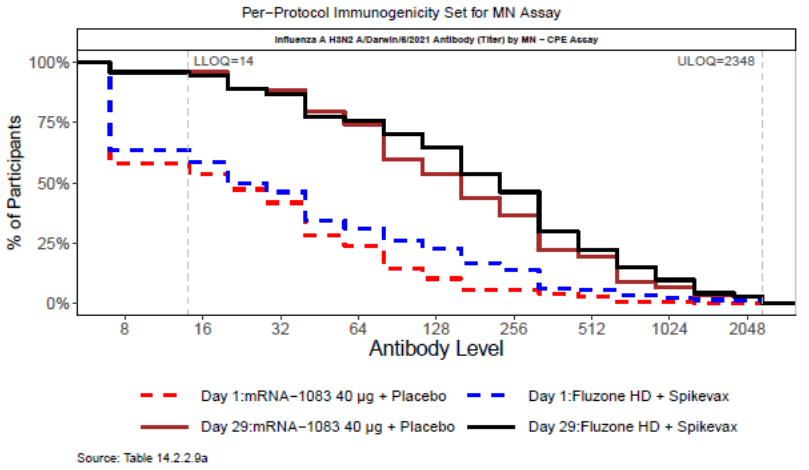
Table 23: Neutralising antibody levels measured by MN-CPE for vaccine-matched seasonal Influenza A and B Strains at Day 29 - Cohort A (Per-Protocol Immunogenicity Set for Microneutralisation Assay)

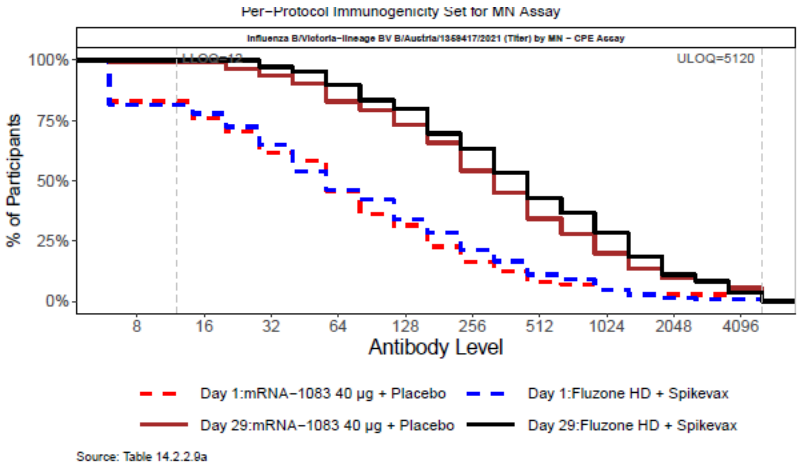
	mRNA-1083 40 µg + Placebo (N=146)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI)	n[a]	GM Level (95% CI)	Adjusted GM Level (95% CI)	GMFR (95% CI)
Influenza A/H1N1	146	17.7 (13.8, 22.7)	146	109.7 (81.7, 147.1)	116.7 (93.0, 146.5)	6.20 (4.86, 7.92)
Influenza A/H3N2	146	24.1 (19.5, 29.8)	146	146.1 (117.5, 181.8)	158.2 (130.8, 191.3)	6.07 (4.93, 7.47)
Influenza B/Victoria	146	60.2 (46.2, 78.3)	146	318.1 (251.5, 402.5)	324.8 (268.8, 392.5)	5.29 (4.19, 6.66)
	Fluzone HD + Spikevax (N=146)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI)	n[a]	GM Level (95% CI)	Adjusted GM Level (95% CI)	GMFR (95% CI)
Influenza A/H1N1	145	20.9 (16.3, 26.8)	145	84.0 (63.1, 111.8)	78.9 (62.8, 99.1)	4.02 (3.16, 5.10)
Influenza A/H3N2	145	33.0 (25.6, 42.7)	145	179.4 (142.1, 226.4)	165.6 (136.9, 200.4)	5.43 (4.25, 6.94)
Influenza B/Victoria	145	65.3 (49.7, 85.9)	145	423.3 (340.0, 526.8)	414.5 (342.8, 501.2)	6.48 (5.03, 8.34)

CI = Confidence Interval; GMT = Geometric Mean Titre; GMFR = Geometric Mean Fold Rise. n = Number of participants with non-missing data at the corresponding timepoint.

Figure 5: Reverse Cumulative Distribution Function of Antibody Levels (MN-CPE) for Vaccine-Matched Influenza A and B strains







Cohort B (Participants ⩾50 to <65 years of age)

Superiority analyses

In Cohort B, superiority of mRNA-1083 as compared with Fluarix + Spikevax was demonstrated for all 4 influenza strains and the SARS-CoV-2 variant for both GM level and SCR/SRR.

Neutralising antibody responses for influenza

Table 24: Neutralising Antibody Levels Measured by Microneutralisation Assay for Vaccine-matched Seasonal Influenza A and B Strains at Day 29 - Cohort B (Per-Protocol Immunogenicity Set for Microneutralisation Assay)

	mRNA-1083 40 µg + Placebo (N=147)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI) [b]	n[c]	GM Level (95% CI) [b]	Adjusted GM Level (95% CI)[d]	GMFR (95% CI) [b]
Influenza A/H1N1	147	108.3 (85.2, 137.8)	147	946.8 (729.7, 1228.4)	867.0 (700.4, 1073.2)	8.74 (7.03, 10.87)
Influenza A/H3N2	147	194.1 (164.1, 229.6)	147	645.8 (519.1, 803.5)	655.3 (553.7, 775.7)	3.33 (2.76, 4.01)
Influenza B/Victoria	147	749.7 (621.1, 905.0)	147	2901.5 (2457.6, 3425.6)	2732.5 (2539.7, 3164.1)	3.87 (3.27, 4.58)

	mRNA-1083 40 µg + Placebo (N=147)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI) [b]	n[c]	GM Level (95% CI) [b]	Adjusted GM Level (95% CI)[d]	GMFR (95% CI) [b]
Influenza B/Yamagata	147	395.7 (320.6, 488.3)	147	1449.6 (1222.5, 1719.0)	1372.6 (1178.7, 1598.4)	3.66 (3.02, 4.44)
	Fluarix + Spikevax (N=147)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI) [b]	n[c]	GM Level (95% CI) [b]	Adjusted GM Level (95% CI)[d]	GMFR (95% CI) [b]
Influenza A/H1N1	147	83.2 (66.2, 104.6)	147	428.1 (327.0, 560.4)	467.5 (377.6, 578.7)	5.14 (4.01, 6.60)
Influenza A/H3N2	147	202.7 (171.1, 240.1)	147	393.9 (324.7, 477.9)	388.2 (328.0, 459.5)	1.94 (1.64, 2.31)
Influenza B/Victoria	147	576.1 (460.5, 720.7)	147	1883.1 (1571.4, 2256.5)	1999.5 (1726.8, 2315.4)	3.27 (2.66, 4.02)
Influenza B/Yamagata	147	313.3 (249.4, 393.5)	147	1071.3 (883.8, 1298.4)	1131.4 (971.6, 1317.6)	3.42 (2.79, 4.19)

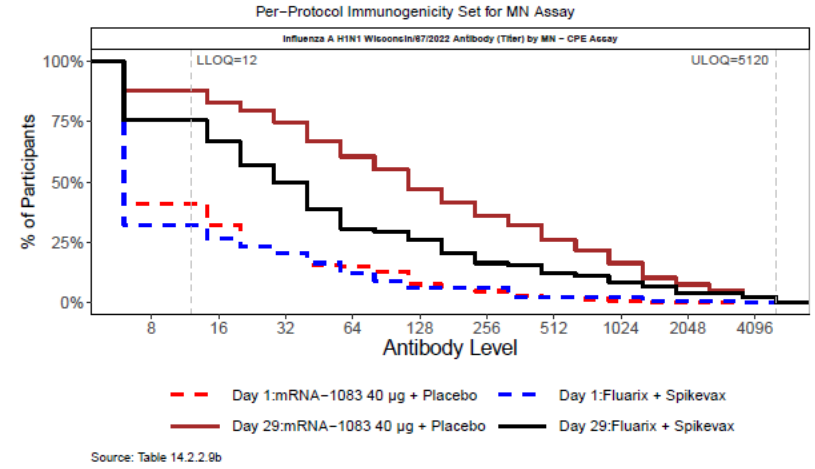
Table 25: Neutralising Antibody Levels Measured by MN-CPE for Vaccine-matched Seasonal Influenza A and B Strains at Day 29 - Cohort B (Per-Protocol Immunogenicity Set for Microneutralisation Assay)

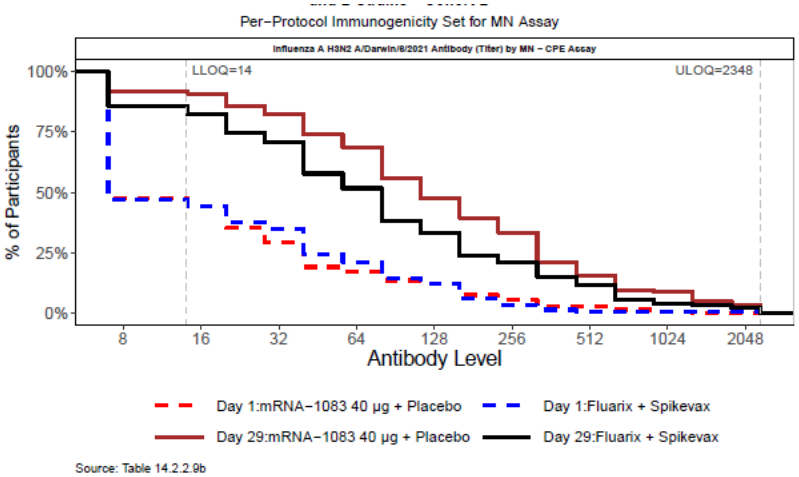
	mRNA-1083 40 µg + Placebo (N=147)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI)	n[a]	GM Level (95% CI)	Adjusted GM Level (95% CI)	GMFR (95% CI)
Influenza A/H1N1	147	14.0 (11.4, 17.3)	147	127.4 (93.5, 173.6)	123.2 (94.5, 160.5)	9.08 (6.82, 12.09)
Influenza A/H3N2	147	19.0 (15.4, 23.5)	147	122.7 (96.4, 156.1)	124.1 (101.4, 151.9)	6.47 (5.21, 8.03)
Influenza B/Victoria	147	58.2 (44.4, 76.1)	147	331.2 (260.0, 421.9)	296.4 (244.3, 359.8)	5.69 (4.55, 7.13)
	Fluarix + Spikevax (N=147)					
	Day 1 (Baseline)		Day 29			
	n[a]	GM Level (95% CI)	n[a]	GM Level (95% CI)	Adjusted GM Level (95% CI)	GMFR (95% CI)
Influenza A/H1N1	147	12.6 (10.2, 15.7)	147	45.6 (33.8, 61.6)	47.2 (36.2, 61.5)	3.61 (2.74, 4.75)
Influenza A/H3N2	147	19.6 (15.9, 24.3)	147	71.0 (55.6, 90.8)	70.3 (57.4, 86.0)	3.62 (2.88, 4.54)
Influenza B/Victoria	147	38.4 (29.5, 50.0)	147	215.1 (169.8, 272.4)	240.3 (198.0, 291.7)	5.60 (4.42, 7.08)

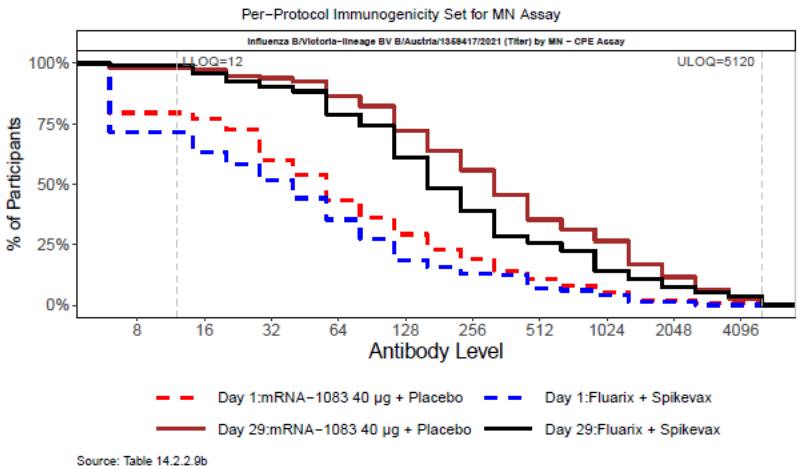
CI = Confidence Interval; GMT = Geometric Mean Titre; GMFR = Geometric Mean Fold Rise. n = Number of

participants with non-missing data at the corresponding timepoint.

Figure 6 Reverse Cumulative Distribution Function (MN-CPE) of Antibody Levels for Vaccine-Matched Influenza A and B strains







Exploratory analyses

Humoral Immune Responses 6 months after vaccination

Antibody responses against influenza and SARS-CoV-2 6 months after vaccination were investigated in approximately 400 subjects per group in the PPIS.

Influenza Antibody Response

In Cohort A, GM levels for influenza decreased compared to Day 29 but were higher than baseline for the influenza A strains while GM levels of B strains were around baseline in both groups. Day 181 GM levels and GMFRs for influenza were numerically higher in the mRNA-1083 + placebo group vs Fluzone HD + Spikevax group for the influenza A strains but were similar for influenza B strains. Day 181 GMRs (95% CI) were 1.206 (1.082, 1.343) for A/H1N1, 1.135 (1.021, 1.263) for A/H3N2, 1.064 (0.977, 1.159) for B/Victoria, and 1.038 (0.963, 1.118) for B/Yamagata.

In Cohort B, GM levels for influenza decreased compared to Day 29 but were higher than baseline for the influenza A strains. Day 181 GM levels and GMFR for influenza were numerically higher in mRNA-1083 + placebo group vs Fluarix + Spikevax group for all 4 influenza strains. Day 181 GMR of mRNA-1083 + placebo group vs Fluarix + Spikevax group (95% CI) were 1.273 (1.132, 1.431) for A/H1N1, 1.322 (1.182, 1.479) for A/H3N2, 1.132 (1.035, 1.237) for B/Victoria, and 1.105 (1.018, 1.199) for B/Yamagata.

SARS-CoV-2 Neutralising Antibody Response

The antibody responses were clearly increased over baseline 6 months after vaccination with mRNA-1083 or comparator vaccines in both cohorts with a trend for numerically higher immune responses after vaccination with mRNA-1083 (e.g. Cohort A D181 GMT: 557.3 [490.1, 633.8] vs 385.1 [337.6, 439.3]; Cohort B D181 GMT: 629.4 [559.3, 708.4] vs 461.2 [406.1, 523.8]).

Humoral Immune Responses to Other SARS-CoV-2 Variants

SARS-CoV-2 antibody responses to JN.1 (prevalent variant of interest) were assessed using PsVNA in a randomly selected immunogenicity subset of approximately 60 participants from each group in the PPIS. As expected, antibody responses against JN.1 were lower compared to responses against XBB-1-5 (vaccine-matched) across vaccine groups but trended to be higher after vaccination with mRNA-1083 compared to the comparator vaccines in both cohorts (e.g. Cohort A Day 29 GM ID50: 801.8 [95% CI: 584.2, 1100.4] vs 383.5 [95% CI: 269.2, 546.1]; GMFR: 25.10 [95% CI: 18.20, 34.63] vs 11.80 [95% CI: 8.46, 16.45]).

Pre-defined and post-hoc subgroup analyses

The primary immunogenicity endpoints were also analysed by subgroups.

Subgroup Analyses by Age and vaccine status

Cohort A (Participants ⩾65 years of age)

Figure 7: Forest Plot GMR A/H1N1 Cohort A

Forest plot of Geometric Mean Ratios of Antibody Levels for Vaccine-Matched Seasonal Influenza A and B and SARS-CoV-2 Measured on Day 29 by Subgroup — Cohort A
Per-Protocol Immunogenicity Set

Antibody: Influenza A H1N1 Antibody Level (Titer) by HAI Assay (LLOQ: 10, ULOQ: 3620)

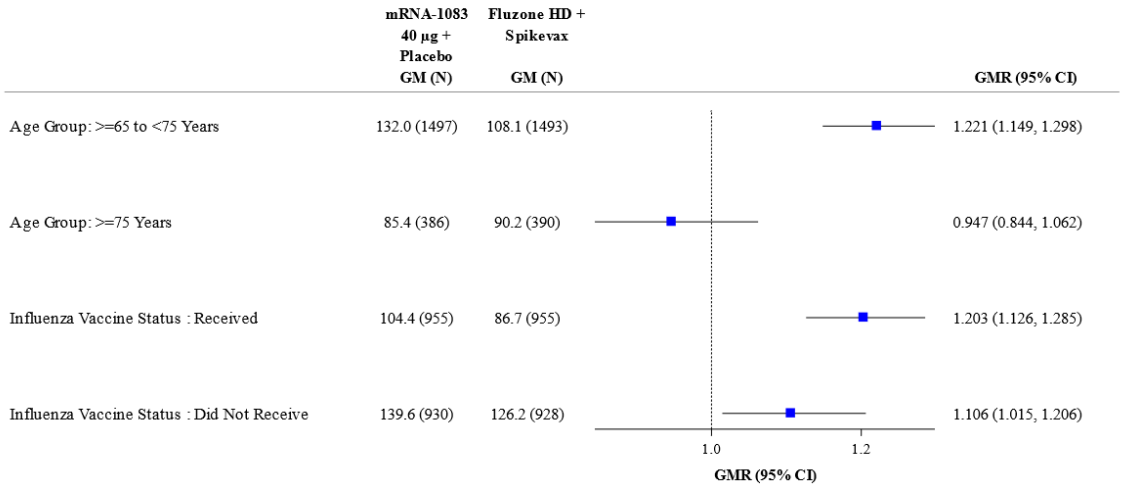


Figure 8: Forest Plot GMR A/H3N2 Cohort A

Figure 14.2.1.1a
Forest plot of Geometric Mean Ratios of Antibody Levels for Vaccine-Matched Seasonal Influenza A and B and SARS-CoV-2 Measured on Day 29 by Subgroup — Cohort A
Per-Protocol Immunogenicity Set

Antibody: Influenza A H3N2 Antibody Level (Titer) by HAI Assay (LLOQ: 10, ULOQ: 5120)

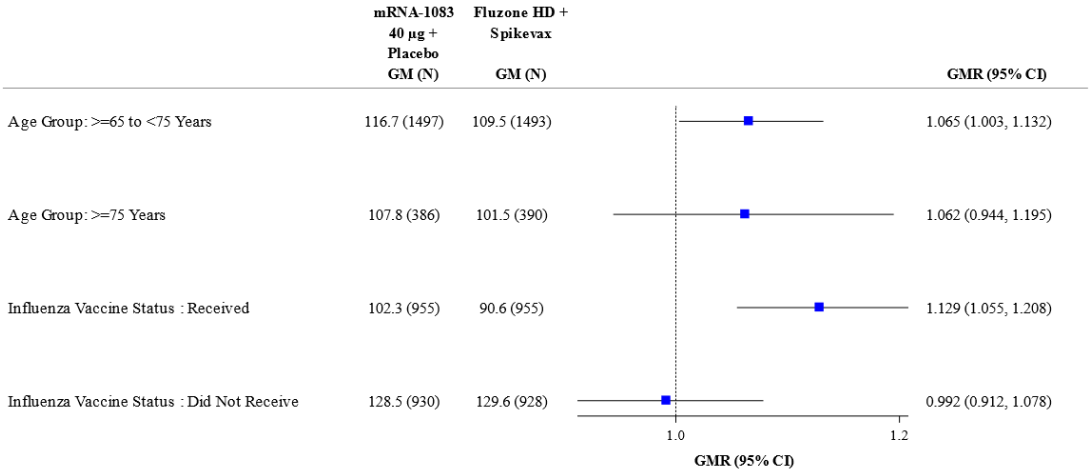


Figure 9: Forest Plot GMR B/Victoria Cohort A

Figure 14.2.1.1a
Forest plot of Geometric Mean Ratios of Antibody Levels for Vaccine-Matched Seasonal Influenza A and B and SARS-CoV-2 Measured on Day 29 by Subgroup — Cohort A
Per-Protocol Immunogenicity Set

Antibody: Influenza B/Victoria-lineage Antibody Level (Titer) by HAI Assay (LLOQ: 10, ULOQ: 1356)

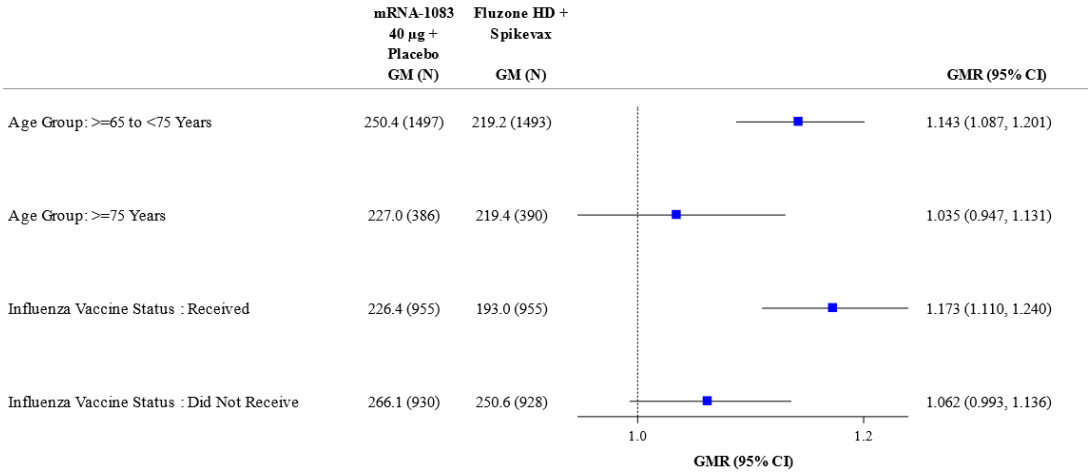


Figure 10: Forest Plot GMR B/Yamagata Cohort A

Figure 14.2.1.1a
Forest plot of Geometric Mean Ratios of Antibody Levels for Vaccine-Matched Seasonal Influenza A and B and SARS-CoV-2 Measured on Day 29 by Subgroup — Cohort A
Per-Protocol Immunogenicity Set

Antibody: Influenza B/Yamagata-lineage Antibody Level (Titer) by HAI Assay (LLOQ: 10, ULOQ: 1280)

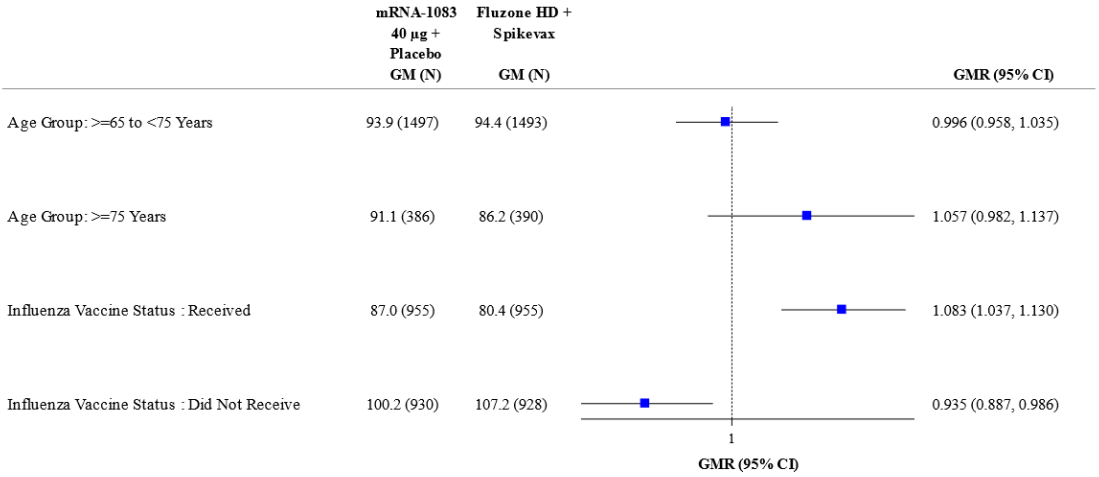
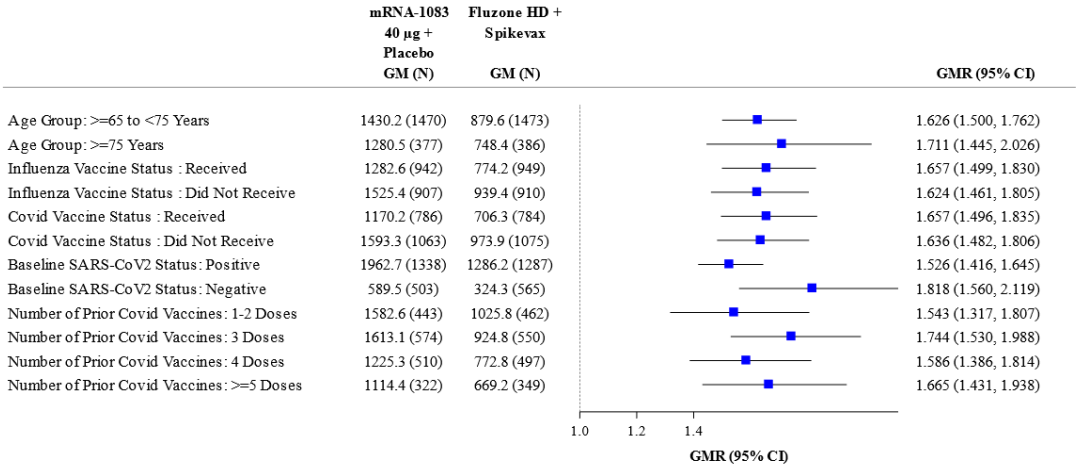


Figure 11: Forest Plot GMR SARS-CoV-2 Cohort A

Figure 14.2.1.1a
Forest plot of Geometric Mean Ratios of Antibody Levels for Vaccine-Matched Seasonal Influenza A and B and SARS-CoV-2 Measured on Day 29 by Subgroup — Cohort A
Per-Protocol Immunogenicity Set

Antibody: SARS-CoV-2 Omicron XBB.1.5 Antibody Level (AU/mL) by PsVNA Assay (LLOQ: 38, ULOQ: 6960)



Cohort B (Participants ⩾50 to <65 years of age)

Figure 12: Forest Plot GMR A/H1N1 Cohort B

Figure 14.2.1.1b
Forest plot of Geometric Mean Ratios of Antibody Levels for Vaccine-Matched Seasonal Influenza A and B and SARS-CoV-2 Measured on Day 29 by Subgroup — Cohort B
Per-Protocol Immunogenicity Set

Antibody: Influenza A H1N1 Antibody Level (Titer) by HAI Assay (LLOQ: 10, ULOQ: 3620)

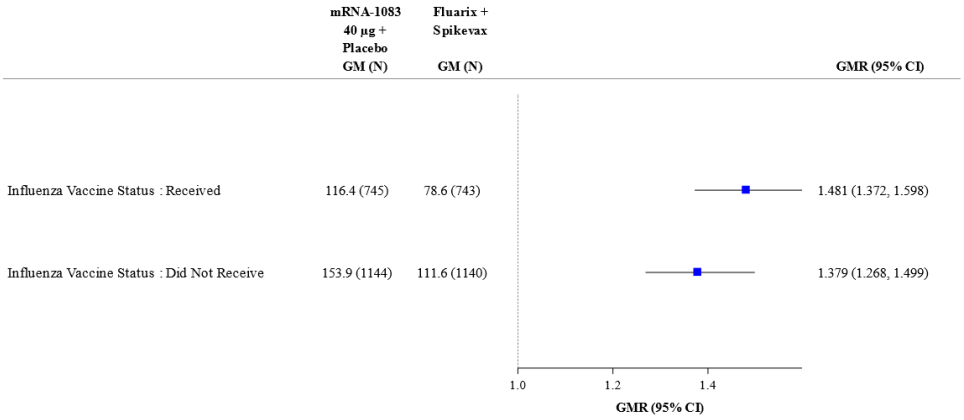


Figure 13: Forest Plot GMR A/H3N2 Cohort B

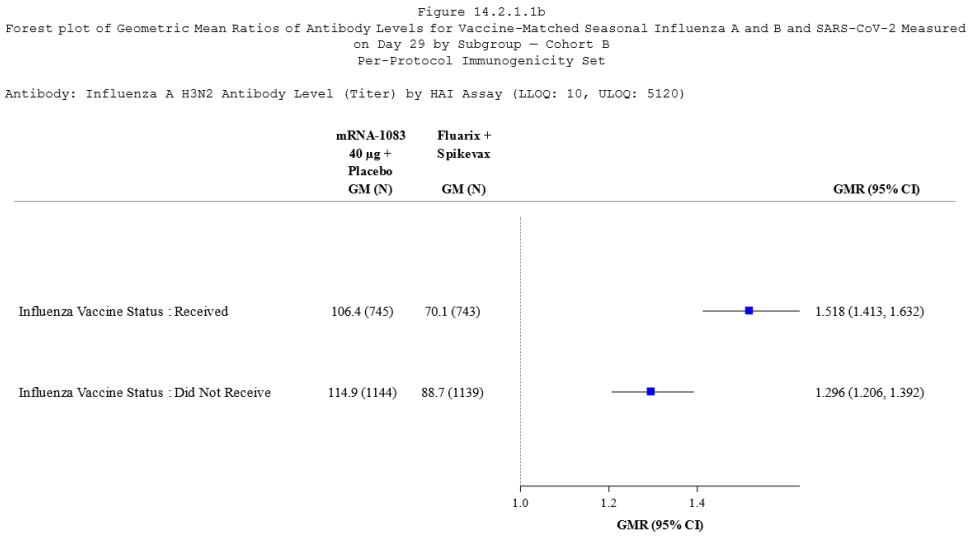


Figure 14: Forest Plot GMR B/Victoria Cohort B

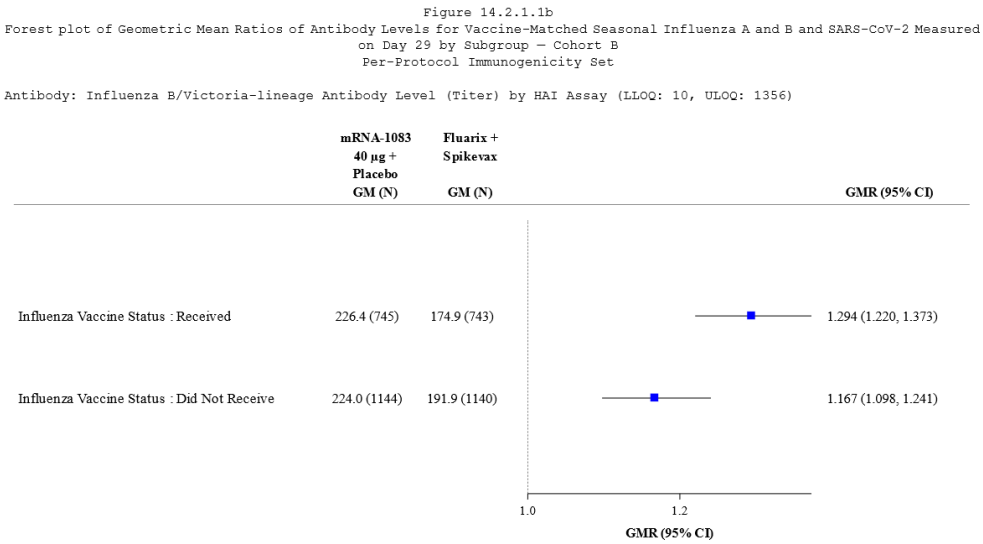


Figure 15: Forest Plot GMR B/Yamagata Cohort B

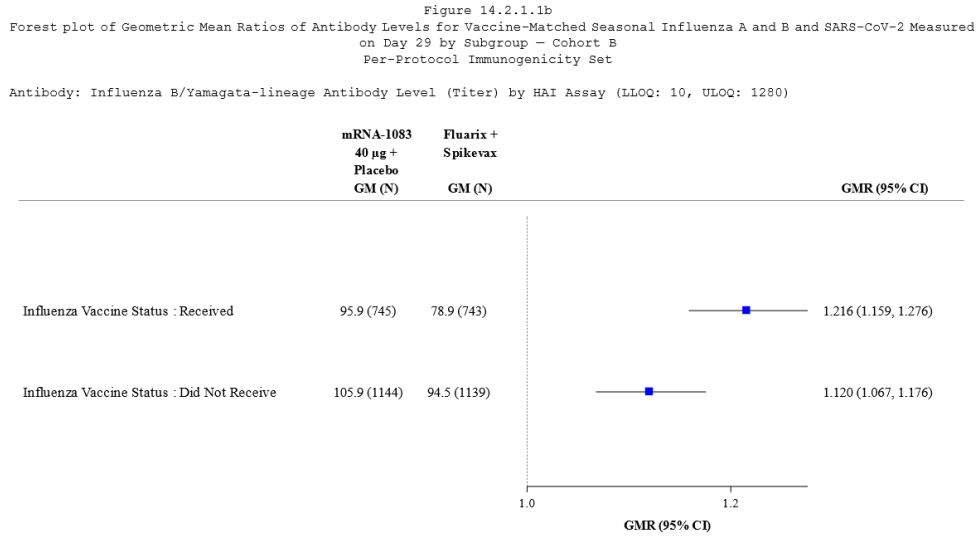
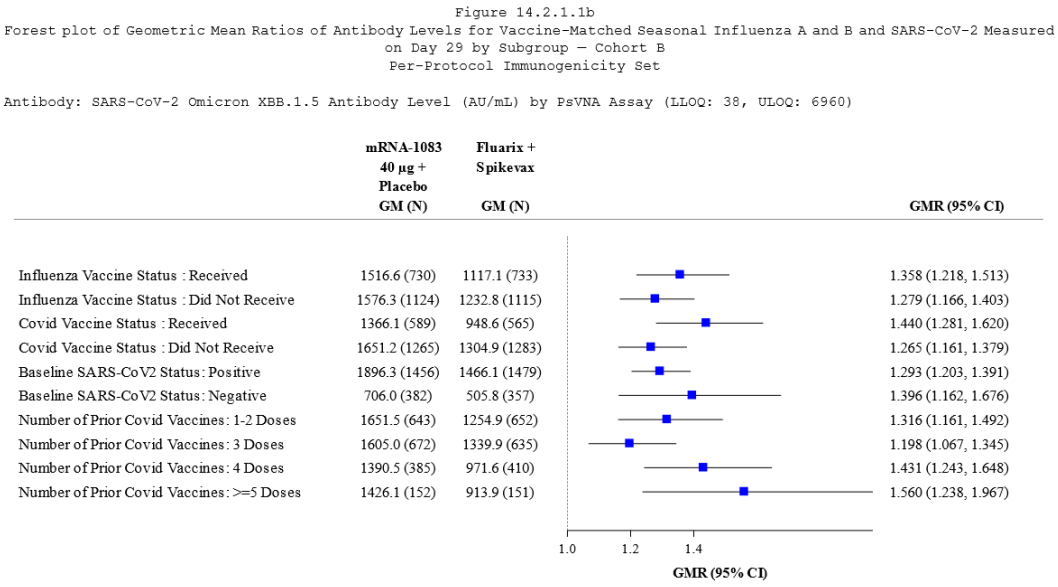


Figure 16: Forest Plot GMR SARS-CoV-2 Cohort B



Supportive studies

Study mRNA-1083-P201

mRNA-1083-P201 is a 2-Part, Phase 2, randomised, observer-blind study evaluating the safety, reactogenicity, and immunogenicity in relation to product critical quality attributes (including purity) of mRNA-1083 in adults aged ≥50 to <65 years. In Part 1 of the study, ~600 participants were randomised 1:1:1:1 to receive one of four lots of mRNA-1083 (Lots A, B, C, D). In Part 2, ~300 participants were randomised 1:1 to receive one of two lots of mRNA-1083 (Lots A, E). All participants received a single intramuscular injection of mRNA-1083 40 ug from their respective lot, all identical in composition but varying in refrigerated storage duration and mRNA purity. Each mRNA-1083 dose contained 8.3 µg per each four influenza strains (A/H1N1, A/H3N2, B/Victoria and B/Yamagata), and 6.7 µg of SARS-CoV-2. Across the purity range evaluated (57% to 83%), the effective delivered dose (EDD) per influenza strain ranged from 4.7 µg to 6.9 µg, and the SARS-CoV-2 EDD from 3.8 µg to 5.6 µg. Immunogenicity was assessed at Day 29 by haemagglutination inhibition (HAI) assay for influenza and PsVNA for SARS-CoV-2. Day 29 HAI GMTs and SARS-CoV-2 PsVNA GMTs were comparable across all lots in both Part 1 and Part 2.

Study mRNA-1283-P301

Study mRNA-1283-P301 is a global, randomised, observer-blind, active-controlled Phase 3 study. Participants were randomised 1:1 to receive a single 10 µg dose of mRNA-1283 or a single 50 µg dose of mRNA-1273 (both targeting the original SARS-CoV-2 and the Omicron BA.4/BA.5 variant) with stratification by age (≥12 to <18, ≥18 to <65, and ≥65 years). Study enrolment occurred from March to August 2023; 5706 participants received mRNA-1283 and 5711 received mRNA-1273. Symptom surveillance for COVID-19 included biweekly electronic diary prompts and clinical evaluation and testing based on participant-reported symptoms. A case was defined as PCR confirmed SARS-CoV-2 infection with at least 1 clinical symptom consistent with COVID-19.

The primary noninferiority rVE objective was met given that the lower bound of the rVE CI was above -10%, rVE (99.4% CI) = 9.31% (-6.58, 22.83), p=0.0005. Supportive rVE analyses were also performed based on COVID-19 events through the data cutoff date 23 Feb 2024 [rVE=7.34% (95%

CI: -3.43, 16.98)] and based on the secondary COVID-19 definition with events through 31 Jan 2024 [rVE=10.50% (95% CI: -1.01, 20.69]. These results suggest that the estimate of relative vaccine efficacy of mRNA-1283 as compared to the standard-of-care vaccine mRNA-1273 was ~9% and consistent regardless of the data cutoff or case definition utilized in the analysis.

The primary immunogenicity objective was to demonstrate noninferior neutralising antibody responses of mRNA-1283 10 µg when compared to mRNA-1273 50 µg. This prespecified primary objective was based on the Day 29 GMR and SRR difference. The primary immunogenicity objective was met with noninferior neutralising antibody responses of mRNA-1283.222 vs mRNA-1273 (BA.4/BA.5 GMR was 1.335 [95% CI: 1.194, 1.492], with the lower bound of the CI >0.667, SRR difference was 14.4% [95% CI:9.3, 19.4], with the lower bound of the CI >-10%; Day 29 D614G GMR was 1.240 [95% CI:1.128, 1.362] with the lower bound of the CI >0.667, SRR difference was 10.7% [95% CI:6.0, 15.4] with the lower bound of the 95% CI of the SRR-difference >-10%). The neutralising antibody responses against the variants contained in the study vaccines were higher with mRNA-1283 vs mRNA-1273 as defined by the lower bound of 95% CIs on the GMRs that excluded the value '1' and the lower bound of 95% CIs on the SRR differences that excluded the value '0.'

Study mRNA-1010-P301

This was a global, multicentre, Phase 3, randomised, stratified, observer-blind, active-controlled study to evaluate the reactogenicity and safety, and noninferior immunogenicity of messenger ribonucleic acid (mRNA)-1010 versus an authorised seasonal influenza vaccine in medically stable adults ≥18 years. Participants were randomly assigned in a 1:1 ratio to receive a single dose of 50 µg mRNA-1010 or a single dose of an authorised seasonal influenza vaccine as an active comparator (Fluarix Tetra 60 µg), with stratification based on age categories (18 to <50 years, ≥50 to <65 years, or ≥65 years, such that at least 50% of enrollees were ≥50 years and approximately 20% were ≥65 years) and influenza vaccine status in the prior 12 months (received or did not receive). The primary objective of this study was to evaluate the humoral immunogenicity of mRNA-1010 relative to that of the active comparator against vaccine-matched influenza A and B strains at Day 29. A secondary objective of this study was to evaluate relative vaccine efficacy to prevent influenza caused by any strain of influenza virus. For this purpose, participants were issued eDiaries for weekly reporting of symptoms of potential influenza-like illness (ILI). If a participant reported ILI symptoms, staff members at the study site were to collect a nasopharyngeal (NP) swab within 72 hours of symptom onset. The NP swab specimens were evaluated by reverse transcription polymerase chain reaction (RT-PCR) for influenza and other respiratory pathogens. A total of 6102 participants were randomised in this study, including 3045 participants in the mRNA-1010 group and 3057 participants in the Fluarix group (Randomisation Set).

Vaccination with a single dose of mRNA-1010 at 50 µg demonstrated noninferiority of Ab responses (GMR and SCR) for both influenza A strains (A/H1N1 and A/H3N2) at Day 29 (lower bound of 97.5% CI >0.667 for GMR and > 10% for SCR difference) compared with Fluarix. Noninferiority was not met based on GMR or SCR for the influenza B/Victoria and B/Yamagata-lineage strains at Day 29.

In the mITT Set, a total of 118 RT-PCR-confirmed protocol-defined influenza cases starting 14 days after injection were reported, including 64 cases (2.1%) in the mRNA-1010 group and 54 cases (1.8%) in the Fluarix group. The rVE of mRNA-1010 for protocol-defined ILI cases was numerically lower compared with Fluarix for protection against any influenza A or B strain (rVE -18.038% [95% CI: -72.816%, 19.114%]). For influenza A strains, rVE (95% CI) was 17.161% (-45.712%, 53.285%). For influenza B strains, rVE (95% CI) was -66.003% (-187.879%, 2.341%).

Study mRNA-1010-P303

Study mRNA-1010-P303 was a Phase 3, randomised, stratified, observer blind, active controlled study to evaluate the immunogenicity, reactogenicity and safety of an optimized mRNA-1010 seasonal

influenza vaccine in adults 18 years and older. Part A, the initial evaluation of the optimized vaccine, was conducted from Apr to Nov 2023 in the US. Based on the favourable results in Part A (which used vaccines per WHO NH 2022/2023 recommendations, did not have a high-dose comparator for participants ≥65 years, and did not include superiority as a prespecified evaluation), Parts B and C were conducted in separate age groups using age-appropriate comparators. Study mRNA- 1010-P303 Parts B and C were conducted in the US from Nov 2023 to Jun 2024 and used vaccines per WHO NH 2023/2024 recommendations. The immunogenicity objectives in Study mRNA-1010-P303 Parts B and C were to evaluate the noninferiority (primary) and superiority (secondary) of the humoral immune response to mRNA-1010 versus an authorised standard-dose (Part B) or high-dose (Part C) influenza vaccine as measured by GMT and SCR at Day 29 by HAI assay for all influenza A and B strains contained in the vaccine. In Part B, participants ≥18 to <65 years were randomised 1:1 to receive a single IM dose of mRNA-1010 (N=1498) or authorised standard-dose influenza vaccine (N=1490). In Part C, participants ≥65 years were randomised 1:1 to receive a single IM dose of mRNA-1010 (N=1504) or authorised high-dose influenza vaccine (N=1492).

Noninferiority and superiority of mRNA-1010 were demonstrated at Day 29 for all influenza A and B strains contained in the vaccine compared with an authorised standard dose influenza vaccine (Fluarix QIV) among participants ≥18 to <65 years in Part B based on GMR and SCR difference and compared with an authorised high-dose influenza vaccine (Fluzone HD QIV) among participants ≥65 years in Part C based on GMR and SCR difference.

Study mRNA-1010-P304

Study mRNA-1010-P304 was a Phase 3, randomised, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 candidate seasonal influenza vaccine compared with an authorised inactivated seasonal influenza vaccine in adults ≥50 years of age. Participants were randomised in a 1:1 ratio to receive a single injection of either mRNA-1010 or SD comparator. Randomisation was stratified by age category at Screening and influenza vaccine status in the previous influenza season. Approximately 50% of enrolled participants were to be ≥65 years of age at Screening, including approximately 10% who were ≥75 years of age at Screening. The study initiation date was 16 Sep 2024 (first participant first visit) and the presented analyses are based on a data cutoff date of 30 Apr 2025 and database lock of 03 Jun 2025. This multi-centre study was conducted at 301 sites in 11 countries in North America, Europe, and East Asia. A total of 40,805 participants were randomised in this study.

The primary objectives of the study were to evaluate the safety and reactogenicity of mRNA-1010 and to evaluate rVE of mRNA-1010 versus an active comparator against RT-PCR-confirmed protocol-defined ILI caused by any influenza A or B strains. The primary efficacy endpoint of this study was the "First episode of RT-PCR-confirmed protocol-defined ILI that begins at least 14 days after study intervention through the end of the influenza season caused by any influenza A or B strains". An RT-PCR-confirmed protocol-defined ILI required a positive nasopharyngeal (NP) swab test for influenza by RT-PCR. In addition, both of the following symptoms had to be present within ±7 days of the NP swab collection date:

- at least 1 systemic symptom (oral temperature >37.2°C (>99.0°F), chills, feverish, tiredness, headaches, or myalgia), AND
- at least 1 respiratory illness symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing)

The secondary objectives included additional efficacy evaluations based on other ILI case definitions and the evaluation of the humoral immunogenicity of mRNA-1010 relative to that of an active comparator against vaccine-matched influenza A and B strains in a subset of 2400 participants from

North America where trivalent influenza vaccine (TIV) SD comparator was used. The evaluation of HAI titres as a surrogate of risk and protection against RT-PCR-confirmed protocol-defined ILI (CoR and CoP) for mRNA-1010 and an active comparator was an additional secondary objective.

Under the assumption of proportional hazards and with 1:1 randomisation of mRNA-1010 and active comparator, a total of 836 cases in the PP Set will provide at least 80% power to establish an NI claim with a selected NIM of 10% (i.e., H_0[1]: rVE ≤-10%) assuming a true rVE of 10% using a log-rank test statistic with an overall 1-sided Type I error rate of 2.5%.

This study enrolled medically stable adult participants >50 years of age. A key exclusion criterion was any history of a diagnosis or condition that, in the judgment of the Investigator, was clinically unstable or could affect participant safety, assessment of study endpoints including immune response, or adherence to study procedures. In addition, participants who received an authorised seasonal influenza vaccine within 180 days (or planned anytime during study) or any vaccine approved by a local health agency within 28 days prior to Day 1 (Baseline) or any planned vaccine within 14 days after Day 1 were excluded.

mRNA-1010 was administered as a single intramuscular (IM) injection at a total mRNA dose level of 37.5 µg (TIV, 12.5 µg per strain). The SD comparator administered in this study was an SD authorised inactivated seasonal influenza vaccine administered as a single IM injection. Study interventions were administered such that TIV/quadrivalent influenza vaccine (QIV) comparator use was dictated by region, with TIV used in North America and QIV in the Rest of the World (Europe and East Asia).

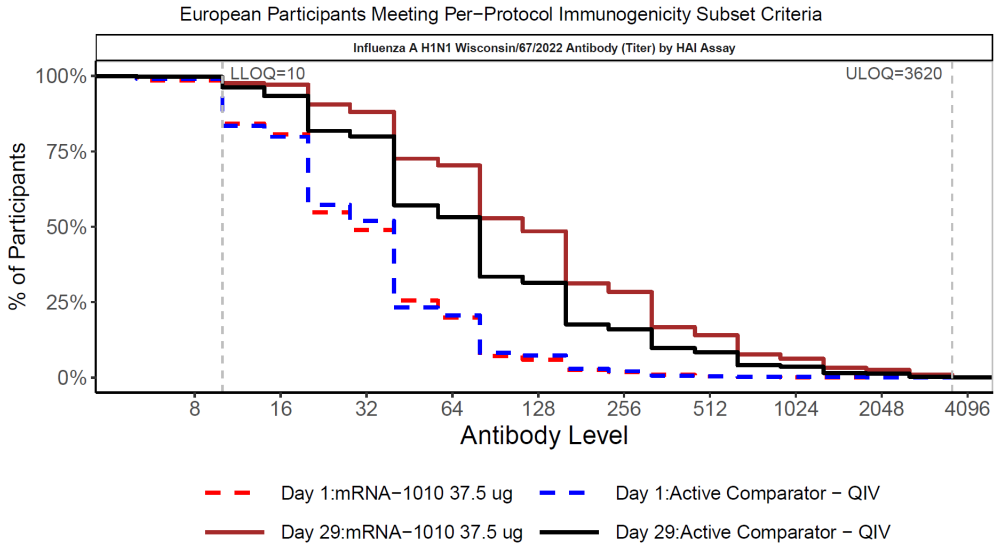
As of the data cut-off, a total of 40,805 participants were randomised: 20,402 to the mRNA-1010 group and 20,403 to the SD comparator group. Of the total randomised, 40,703 (99.8%) participants (20,349 [99.7%] in the mRNA-1010 group vs 20,354 [99.8%] in the SD comparator group) received study injection. Discontinuations from the study were similar between the groups. The most common reason for discontinuation in both groups was lost to follow-up (402 [2.0%] participants vs 394 [1.9%] participants). No study discontinuations were due to reactogenicity, 3 participants in each group discontinued due to an unsolicited AE.

The Safety Set included a total of 40,703 adults with a median (range) age of 64.0 years (50 to 97 years). More than half of the participants were female (23,149 [56.9%] participants). The racial composition was as follows: 33,625 (82.6%) participants were White, 5385 (13.2%) participants were Black or African American, with 4214 (10.4%) identifying as Hispanic or Latino. Almost half of the participants (19,116 [47.0%]) had received a seasonal influenza vaccine in the previous 12 months at the time of Screening. Frailty testing was assessed in participants aged ≥65 years, among whom more than 25% of the population was considered vulnerable or frail. There were no notable differences in the demographic characteristics between the mRNA-1010 and SD comparator groups.

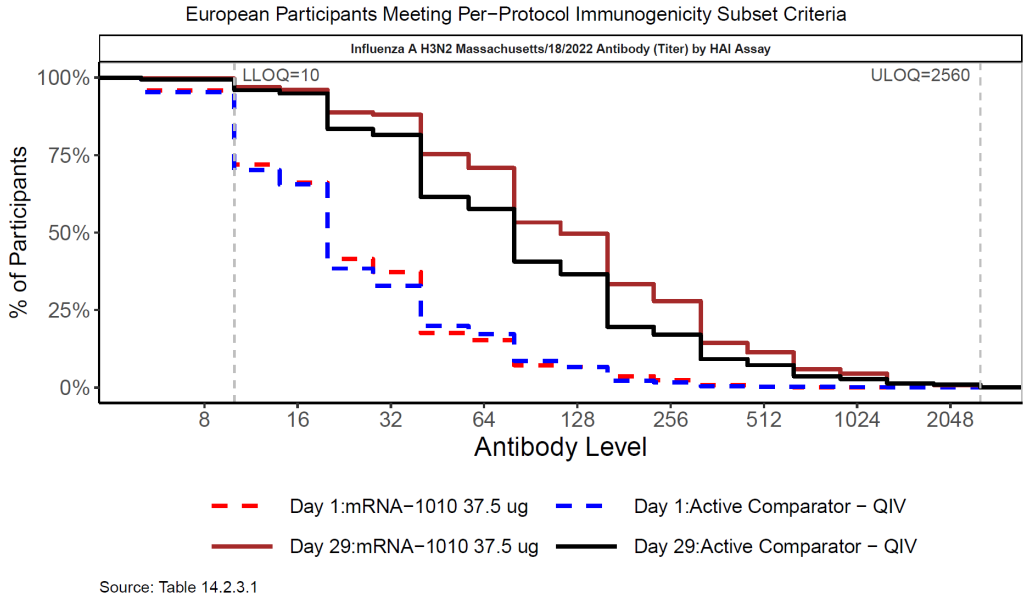
In adults ≥50 years of age, a single dose of mRNA-1010 (37.5 µg; TIV) demonstrated higher efficacy than SD comparator vaccine in the prevention of RT-PCR-confirmed protocol-defined ILI. As of the data cut-off, a total of 968 participants (411 [2.0%] participants in the mRNA-1010 group and 557 [2.8%] participants in the SD comparator group) had RT-PCR-confirmed protocol-defined ILI in the PP Set. The rVE was 26.6% (95% CI: 16.7, 35.4), which met all prespecified efficacy success criteria. The rVE of mRNA-1010 was evident across A and B influenza strains with consistent rVE point estimates, including for influenza B (A/H1N1=29.6% [95% CI: 16.4, 40.7]; A/H3N2=22.2% [95% CI: 4.3, 36.9]; and B=29.1% [95% CI: -18.5, 57.5]). rVE was also consistent across population subgroups, including the subgroup of adults 65 years of age an older where mRNA-1010 rVE was 27.4% (95% CI: 12.1, 40.0). The robustness of mRNA-1010 efficacy was also evident in the consistency of rVE across different ILI case definitions, including the secondary efficacy endpoint with the modified CDC-defined ILI case definition (rVE: 23.5% [95% CI: 9.0, 35.8]).

The HAI Ab responses (Day 29 GMTs, seroconversion rates [SCRs], and GMFRs) were higher in the mRNA-1010 than in the SD comparator for all tested influenza strains: The GMR point estimates were A/H1N1: 1.824 [95% CI: 1.691, 1.967]; A/H3N2: 1.589 [95% CI: 1.476, 1.711]; B: 1.673 [95% CI: 1.574, 1.778]. The SCR differences were A/H1N1: 27.95% [95% CI: 24.09, 31.73]; A/H3N2: 19.99% (95% CI: 15.99, 23.92); B: 25.33% [95% CI: 21.65, 28.95]. The higher Ab responses to mRNA-1010 vs SD comparator (i.e., GMR and SCR difference, for A/H1N1, A/H3N2, and B/Victoria) were evident across study subgroups, including the subgroup of adults 65 years and older. The RCDCs also indicated higher Ab responses after mRNA-1010 compared with the standard dose comparator.

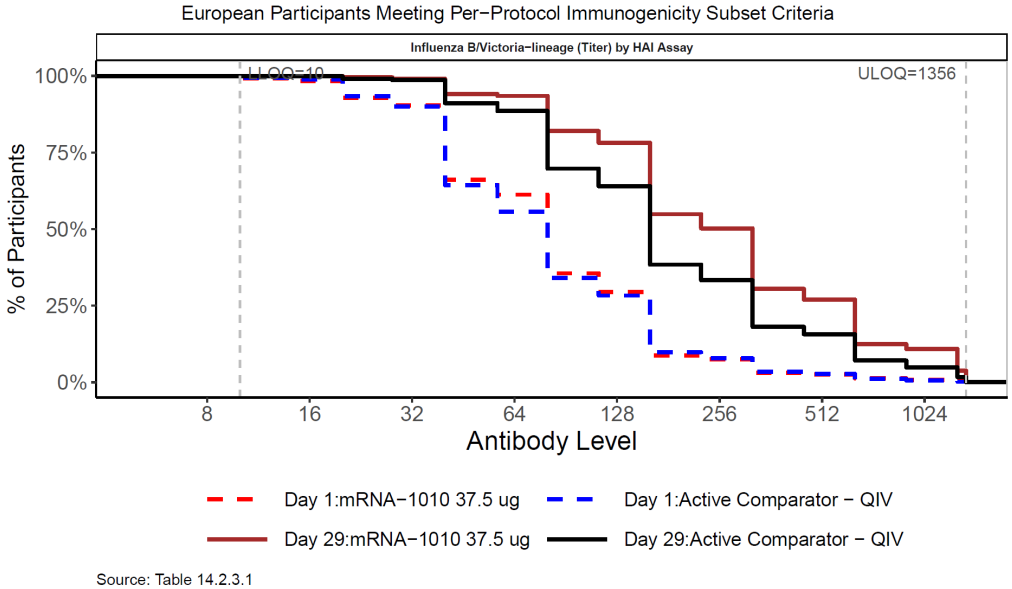
Figure 17 Reverse Cumulative Distribution Function of Antibody Levels for Vaccine-Matched Influenza A and B strains – European participants



Source: Table 14.2.3.1



Source: Table 14.2.3.1



Source: Table 14.2.3.1

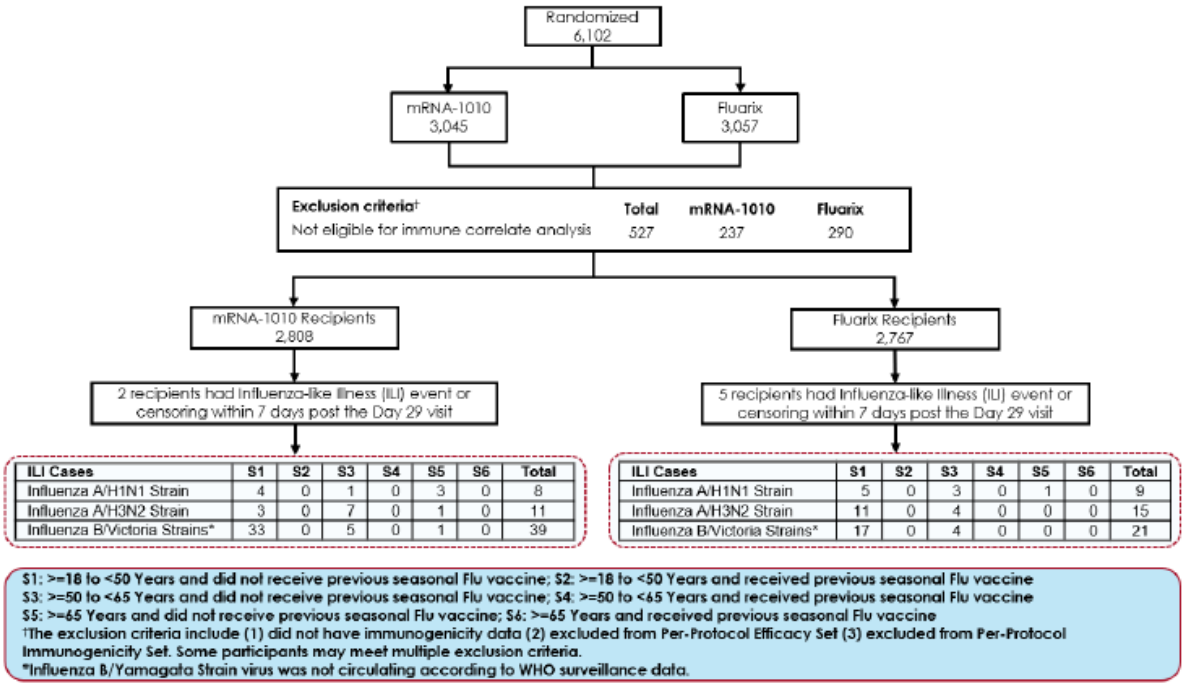
Correlate of protection reports

Correlate of protection report mRNA-1010-P301

Study P301 collected immunogenicity (anti-HA data) in all participants and vaccine efficacy was a secondary objective with active surveillance for cases. The availability of both immunogenicity and efficacy data for all participants in P301 enabled a detailed analysis of the predictiveness of HAI titres on the likelihood of protection against influenza infection.

The figure below displays the flow chart for the selection of the Day 29 marker analysis set from all randomised participants. The Day 29 marker analysis set was a subset of the participants in both the per-protocol (PP) efficacy set and per-protocol immunogenicity (PP IMM). Participants who had a strain-specific ILI event or were censored within 7 days post their Day 29 visit were excluded from correlate analysis, due to the concern that their Day 29 HAI titre may have been impacted by the potential influenza virus infection, hence not suitable for the analysis of CoR/CoP.

Figure 18: Flow chart of deriving Day 29 marker analyses sets for seasonal influenza endpoints of ILI caused by influenza A/H1N1, A/H3N2 and B/Victoria strains



ILI Cases	S1	S2	S3	S4	S5	S6	Total
Influenza A/H1N1 Strain	4	0	1	0	3	0	8
Influenza A/H3N2 Strain	3	0	7	0	1	0	11
Influenza B/Victoria Strains*	33	0	5	0	1	0	39

ILI Cases	S1	S2	S3	S4	S5	S6	Total
Influenza A/H1N1 Strain	5	0	3	0	1	0	9
Influenza A/H3N2 Strain	11	0	4	0	0	0	15
Influenza B/Victoria Strains*	17	0	4	0	0	0	21

S1: >=18 to <50 Years and did not receive previous seasonal Flu vaccine; S2: >=18 to <50 Years and received previous seasonal Flu vaccine
S3: >=50 to <65 Years and did not receive previous seasonal Flu vaccine; S4: >=50 to <65 Years and received previous seasonal Flu vaccine
S5: >=65 Years and did not receive previous seasonal Flu vaccine; S6: >=65 Years and received previous seasonal Flu vaccine
†The exclusion criteria include (1) did not have immunogenicity data (2) excluded from Per-Protocol Efficacy Set (3) excluded from Per-Protocol Immunogenicity Set. Some participants may meet multiple exclusion criteria.
*Influenza B/Yamagata Strain virus was not circulating according to WHO surveillance data.

A Cox proportional hazard (PH) regression model was used to study the Day 29 HAI titres as CoRs and potential CoPs against the strain-specific ILI endpoints including A/H1N1-ILI, A/H3N2-ILI, and B/Victoria-ILI, adjusted by the baseline risk scores. The Day 29 marker analysis set was used to conduct the analysis for each strain-specific ILI endpoint respectively, and participants who had early ILI event or censoring within 7 days post Day 29 visit were excluded from the analysis. A stepwise approach was applied, starting with univariate analyses. After determining that the univariate analyses performed as expected, more complex multivariate analyses were conducted to account for potential interrelatedness between the responses measured against all 4 strains.

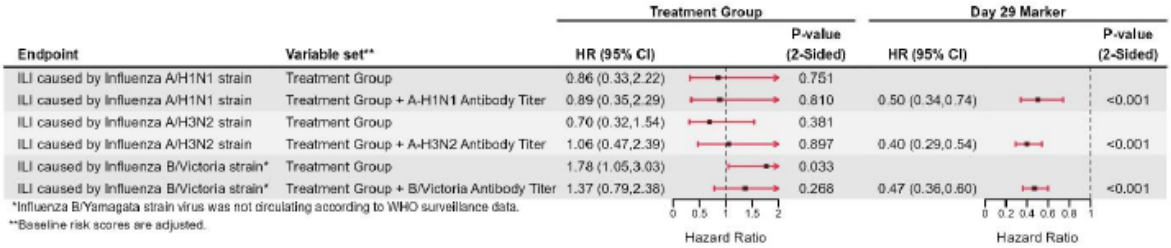
For each ILI endpoint caused by each strain, two parsimonious Cox PH regression models were conducted.

Model 1 included the strain-specific ILI endpoint as the dependent variable with the treatment group as a single covariate adjusted by the baseline risk scores. Results from this model are presented in the figure below in the rows with 'variable set' as 'treatment group' and represent the marginal treatment effect (mRNA-1010 vs. Fluarix).

Model 2 included the strain-specific ILI endpoint as the dependent variable, the treatment group and strain-specific Day 29 HAI titre were covariates, adjusted by the baseline risk scores. Results from this model are presented in the figure below in rows with 'variable set' as 'treatment group + corresponding antibody titres'. The conditional effects of the treatment group, and Day 29 HAI titre are presented respectively.

The figure below displays the corresponding Cox PH model summary for the marginal treatment effect, and the conditional effects for the treatment group and the Day 29 HAI titre respectively. According to the Applicant, the univariate-antibody Cox PH regression model indicates that the strain-specific Day 29 HAI titre is CoR/CoP for the strain-specific ILI endpoint, hence supporting Day 29 HAI titre as surrogate endpoint for seasonal influenza vaccine efficacy for both mRNA-1010 and Fluarix vaccines.

Figure 19: Cox PH regression model summary for studying correlates of the strain-specific day 29 HAI titre with the corresponding strain specific ILI endpoints including A/H1N1-ILI, A/H3N2-ILI and B/Victoria-ILI conditional on the treatment group by adjusting baseline risks scores



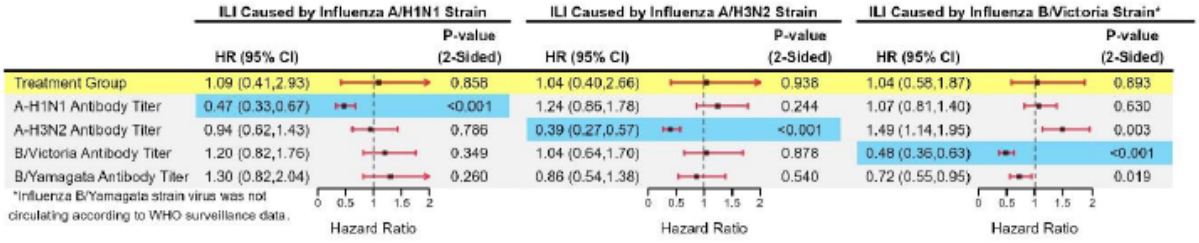
		Treatment Group		Day 29 Marker	
Endpoint	Variable set**	HR (95% CI)	P-value (2-Sided)	HR (95% CI)	P-value (2-Sided)
ILI caused by Influenza A/H1N1 strain	Treatment Group	0.86 (0.33,2.22)	0.751		
ILI caused by Influenza A/H1N1 strain	Treatment Group + A-H1N1 Antibody Titer	0.89 (0.35,2.29)	0.810	0.50 (0.34,0.74)	<0.001
ILI caused by Influenza A/H3N2 strain	Treatment Group	0.70 (0.32,1.54)	0.381		
ILI caused by Influenza A/H3N2 strain	Treatment Group + A-H3N2 Antibody Titer	1.06 (0.47,2.39)	0.897	0.40 (0.29,0.54)	<0.001
ILI caused by Influenza B/Victoria strain*	Treatment Group	1.78 (1.05,3.03)	0.033		
ILI caused by Influenza B/Victoria strain*	Treatment Group + B/Victoria Antibody Titer	1.37 (0.79,2.38)	0.268	0.47 (0.36,0.60)	<0.001

*Influenza B/Yamagata strain virus was not circulating according to WHO surveillance data.
**Baseline risk scores are adjusted.

Day 29 HAI titer demonstrated statistically significant correlates with the ILI endpoints. Conditional on the Day 29 HAI titer, the treatment effect is not statistically significant

Further, multivariate Cox PH models were carried out for each of the influenza endpoints of ILI caused by influenza A/H1N1, A/H3N2, and B/Victoria respectively. Each of these 3 models incorporate treatment groups (mRNA-1010, Fluarix), Day 29 HAI titres for all 4 strains, and are adjusted by the baseline risk scores. The figure below displays the corresponding multivariable-antibody Cox PH model summary for each strain-specific ILI endpoint including the hazard ratio in treatment group and per an SD increase in each Day 29 HAI titre and the corresponding p-values.

Figure 20: Summary of multivariate analysis of day 29 HAI titres for predicting influenza infections caused by each strain type



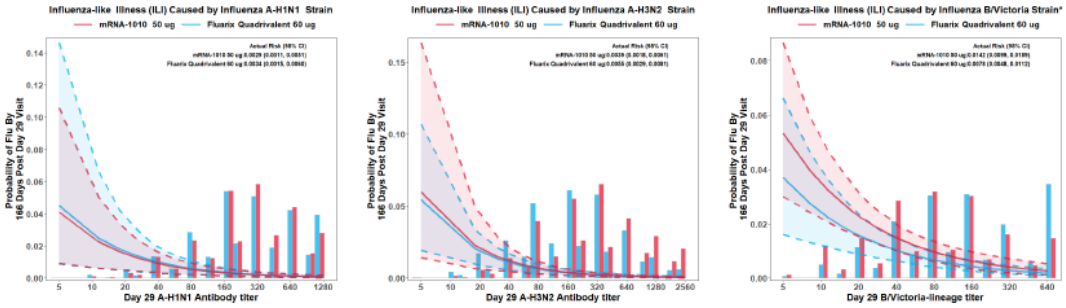
	ILI Caused by Influenza A/H1N1 Strain		ILI Caused by Influenza A/H3N2 Strain		ILI Caused by Influenza B/Victoria Strain*	
	HR (95% CI)	P-value (2-Sided)	HR (95% CI)	P-value (2-Sided)	HR (95% CI)	P-value (2-Sided)
Treatment Group	1.09 (0.41,2.93)	0.858	1.04 (0.40,2.66)	0.938	1.04 (0.58,1.87)	0.893
A-H1N1 Antibody Titer	0.47 (0.33,0.67)	<0.001	1.24 (0.86,1.78)	0.244	1.07 (0.81,1.40)	0.630
A-H3N2 Antibody Titer	0.94 (0.62,1.43)	0.786	0.39 (0.27,0.57)	<0.001	1.49 (1.14,1.95)	0.003
B/Victoria Antibody Titer	1.20 (0.82,1.76)	0.349	1.04 (0.64,1.70)	0.878	0.48 (0.36,0.63)	<0.001
B/Yamagata Antibody Titer	1.30 (0.82,2.04)	0.260	0.86 (0.54,1.38)	0.540	0.72 (0.55,0.95)	0.019

*Influenza B/Yamagata strain virus was not circulating according to WHO surveillance data.

For analysis of each endpoint, the multivariate model included treatment group, Day 29 HAI titers against all strains and baseline risk scores.
ILI caused by Influenza B cases were assumed to be B/Victoria based on epidemiologic data showing no circulation of B/Yamagata.

Based on the fitted multivariate Cox PH models for ILI caused by a specific strain, the predictive risk of getting ILI caused by each strain was estimated by Day 29 A/H1N1, Day 29 A/H3N2, and Day 29 B/Victoria HAI titres by averaging the potential confounding covariates including non-strain-specific HAI titres and baseline risk scores. The predictive risk of ILI by Day 29 HAI titres as well as the bootstrapped pointwise 95% Confidence intervals are presented in the figure below.

Figure 21: Influenza infection risk given by strain type day 29 HAI biomarker titre level by strain type



*ILI caused by B strains were assumed to be B/Victoria based on epidemiology data showing no circulation of B/Yamagata.

The histograms display the distribution of D29 HAI titers of the Fluarix (blue) and the mRNA-1010 (red) recipients. The probability of having ILI (solid line) was estimated individually for Fluarix (blue) and mRNA-1010 (red) recipients; and the confidence interval (dotted line) was determined through bootstrap resampling.

Correlate of protection report mRNA-1010-P304

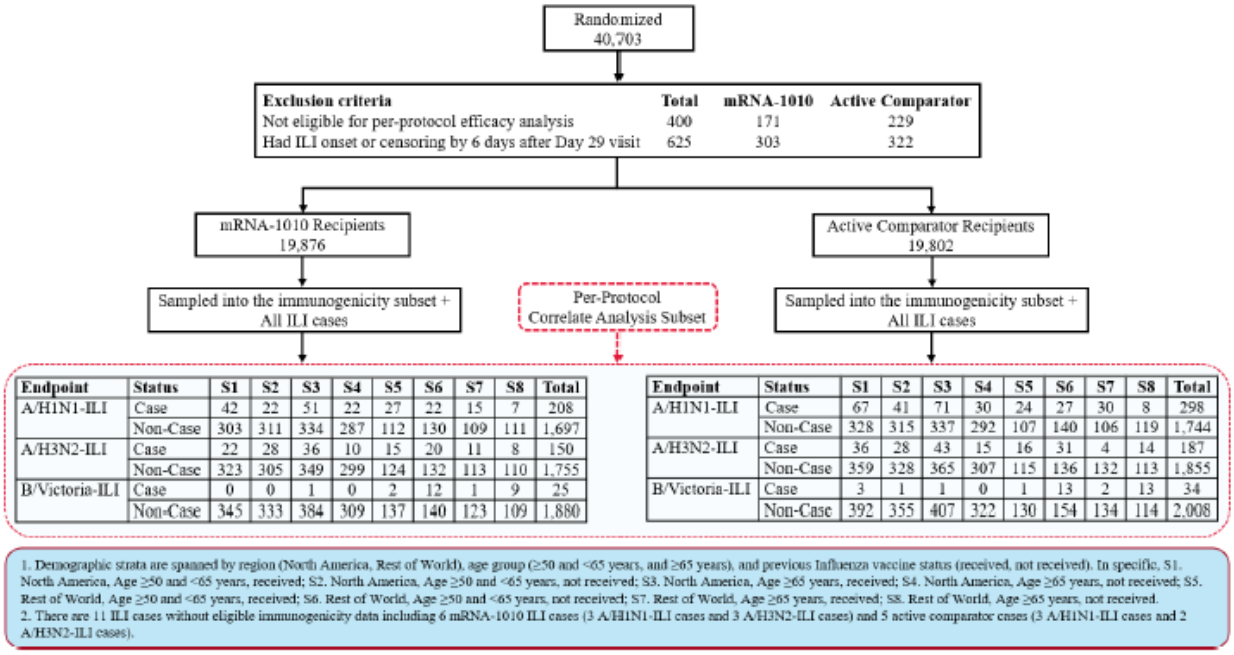
The applicant provided an immune correlate analysis for the P304 study, conducted in accordance with the CoP statistical analysis plan (Version 2.0, dated 18-Apr-2025) with prespecified statistical criteria. According to the applicant, the primary objective of this analysis was not to establish HAI titres as a surrogate endpoint, it aligns with a longstanding precedent in the influenza field supporting HAI as a surrogate reasonably likely to predict clinical benefit. The approach in Study P304 is to provide modern, causal inference–based evidence that HAI titres continue to fulfill this role for mRNA-based influenza vaccines, such as mRNA-1010, in the same manner as for egg-based influenza vaccines.

The study cohort for the immune correlates analysis comprised all participants in the Per Protocol Set (PPS), excluding those who experienced an ILI event caused by any influenza A or B strain, or were censored prior to 6 days after Day 29 visit. This exclusion criterion was applied to adjust potential bias from natural influenza infection that could alter Day 29 HAI titres.

A pre-specified case-cohort sampling design was implemented to assess Day 1 (baseline) and Day 29 HAI titres. This design involved a stratified random sample of trial participants from the Full Analysis Set (FAS) along with all RT-PCR confirmed ILI cases caused by any influenza A or B strain. The random sample was stratified by the key baseline covariates: region (North America vs. Rest of the world), age group (≥50 and <65 years vs. ≥65 years), and influenza vaccination status in the previous influenza season (received vs. not received).

The Per-Protocol Correlate Analysis Subset (PPCAS) includes participants from the case-cohort immunogenicity subset who also met the inclusion criteria for the immune correlate study cohort. Within the PPCAS, the stratified random subcohort is referred to as the "immunogenicity subcohort". The PPCAS serves as the analysis population for all immune correlate analyses (see figure below). For each participant in the PPCAS, an inverse probability of sampling weight (IPSweight) was calculated and applied to account for the case-cohort sampling design.

Figure 22: Flow Chart of Study Participants From Full Analysis Set (FAS) to the Per-Protocol Correlate Analysis Set (PPCAS) for Seasonal Influenza Endpoints of Influenza-like Illness Caused by Influenza A/H1N1, A/H3N2, and B/Victoria Strains



Abbreviations: ILI = influenza-like illness; mRNA = messenger RNA.

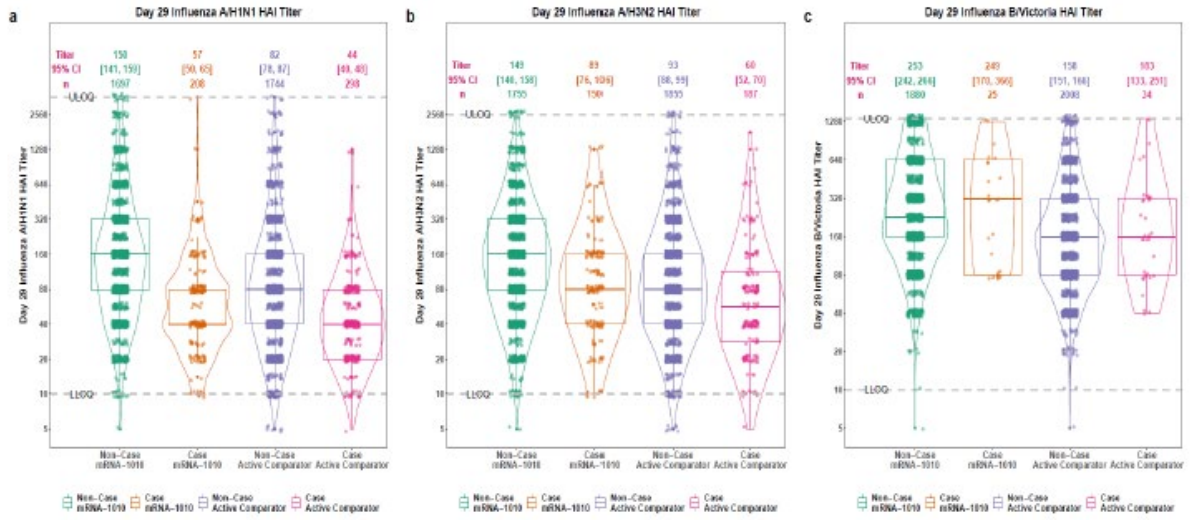
For influenza A-strains (A/H1N1 and A/H3N2), the GMT at Day 29 were significantly lower in the corresponding strain ILI cases compared to non-cases in both mRNA-1010 and active comparator vaccine groups with lower bounds of 95% CIs less than 1. For influenza B/Victoria, the pattern was less consistent. In the mRNA-1010 group, Day 29 HAI titres were numerically lower in B/Victoria-ILI cases than in non-cases, although the case-to non-case GMT ratio was not statistically significant. Conversely, in the active comparator group, Day 29 HAI titres were numerically higher in B/Victoria-ILI cases than in non-cases (see table and figure below).

Table 26: Day 29 Influenza Strain-Specific HAI GMT by the Corresponding Strain ILI Case/Non-Case Strata in mRNA-1010 and Active Comparator Vaccine Group in the PPCAS.

Immunologic Marker	Treatment Group	Cases GMT (95% CI)		Non-Cases GMT (95% CI)		Ratio of GMT (Cases/Non-Cases) (95% CI)
		n	Day 29 HAI	n	Day 29 HAI	
Influenza A/H1N1 HAI Titer	mRNA-1010	208	57 (50, 65)	1697	150 (141, 159)	0.4 (0.3, 0.4)
	Active Comparator	298	44 (40, 48)	1744	82 (78, 87)	0.5 (0.5, 0.6)
Influenza A/H3N2 HAI Titer	mRNA-1010	150	89 (76, 106)	1755	149 (140, 158)	0.6 (0.5, 0.7)
	Active Comparator	187	60 (52, 70)	1855	93 (88, 99)	0.6 (0.5, 0.8)
Influenza B/Victoria HAI Titer	mRNA-1010	25	249 (170, 366)	1880	253 (242, 266)	1.0 (0.7, 1.4)
	Active Comparator	34	183 (133, 251)	2008	158 (151, 166)	1.2 (0.8, 1.6)

Abbreviations: CI = confidence interval; GMT = geometric mean titer ratio; mRNA = messenger RNA.

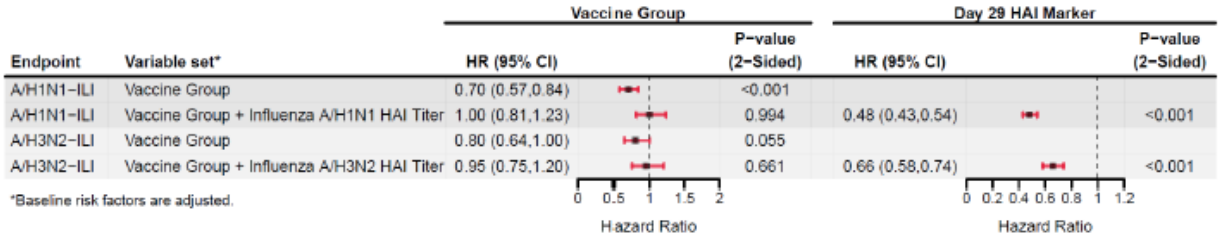
Figure 23: Day 29 Influenza Strain-Specific HAI Antibody Titres by the Corresponding Strain ILI Case/Non-Case Strata in mRNA-1010 and Active Comparator Vaccine Group in the PPCAS



Abbreviations: CI = confidence interval; mRNA = messenger RNA.

The summary of the CoR regression model for evaluating the correlates of the Day 29 A-strain HAI titres with the corresponding A-Strain ILI endpoints conditional on the Vaccine Group by adjusting baseline risk factors is shown in the figure below.

Figure 24: Cox Regression Model Summary for Evaluating the Correlates of the Day 29 A-strain HAI Titres with the Corresponding A-Strain ILI Endpoints Conditional on the Vaccine Group by Adjusting Baseline Risk Factors

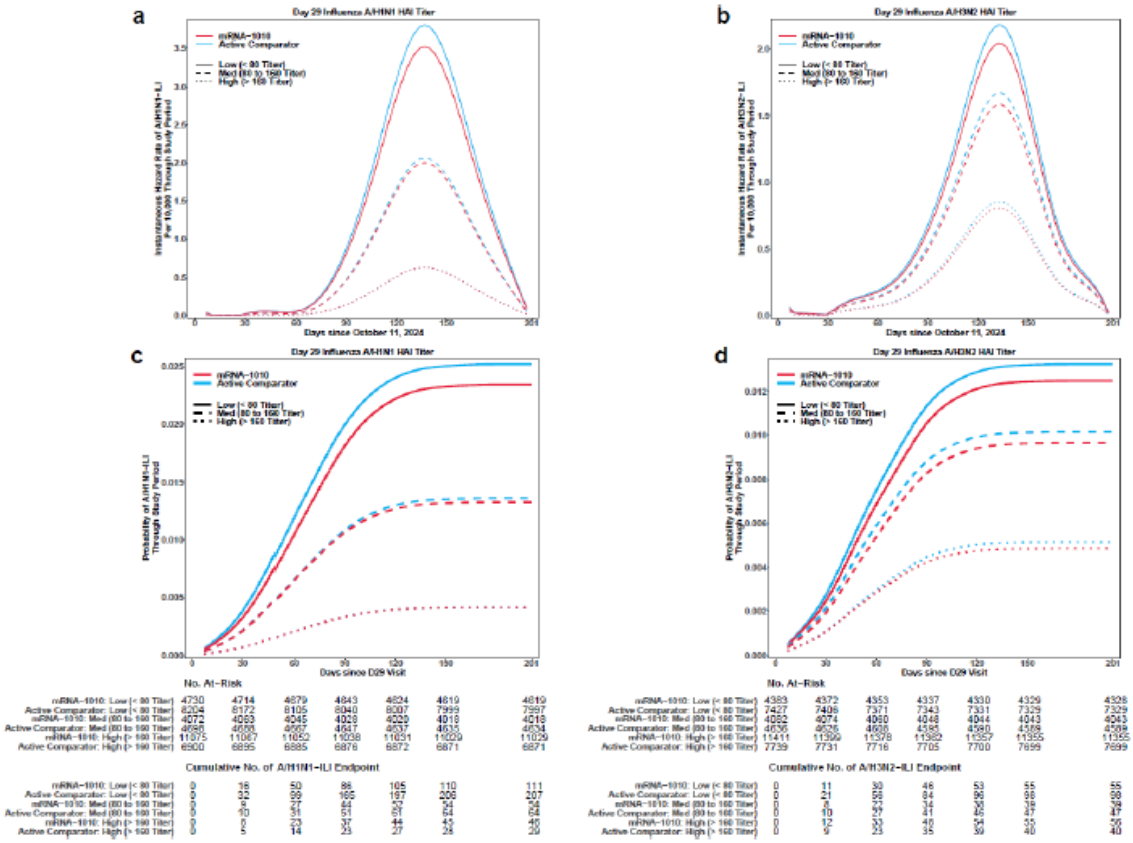


Abbreviations: CI = confidence interval; HR = hazard ratio; ILI = influenza-like illness; WHO = World Health Organization.

Day 29 HAI titer demonstrated statistically significant correlates with the ILI endpoints. Conditional on the Day 29 HAI titer, the treatment effect is not statistically significant.

The secondary CoR analysis was performed to evaluate the association between categorical Day 29 A-strain HAI titre levels, defined by tertiles (low, medium, high), and the risk of the corresponding strain ILI endpoint for both influenza A strains. The tertiles were determined using the one-third and two-third quantiles of the overall Day 29 A-strain HAI titres across both vaccine groups. The figure below displays the covariate-adjusted instantaneous hazard rate and cumulative incidence of A-strain ILI by Day 29 A-strain HAI titre tertiles in both the mRNA- 1010 and active comparator vaccine groups.

Figure 25: Influenza A-Strain ILI Risk By the Corresponding Day 29 A-Strain HAI Tertiles in mRNA-1010 and Active Comparator Vaccine Groups in the PPCAS



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Endpoint	Day 29 HAI Marker	Tertile	No. Case/No. At-Risk (Attack Rate)† mRNA-1010	No. Case/No. At-Risk (Attack Rate)† Active Comparator	Hazard Ratio Point Est. (95% CI)	P-value (2-Sided)	Overall P-value (2-Sided)	FWER-Adjusted P-value	FDR-Adjusted P-value
A/H1N1-ILI	Influenza A/H1N1 HAI Titer	Low (< 80 Titer)	111/4728 (0.0235)	207/8201 (0.0252)	1 (N/A)	N/A	< 0.001	< 0.001	< 0.001
		Med (80 to 160 Titer)	54/4071 (0.0133)	64/4697 (0.0136)	0.57 (0.45,0.72)	< 0.001			
		High (> 160 Titer)	46/11074 (0.0042)	29/6899 (0.0042)	0.19 (0.14,0.24)	< 0.001			
A/H3N2-ILI	Influenza A/H3N2 HAI Titer	Low (< 80 Titer)	55/4381 (0.0126)	98/7424 (0.0132)	1 (N/A)	N/A	< 0.001	< 0.001	< 0.001
		Med (80 to 160 Titer)	39/4081 (0.0096)	47/4634 (0.0101)	0.79 (0.59,1.05)	0.100			
		High (> 160 Titer)	56/11409 (0.0049)	40/7738 (0.0052)	0.41 (0.31,0.54)	< 0.001			

Abbreviations: CI = confidence interval; HR = hazard ratio; ILI = influenza-like illness; HAI = hemagglutination inhibition.

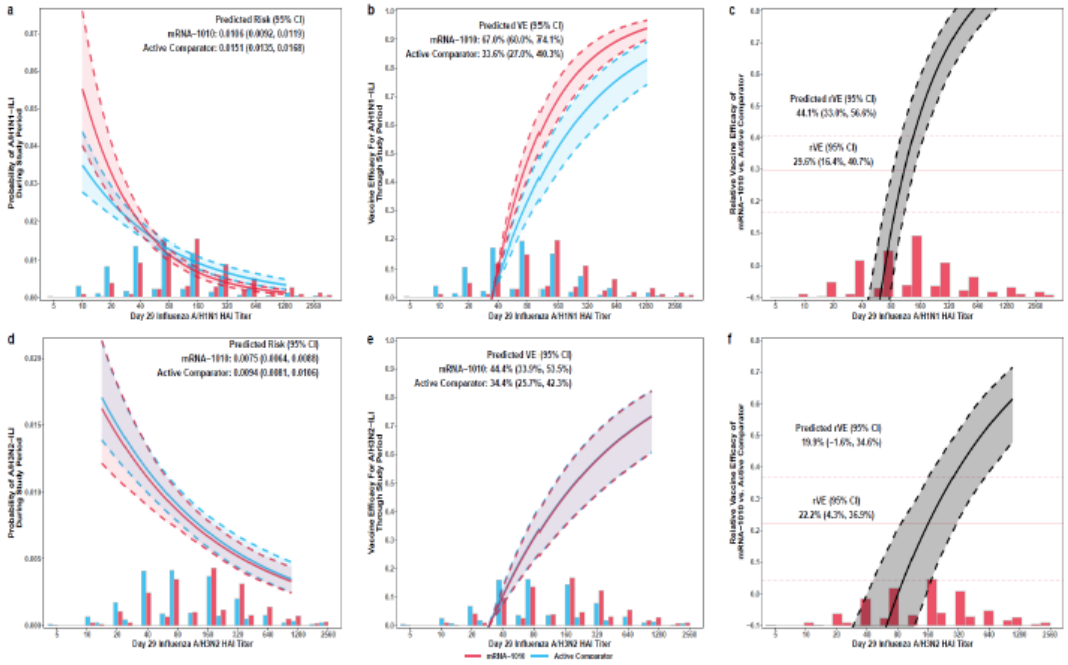
Baseline risk factors (Age group: 50 – 64 years of age vs. ≥65 years of age; previous influenza vaccine status: received vs. not received; baseline risk scores) were adjusted in the Cox regression models. The maximum follow-up time after Day 29 visit is 201 days.

†No. Case: Estimated number of participants in the study cohort receiving mRNA-1010 or the active comparator vaccine with the strain-specific ILI onset by 201 days post Day 29 visit. No. At-Risk: Estimated number of participants in the study cohort receiving mRNA-1010 or the active comparator vaccine not experiencing the strain-specific ILI endpoint onset by 6 days post Day 29 visit.

The figure below shows the primary and secondary CoP analysis for A-strain ILI endpoints based on the corresponding Day 29 A-strain HAI titres, including:

1. marginalized covariate-adjusted cumulative incidence curves of A-strain ILI during the study period across a range of assigned Day 29 A-strain HAI titres by mRNA-1010 and the active comparator
2. counterfactual placebo-controlled vaccine efficacy against A-strain ILI across the same titre range by mRNA-1010 and the active comparator
3. relative vaccine efficacy (rVE) against A-strain ILI across a range of Day 29 A-strain HAI titres for mRNA-1010 as compared to active comparator.

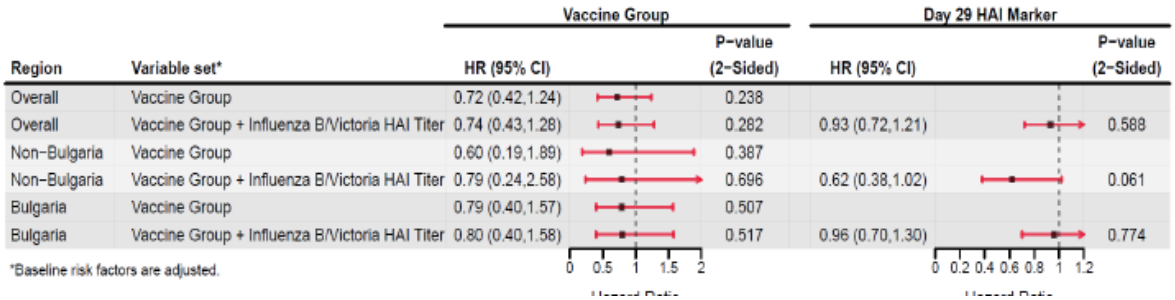
Figure 26: Primary and Secondary CoP Analysis for A-Strain ILI Endpoints by Corresponding Day 29 A-Strain HAI Titres



Abbreviations: CI = confidence interval; HAI = hemagglutination inhibition; ILI = influenza-like illness; mRNA = messenger ribonucleic acid; rVE = relative vaccine efficacy; VE = vaccine efficacy.
(a) and (d): Solid red (mRNA-1010) and blue (the active comparator) curves demonstrate point estimates of the marginalized covariate-adjusted cumulative incidence of A/H1N1 and A/H3N2 ILI endpoints during the study period by mRNA-1010 and the active comparator vaccine across a range of assigned HAI titers (within 2.5th to 97.5th percentiles of observed Day 29 HAI titers in both the mRNA-1010 and the active comparator vaccine groups). Dashed red and blue curves along with the shades represent the bootstrap pointwise 95% CIs. (b) and (e): Solid red and blue curves represent point estimates of counterfactual-placebo controlled vaccine efficacy of A/H1N1 and A/H3N2 ILI endpoints during the study by mRNA-1010 (red) and the active comparator vaccine (blue) across a range of HAI titers. And the dashed curves are for the corresponding bootstrap pointwise 95% CIs. (c) and (f): Solid black curve shows the point estimate of rVE for mRNA-1010 across a range of specified HAI titers, remaining above -10%. The dashed black curve is for the corresponding bootstrap pointwise 95% CI. The histograms of the observed Day 29 HAI titers by mRNA-1010 (red) and the active comparator (blue) are overlayed on the bottom of cumulative incidence plots (a, d), VE plots (b, e), and rVE plots (c, f) (only mRNA-1010 was shown). Baseline risk factors are adjusted in the IPS-weighted Cox regression model.

The summary of the CoR regression model for evaluating the correlate of Day 29 B/Victoria HAI titre and the respective ILI Endpoint by regions in the PPCAS is shown in the figure below.

Figure 27: CoR Regression Model Summary for Evaluating the Correlate of Day 29 B/Victoria HAI titre and the respective ILI Endpoint by Regions in the PPCAS



Region	Variable set*	Vaccine Group HR (95% CI)	Vaccine Group P-value (2-Sided)	Day 29 HAI Marker HR (95% CI)	Day 29 HAI Marker P-value (2-Sided)
Overall	Vaccine Group	0.72 (0.42,1.24)	0.238		
Overall	Vaccine Group + Influenza B/Victoria HAI Titer	0.74 (0.43,1.28)	0.282	0.93 (0.72,1.21)	0.588
Non-Bulgaria	Vaccine Group	0.60 (0.19,1.89)	0.387		
Non-Bulgaria	Vaccine Group + Influenza B/Victoria HAI Titer	0.79 (0.24,2.58)	0.696	0.62 (0.38,1.02)	0.061
Bulgaria	Vaccine Group	0.79 (0.40,1.57)	0.507		
Bulgaria	Vaccine Group + Influenza B/Victoria HAI Titer	0.80 (0.40,1.58)	0.517	0.96 (0.70,1.30)	0.774

*Baseline risk factors are adjusted.

5.3.3. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.4. Overall discussion and conclusions on clinical efficacy

Discussion

The proposed indication for the mCOMBRIAX vaccine was the prevention of diseases associated with seasonal influenza viruses represented in the vaccine and SARS-CoV-2 in individuals 50 years of age and older.

The development program of mRNA-1083 comprises a completed Phase 1/2 dose-ranging study (mRNA-1083-P101) and a completed Phase 3 study (mRNA-1083-P301).

Additionally, the applicant provided several supportive studies, including several Phase 3 studies evaluating the safety, reactogenicity and immunogenicity/relative vaccine efficacy of the single components (mRNA-1283 and mRNA-1010) of the mRNA-1083 vaccine. Further, the applicant provided correlate of risk/protection reports based on the results of study mRNA-1010-P301/mRNA-1010-P304 to demonstrate HAI titres continue to fulfil the role of a surrogate reasonably likely to predict benefit for mRNA-based influenza vaccines, such as mRNA-1010, in the same manner as for egg-based influenza vaccines.

All clinical studies submitted with the mRNA-1083 vaccine have used the quadrivalent formulation of mCOMBRIAX, which includes the B/Yamagata lineage and delivers a total of 40 µg per dose. For the studies submitted with mRNA-1010, studies mRNA-1010-P301 and mRNA-1010-P303 were performed using a four-strain seasonal influenza vaccine composition, while mRNA-1010-P304, the efficacy trial, employed a trivalent seasonal influenza mRNA vaccine aligned with the current WHO and EMA/ETF recommendations. The outcomes of the mRNA-1083 can be extrapolated to mCOMBRIAX, as the haemagglutinin components are identical except for the omission of B/Yamagata in line with the WHO/ETF recommendations.

The initially proposed indication wording was "diseases associated with influenza viruses and SARS-CoV-2". Considering the application is based on immunobridging against active comparators for which efficacy beyond influenza and COVID-19 has not been indicated, upon request of the CHMP the wording was updated to reflect in the indication "prevention of influenza disease and COVID-19".

Main Study mRNA-1083-P301

Study design and conduct

Study mRNA-1083-P301 was a multicentre Phase 3, randomised, observer blind, active-controlled study to investigate the immunogenicity, reactogenicity, and safety of a single 40 µg dose of mRNA-1083 multicomponent influenza and COVID-19 vaccine in healthy adults ≧50 years of age.

Study P301 was conducted in 2 independent sub-studies (i.e. Cohort A: ≥65 years of age and Cohort B: ≥50 to <65 years of age). Statistical hypotheses (including non-inferiority and superiority analyses of antibody responses) were tested separately for Cohort A and Cohort B. This approach as an alternative to two separate studies is acceptable.

In each cohort, participants were randomised 1:1 to one of the two treatment groups (Cohort A: mRNA-1083 + placebo or Fluzone HD [Tradename in the EU: "Efluelda Tetra")] + Spikevax; Cohort B: mRNA-1083 + placebo or Fluarix + Spikevax). The selection of comparators, particularly the use of age-appropriate influenza vaccines, is considered adequate. The assigned study intervention was administered as a single intramuscular injection. This is acceptable.

In Cohort A, randomisation was stratified by age groups (≥65 to <75 years and ≥75 years of age). In both cohorts, randomisation was stratified by the influenza vaccine status in the most recent influenza season. This is considered acceptable. It is unclear, however, why stratification by COVID-19 vaccination history was not considered. While stratification and the corresponding adjustment of statistical analyses could have improved sensitivity to demonstrate differences in immune response, the impact on bias or Type I error control is not deemed substantial, particularly considering the numerical advantage in COVID-19 immune response parameters.

The study was observer-blind. Procedures for allocation of participants and blinding were adequately described, and no issues were identified.

The immunobridging approach to infer efficacy against COVID-19 is considered acceptable. However, conclusions on the efficacy of mRNA-1083 against influenza appear difficult based on the applied immunobridging between mRNA- and protein-based vaccine constructs. The applicant received EMA Scientific Advice on the combination vaccine in September 2023 (EMA/SA/0000143761) and December 2024 (EMA/SA/0000121008) where several issues were raised in this regard (please refer to discussion further below).

The study included healthy adults either ≥65 years of age (Cohort A) or 50 to <65 years of age (Cohort B) at the time of consent. Included subjects were fully vaccinated for COVID-19 primary series. Main exclusion criteria were COVID-19 vaccination or SARS-CoV-2 infection ≤90 days prior to study vaccination as well as vaccination with a seasonal influenza vaccine or a positive influenza test ≤150 days prior to study vaccination. The selected study population is considered appropriate.

For the evaluation of immunogenicity, serum antibody levels against SARS-CoV-2 and influenza were investigated. Participants had blood collection at baseline and at Day 29. Immunogenicity was also evaluated in a subset of participants at Day 181 (first 800 participants in each cohort). Blood samples were analysed in a central laboratory. This is considered appropriate. No symptom surveillance or tests for possible infections with influenza or SARS-CoV-2 after vaccination were planned which is considered a missed opportunity for generation of potentially valuable data. Also, cell-mediated immunity, which could have been particularly informative for the novel influenza component, was not investigated.

Serum nAb levels for influenza as measured by MN assay as well as cross-reactive serum nAb levels as measured by PsVNA to SARS-CoV-2 JN.1 variant were collected in a random subset, for which the method of random sampling was added as an Appendix to the SAP just before database lock on April 9th and performed by an unblinded team. After request, the Applicant clarified that the unblinded

study team had access to unblinded IRT data to be able to randomly select a subset based on stratification factors and treatment assignment. In addition, the selection criteria for the PPIS MN dataset were clarified. The approach is considered acceptable.

The primary immunogenicity objective in both sub-studies, Cohort A (≥65 years) and Cohort B (≥50 to <65 years of age), was to evaluate the humoral immune responses of mRNA-1083 for non-inferiority relative to active comparators against vaccine-matched strains for influenza and SARS-CoV-2 at Day 29.

In total, 10 coprimary immunogenicity endpoints were investigated to determine immunogenicity against the 4 influenza strains and SARS-CoV-2: Five coprimary endpoints based on influenza and SARS-CoV-2 GM level at Day 29, and five coprimary endpoints based on influenza SCR or SARS-CoV-2 SRR at Day 29. The selection of co-primary endpoints is endorsed. The NI in GM level was demonstrated by the lower bound of the 2-sided 97.5% CI of the GMR ruling out 0.667 (lower bound >0.667) using a NIM of 1.5. The NI in SCR or SRR was demonstrated by the lower bound of the 2-sided 97.5% CI of the SCR or SRR difference at Day 29 using a NIM of 10%. Clinical justification for the non-inferiority margins was missing in the dossier. However, success criteria can be considered reasonable and are in line with other vaccine trials. The criteria were also accepted during scientific advice (EMA/SA/0000143761) and therefore, no issue is raised.

No specific estimand was pre-specified in the protocol. While the study was started years after *ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017)* had come into effect. Upon request, the applicant provided a more detailed estimand definition. Not all definitions are in the spirit of the estimand framework (e.g. the population is simply defined in terms of the analysis population which is difficult to interpret with respect to a clinically relevant estimand). Nevertheless, considering the number of subjects excluded from the full analysis set is limited, and there is less value in defining the estimand after the study has finished, the issue is not further pursued.

A secondary immunogenicity objective was to evaluate the humoral immune responses of mRNA-1083 for superiority relative to active comparators for influenza and SARS-CoV-2 at Day 29. If the NI success criteria of the co-primary endpoints for GM level were met, superiority was tested sequentially for influenza GM level, SARS-CoV-2 GM level, influenza SCR, SARS-CoV-2 SRR. No estimand was defined with regard to secondary objectives. However, such claims are not considered informative and reliable beyond conclusions on (potentially) sufficient immunogenicity, as it is unclear to what extent superiority in immunogenicity could be translated to corresponding and relevant advantages in terms of vaccine efficacy. Consequently, this issue is not pursued.

Another secondary objective was to evaluate the humoral immune responses for influenza across study intervention groups at Day 29 using the MN assay. The secondary analysis of neutralising antibody responses was recommended during scientific advice (EMA/SA/0000143761) and is considered of high relevance for immunological conclusions in this immunobridging study. In addition, humoral immune responses against influenza and SARS-CoV-2 were investigated up to 6 months in a subset of participants as an exploratory objective which is acknowledged.

Planned statistical analyses are acceptable. However, some uncertainties remain with respect to the confirmatory strategy and multiplicity control. Particularly, details regarding the strategy to control multiplicity within sets of secondary superiority hypotheses are lacking and it remains unclear to what extent corresponding results would support an interpretation in terms of successful demonstration of superior immune response for influenza strains in Cohort A. Considering, however, that claims with respect to superior immunogenicity are not considered informative and relevant, the issue is not pursued.

Study P301 was conducted at 146 enrolling centres in the US. The participant flow and the numbers analysed have been presented in sufficient detail and are comprehensible. In Cohort A, 4017 subjects were dosed (2011 participants in the mRNA-1083 group and 2006 participants in the Fluzone HD + Spikevax group). In Cohort B, 3998 subjects were dosed (1993 participants in the mRNA-1083 group and 2005 participants in the Fluarix + Spikevax group). The majority of subjects was White. Overall baseline characteristics such as race, sex and BMI were balanced between groups. Baseline characteristics in the different analysis sets were balanced across vaccine groups. In Cohort A, the majority of subjects (79.3%) were ≥65 to <75 years of age and the median age was 70 years in both groups. In addition, the baseline status regarding influenza and COVID-19 vaccinations and infections was balanced across groups. Approximately 50% of subjects had received a seasonal influenza vaccine and around 40% had received a COVID-19 vaccine in the 2022/2023 season. In Cohort B, the median age was 58 years in both groups. The age ranged from 50-79 years and 50-77 years in the mRNA-1083 and comparator groups, respectively. The baseline status regarding influenza and COVID-19 vaccinations and infections was also balanced across groups. Approximately 40% of subjects had received a seasonal influenza vaccine and around 30% had received a COVID-19 vaccine in the 2022/2023 season. Taken together, the study population can be considered representative for the intended target population.

Immunogenicity data

In Cohort A and Cohort B, the primary NI objective was evaluated in the PPIS at Day 29 by examining the antibody GM level and SCR/SRR of the mRNA-1083 group as compared to the comparator group by the HAI assay for the 4 vaccine-matched influenza strains and by the PsVNA for the SARS-CoV-2 variant.

Success criterions for NI in the 5 GMR-based endpoints (lower bound of the 2-sided 97.5% CIs of the GMRs >0.667) and the 5 SCR/SRR-based endpoints (the lower bound of the 2-sided 97.5% CIs >-10%) were met in both cohorts. Therefore, the primary immunogenicity objective was met for Cohort A (≥65 years) and Cohort B (≥50 to <65 years of age).

The secondary immunogenicity analyses included a superiority analysis of the GMR and SCR/SRR differences at Day 29 by the HAI assay for the 4 vaccine-matched influenza strains, and by PsVNA for the vaccine-matched SARS-CoV-2 variant. It should be stressed, however, that conclusions with respect to superior immunogenicity are not considered informative or relevant, as it is unclear to what extent they could imply corresponding advantages in terms of efficacy. Consequently, corresponding results are not considered material to the B/R assessment. Methodological shortcomings of the respective analyses (see above) are noted, however, not pursued for further investigation.

Secondary immunogenicity endpoints also included neutralising GM titres at Day 29 and GMFR by MN assay for influenza in a small subset of approximately 150 randomly sampled participants. In these analyses, there was a general trend for higher neutralising antibody responses against influenza after vaccination with mRNA-1083 compared to comparator groups with the exception of B/Yamagata in Cohort A.

Antibody responses against influenza and SARS-CoV-2 at 6 months after vaccination were investigated in approximately 400 subjects per group in the PPIS. In Cohort A, GM levels for influenza decreased compared to Day 29 but were higher than baseline for the influenza A strains while GM levels of B strains were around baseline in both groups. Day 181 GM levels and GMFRs for influenza were numerically higher in the mRNA-1083 + placebo group vs Fluzone HD + Spikevax group for the influenza A strains. In Cohort B, GM levels for influenza decreased compared to Day 29 but were higher than baseline for the influenza A strains. Day 181 GM levels and GMFR for influenza were numerically higher in mRNA-1083 + placebo group vs Fluarix + Spikevax group for all 4 influenza

strains. In contrast, the antibody responses against SARS-CoV-2 were clearly increased over baseline 6 months after vaccination with mRNA-1083 or comparator vaccines in both cohorts with a trend for numerically higher immune responses after vaccination with mRNA-1083. Hence, it appears that a more robust and persistent antibody response against SARS-CoV-2 as compared to influenza is induced by mRNA-1083.

Another exploratory objective was to investigate the SARS-CoV-2 cross-neutralising potential of mRNA-1083. SARS-CoV-2 antibody responses to JN.1 (prevalent variant of interest) were assessed using PsVNA in a randomly selected immunogenicity subset of approximately 60 participants from each group in the PPIS. As expected, antibody responses against JN.1 were lower compared to responses against XBB-1-5 (vaccine-matched) across vaccine groups but trended to be higher after vaccination with mRNA-1083 compared to the comparator vaccines in both cohorts which is acknowledged.

In Cohort A, immunogenicity was investigated in the age subgroups ≥65 to <75 years and ≥75 years according to the primary immunogenicity endpoints at D29. As expected, antibody titres against influenza and SARS-CoV-2 were generally lower in the ≥75 years of age subgroup compared to the ≥65 to <75 years of age subgroup across vaccine groups. A lower Day 29 GMR of the mRNA-1083 group vs the comparator group was observed in the ≥75 years age group compared to the ≥65 to <75 years age group for A/H1N1 whereas GMRs were comparable for A/H3N2 and influenza B strains. Likewise, a lower Day 29 SCR difference of the mRNA-1083 group vs the comparator group was observed in the ≥75 years age group compared to the ≥65 to <75 years age group for A/H1N1 (SCR/SRR Difference -3.8% vs 7.8%). The GMRs against SARS-CoV-2 were overall comparable and the SRR differences were also similar between age groups. Therefore, results of the subgroup analyses for subjects ≥75 years of age resembled results obtained with the overall population, except from the discrepancy regarding A/H1N1. In the subgroup analyses by vaccination status, no major differences in Day 29 GMRs were identified between study vaccination groups. Likewise, no clinically important differences in the subgroup analyses by risk for severe influenza and/or COVID-19, baseline SARS-CoV-2 status, race ethnicity, sex, antipyretics use or BMI were found.

As supportive evidence, results generated with a short cycle and multicycle microneutralization assay were submitted. Results of the multicycle microneutralization (MN-CPE) assay indicate comparable responses after mRNA-1083 compared to inactivated split-virion influenza vaccines.

Taken together, the primary immunogenicity analyses of study P301 show that mRNA-1083 is non-inferior in terms of GMR and SRR/SCR differences to the compared COVID-19 and age-appropriate influenza vaccines in subjects above 50 years of age.

Supportive studies

Phase 1/2 dose response study mRNA-1083-P101

The Phase 1/2 study investigated the reactogenicity and immunogenicity of different dose levels and compositions of mRNA-1083 in adults ≥18 to <80 years of age. Comparators in this study were the authorised influenza (Fluarix and/or Fluzone HD) and SARS-CoV-2 (mRNA-1273) vaccines, as well as the single components of the mRNA-1083 vaccine (mRNA-1283 and mRNA-1010.4).

The primary objective of the study was the investigation of reactogenicity and safety. The secondary objectives were the evaluation of humoral immune responses to vaccine-matched strains for influenza and SARS-CoV-2 across study treatment groups at day 29 by HAI for influenza and PsVNA for SARS-CoV-2. Cell mediated immune response and the occurrence of clinical influenza and COVID-19 in study participants were exploratory objectives. Analyses were descriptive only. The eligibility criteria were reasonable. Overall, the design of the Phase 1/2 study is considered acceptable. Further, the participant flow was comprehensible and the baseline characteristics were overall balanced among the

treatment groups within the respective cohort and age group. However, as the total number of subjects recruited in the Phase 1/2 study was small (approximately 1200 individuals) and several groups were investigated, the number of subjects per group as well as the interpretation of results are limited.

Descriptive immunogenicity results of the Phase 1/2 study mRNA-1083-P101 revealed that all tested mRNA-1083 doses and compositions induced an influenza haemagglutination inhibition antibody response for each of the 4 influenza strains, as well as a SARS-CoV-2 neutralising antibody response against SARS-CoV-2 D614G and SARS-CoV-2 BA.4/5 variant. This response was similar to the respective authorised comparator groups (Fluzone HD or Fluarix and mRNA-1273). No consistent pattern regarding a dose-response relationship in the mRNA-1083 groups was observed in the Phase 1/2 study. Comparison to the single components of the mRNA-1083 vaccine (mRNA-1283 and mRNA-1010.4) revealed that there might be a lower response against SARS-CoV-2 for the combination vaccine.

For the justification of the dose for the Phase 3 study, the applicant explained that although the 30µg dose tested in the Phase 1/2 study had a more favourable reactogenicity profile than the 60µg dose, the immunogenicity data pointed towards a reduced immune response with the lower dose. Thus, the intermediate 40 µg dose was selected for the Phase 3 study, as it was expected to improve immune response while maintaining an acceptable safety profile. No specific criteria seem to have been applied for the selection of the dose. Nevertheless, the approach presented by the applicant is deemed acceptable, as it is the applicant's risk to select a dose for the Phase 3 study which might be able to show a positive B/R balance.

Study mRNA-1083-P201

Data of the mRNA-1083-P201 Phase 2 clinical study were provided to support the EOSL mRNA purity limit of 50%, whereby the antibody responses for SARS-CoV-2 and each influenza strain remained consistent across a wide range of mRNA purity levels (57% to 83%). Based upon these clinical data, the applicant concludes that reduced mRNA purity within the proposed EOSL range does not materially affect antibody responses and that these data demonstrate that a dose delivered at 50% purity delivers sufficient mRNA to elicit protective responses and thereby provide clinical validation of the proposed shelf-life specification. This is supported.

Study mRNA-1283-P301

Study mRNA-1283-P301 was a randomised, observer-blind, multicentre, active-controlled, 2-arm, Phase 3 study in participants aged ≥12 years to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273. Overall, the design of study mRNA-1283-P301 is considered acceptable. In this study, it has been shown that mRNA-1283.222 (bivalent ancestral and Omicron BA.4/5 vaccine) is non-inferior to mRNA-1273.222 in terms of relative efficacy and immunogenicity. It should be noted that the amount of antigen was different compared to that in the to be marketed formulation of mRNA-1083 (10 µg vs 6.7 µg), which could potentially have some influence on the relative VE, although based on immunogenicity results of studies mRNA-1083-P101 and P301 this is considered negligible.

Study mRNA-1010 P301

Study mRNA-1010 P301 was a randomised, stratified, observer-blind, multicentre, active-controlled, Phase 3 study in medically stable adults ≥18 years to investigate the safety and immunogenicity of mRNA-1010 compared with Fluarix. In this study, evaluation of the relative vaccine efficacy to prevent influenza caused by any strain of influenza virus was a secondary objective. Based on the Day 29 immunogenicity results (GMR and SCR differences), it has been shown that mRNA-1010 is non-inferior to Fluarix for both influenza A strains (A/H1N1 and A/H3N2). However, for the influenza

B/Victoria and B/Yamagata lineage strains, mRNA-1010 failed to demonstrate non-inferiority. There were more RT-PCR-confirmed protocol-defined influenza cases in the mRNA-1010 group (64 cases in the mRNA-1010 group and 54 cases in the Fluarix group). Further, although it is acknowledged that the study was not powered to assess rVE, the secondary endpoint evaluating relative vaccine efficacy showed that the rVE of mRNA-1010 was lower compared with Fluarix for protection against any influenza A or B strain (rVE -18.038% [95% CI: -72.816%, 19.114%]).

As a consequence of the results of study mRNA-1010 P301 (and also the terminated study mRNA -1010 P302), the mRNAs corresponding to the B strains were modified to increase the stability of the influenza B HAs. Thus, the results of study mRNA-1010 P301 are based on a different formulation of mRNA-1010, which was not used in the combination vaccine studies and the results are of limited support beyond the A-strains. The applicant was asked to explain how the stability of the proteins/antigens will be ensured when it comes to future strain updates. The applicant will perform in silico analysis on future B strains to demonstrate that the introduced mutations are still applicable. Furthermore, protein expression will be confirmed for each new A or B strain using the in vitro protein expression assay (IVRPE) to further support annual strain updates. The importance to confirm immunogenicity in a suitable animal model has been highlighted to the applicant (refer to the quality discussion section).

Post-hoc analyses within study mRNA-1010-P301 using clinical influenza endpoints and immunogenicity data were performed with the aim to demonstrate a HAI correlate of protection for the mRNA construct (please see further below).

Correlate of protection report mRNA-1010-P301

In study mRNA-1010-P301, immunogenicity (anti-HA data) as well as vaccine efficacy data were collected. Thus, the applicant conducted an immune correlate analysis to evaluate the strain-specific Day 29 HAI titre as correlate of risk (CoR) and correlate of protection (CoP) against the strain-specific ILI endpoint. The acceptability of the HAI as a surrogate endpoint for clinical benefit for mRNA-based influenza vaccines including statistical analysis methodology used to establish the model to correlate vaccine efficacy with HAI surrogate endpoint was already discussed in the December 2024 Scientific Advice procedure (EMA/SA/0000221399), where the approach presented by the applicant was seen critical. Since then, the approach has not changed and the concerns raised in the Scientific Advice procedure are still fully valid. There were several issues with the presented approach how to demonstrate that HAI is a reasonable surrogate marker to predict clinical protection, pertaining to the limited number of cases in study mRNA-1010-P301 for each of the strains to develop the model and the lack of validation on a fit for purpose prospective dataset using predefined success criteria. Additionally, the reliability of the model is questioned based on several methodological shortcomings and results that could imply violations of underlying assumptions. Thus, the correlate of protection analysis initially presented by the applicant is not regarded sufficient to demonstrate that HAI is a reasonable surrogate marker to predict clinical protection of mRNA flu vaccines against ILI.

Study mRNA-1010-P303

Study mRNA-1010 P303 was a randomised, stratified, observer-blind, active-controlled, Phase 3 study in adults ≥18 years to investigate the safety and immunogenicity of an optimized mRNA-1010 vaccine compared to age-appropriate comparators (Fluarix in Part B with participants ≥18 to <65 years and Fluzone in Part C with participants ≥65 years). This study investigated the optimized mRNA-1010 composition (the mRNAs corresponding to the B strains were modified to increase the stability of the influenza B HA). In both Part B and C of the study, non-inferiority and superiority of mRNA-1010 was demonstrated based on GMR and SCR difference for all influenza A and B strains contained in the vaccine.

Study mRNA-1010-P304

The applicant submitted the results of study mRNA-1010-P304. This was a Phase 3, randomised, observer-blind, active-controlled, case-driven study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 candidate seasonal influenza vaccine compared with an authorised inactivated seasonal influenza vaccine in adults ≥50 years of age.

In this study, 20,349 subjects in the mRNA-1010 group vs 20,354 subjects in the SD comparator group received study injection. In total, 968 cases (exceeding the study target of 836 cases) were included from the 2024/2025 influenza season.

The Applicant has indicated that 12 study centres were audited by the Sponsor, also a study audit has been performed. The Applicant has provided an overview of the major findings during the study visits corrective measures taken. Appropriate corrective measures were taken after major observations, in addition major observations were unlikely to impact the findings of the study.

The primary efficacy objective (prevention of RT-PCR-confirmed protocol-defined ILI caused by influenza A or B) was met. In adults ⩾50 years of age, the rVE of mRNA-1010 across A and B influenza strains was 26.6% (95% CI: 16.7, 35.4). The rVE for each strain was: A/H1N1=29.6% [95% CI: 16.4, 40.7]; A/H3N2=22.2% [95% CI: 4.3, 36.9]; and B=29.1% [95% CI: -18.5, 57.5]. The subgroup analyses, also including adults 65 years of age and older were consistent with the overall results (rVE in ⩾65 yoa was 27.4% (95% CI: 12.1, 40.0).

In addition, HAI Ab responses (Day 29 GMTs, seroconversion rates [SCRs], and GMFRs) were higher after mRNA-1010 compared to the SD vaccine for all tested influenza strains. The Day 29 GMRs were A/H1N1: 1.824 [95% CI: 1.691, 1.967]; A/H3N2: 1.589 [95% CI: 1.476, 1.711]; B: 1.673 [95% CI: 1.574, 1.778]. Based on point estimates and CIs as well as RCDCs provided by the applicant, anti-HA antibodies seem higher after vaccination with mRNA-1010 compared to a standard dose inactivated influenza vaccine.

In total immunogenicity data was collected among 3200 participants. Immunogenicity data was reported for approximately 2400 participants originating from the US. The applicant justified the relevance of the immunogenicity findings in the North-American population towards the European population.

The strain specific rVE estimates for the A strains were in line with the immunogenicity data and indicated superior efficacy accompanied by superior immune response over the comparator. Immunogenicity data indicated that mRNA-1010 induced superior HAI responses relative to the SD comparator for the B-lineage. The strain specific efficacy data however showed that rVE for the B lineage was 29.1% (95% CI: -18.5, 57.5), thus not convincingly showing superior efficacy. This however is explained by the low number of B cases observed during the study (59 cases), also reflected by the wide CIs.

Correlate of protection report mRNA-1010-P304

Currently, there is no established serological correlate of protection for influenza.

HAI titres are commonly used in primary immunogenicity endpoints for protein-based seasonal influenza vaccine approvals. It was questioned whether HAI titres can also serve as a surrogate of protection with mRNA vaccines in the same manner as for egg-based inactivated influenza vaccines as other elements of the immune response important for protection might differ between platforms. For this purpose, the applicant planned and performed a Correlate of Risk/Protection (CoR/CoP) analysis of Study 1010-P304 in order to evaluate the surrogacy of HAI titres. The analysis is based on a case-cohort design embedded within a randomised controlled trial that evaluation of HAI titres in a stratified random subcohort (baseline and Day 29) and inclusion of all ILI cases, despite not having to

evaluate HAI titres for all randomised subjects. Consequently, it requires adjustment for sampling imbalance using causal inference methods typically employed in observational studies. Corresponding methodology is considered adequate and has been used for the evaluation of CoPs in other diseases.

CoP evaluation for A Strains (A/H1N1, A/H3N2):

The correlate of protection analysis, indicates a strong inverse association between HAI titres and ILI risks in both treatment groups. In addition, mediation analysis shows at least partial mediation of the treatment effect through HAI titre levels. Nevertheless, results indicate a potential difference in the CoP relationship with case titres consistently higher in the mRNA-1010 group, as well as a significant interaction between titre levels and treatment effect for H1N1. It cannot be excluded that the applicant´s mRNA vaccines required higher titres for protection than the protein-based comparator in study 304.

CoP evaluation for B Strain (B/Victoria)

For the B strains an inverse correlation between HAI titres and ILI risk could not be conclusively demonstrated. In fact, individual results (CoP Report Figure 2) appear to show on average higher titre levels among cases (compared to the corresponding non-case cohort) in the mRNA-1010 group. However, case numbers were quite low for the B strain (25 cases in the mRNA-1010 group versus 34 cases in the active comparator group). Most (~78%) of the B/Victoria lineage cases were observed in Bulgaria (20 cases in the mRNA-1010 group versus 26 cases in the active comparator group).

General aspects of the data package to infer efficacy of mRNA-1083

In the to be marketed formulation the applicant has removed the B/Yamagata (8.3 µg) strain in line with current EMA and WHO recommendations. The recommendation for a trivalent vaccine was addressed in the scientific advice of November 2023 for the component mRNA-1010 influenza vaccine, but no comments were made specifically for the combination vaccine (mRNA-1083). For the mRNA-1083 vaccine, the total dose changed from 40 µg to 31.7 µg due to removal of the B/Yamagata strain. However, by simply removing this strain the mass ratio of total influenza RNA to SARS-CoV-2 RNA changed from 5:1 to 3.75:1. Based on the results of the phase 1/2 study it seems that no effect was seen in the immunogenicity observed for influenza with declining mass ratio and also there was no real effect on the immunogenicity of SARS-CoV-2 with a declining mass ratio for influenza. Mutations for influenza B HA proteins were introduced into the current versions of mRNA-1010 and mRNA-1083 following poor immunogenicity results with the original influenza B constructs. It is not entirely clear whether the stability of the influenza B antigen (and immunogenicity) will be affected with future strain updates. The applicant's proposal to evaluate protein structure/stability using in-silico analysis and in vitro relative protein expression assay (IVRPE) is in principle endorsed. However, additional functional testing is required, and a respective REC has been raised and agreed by BWP.

There was one pivotal Phase 3 study (mRNA-1083-P301) indicating superior immunogenicity of mRNA-1083 versus standard- (50-64 YoA) or high-dose (≥65 YoA) inactivated influenza vaccines for all influenza strains covered in the trivalent formulation. The used immunobridging approach to infer efficacy against COVID-19 is considered acceptable. Currently, there is no mRNA-based influenza vaccine approved. Inferring efficacy of mRNA-1083 against influenza based on the mRNA-1083-P301 immunobridging study (i.e. immunobridging on HAI titres between mRNA- and split-virion vaccine constructs) is therefore more complicated. Given the differences between the constructs, the level of protection afforded by the comparator vaccine may also depend on other elements of the immune response.

Therefore, demonstration of non-inferiority (or even superiority) of HAI GMTs between vaccines based on different manufacturing platforms might not necessarily translate in at least non-inferior relative

efficacy for the experimental vaccine. To address these issues, the applicant provided data from clinical efficacy study mRNA-1010-P304 (influenza-only vaccine based on the same construct).

As discussed above, the results of study mRNA-1010-P304 indicate overall superior rVE in adults ⩾50 years of age, with superior HAI Ab responses after mRNA-1010 compared to the SD vaccine for all tested influenza strains. Despite lower levels of mRNA coding for influenza in mRNA-1083 compared with mRNA-1010, also in study mRNA-1083-P301 superior immunogenicity was observed compared with standard- and high-dose comparators. This was further supported by immune responses observed when measured by the MN-CPE assay (multicycle microneutralisation), indicating comparable neutralising capacity of mRNA-1083 with inactivated influenza vaccine comparators versus standard-dose influenza vaccines. In addition, the results of the CoP report support surrogate properties of HAI titres against influenza A. Although differences in the CoP relationship hamper a direct interpretation of relative immunogenicity results for mRNA-1083 and no inverse correlation between HAI titres and ILI risk could be demonstrated for influenza B/Victoria, rVE results for mRNA-1010 with respect to B/Victoria do still indicate rVE which likely permit extrapolation of sufficient VE to mRNA-1083, despite differences in dose levels.

The extent of protection of mRNA-1083 (mCOMBRIAX) on the other hand is unclear. The impact of the lower flu dose of mRNA-1083 compared to mRNA-1010 on efficacy remains undetermined. While efficacy per se can be assumed based on a) the proved efficacy of mRNA-1010, b) the correlation with HAI titres for the A strains and c) the comparative immunogenicity data in both trials, it is not possible to derive an efficacy estimate for mRNA-1083 based on the CoP report and this is particularly more unclear for the B strain. Therefore, it is considered necessary to further investigate effectiveness in the post-marketing setting. A post-marketing effectiveness study is also requested in accordance with the influenza vaccine guideline (EMA/CHMP/VWP/457259/2014). Therefore, the applicant formally committed to confirm effectiveness of the influenza component of mCOMBRIAX for all included flu strains in a post-marketing study and to submit the corresponding protocol before study initiation.

Conclusions on the clinical efficacy

The primary immunogenicity analyses show that mRNA-1083 is non-inferior to the compared COVID-19 and age-appropriate influenza vaccines in subjects 50 years of age and older in terms of GMR and SRR/SCR differences. Efficacy against COVID-19 can be inferred based on the immunobridging of mRNA vaccines. A study with mRNA-1010 provided evidence that mRNA vaccines can be efficacious against influenza in this age group. Along with HAI titres and supportive multicycle microneutralisation data observed in this study, this supports to infer efficacy also for the influenza component of mRNA-1083 based on the pivotal immunobridging study. The extent of protection remains however unclear and a post-marketing effectiveness study is expected in accordance with the influenza vaccine guideline (EMA/CHMP/VWP/457259/2014). Therefore, the applicant formally committed to confirm effectiveness of the influenza component of mCOMBRIAX for all included flu strains in a post-marketing study and to submit the corresponding protocol before study initiation.

As the outcomes of the mRNA-1083 can be extrapolated to mCOMBRIAX, as the haemagglutinin components are identical except for the omission of B/Yamagata in line with the WHO/ETF recommendations, from a clinical efficacy perspective, mCOMBRIAX is approvable.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Solicited Adverse Reactions (ARs) were assessed using a prespecified list of solicited local and systemic AR terms that were reported by participants daily via eDiary during the 7 days following injection (i.e., the day of injection and 6 subsequent days). Severity grading of reactogenicity occurred automatically based on participant entry into the eDiary according to the grading scales modified from the Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007). If a solicited local or systemic AR continued beyond Day 7 after study injection, participants were to notify the site of the end date. If the participant reported an event after the solicited period (i.e., after Day 7), it was recorded as an AE in the eCRF.

Serious adverse events (SAEs), medically attended adverse events (MAAEs), adverse events of special interest (AESIs), and adverse events (AEs) leading to discontinuation were collected through Day 181/end of study or discontinuation from the study. Unsolicited nonserious AEs that did not meet criteria for the preceding categories were collected through 28 days after injection.

All participants attended in-person clinic visits for Screening, Day 1 (Baseline), and Day 29 (Month 1). There were follow-up safety calls on Day 8 and Day 91 (Month 3). On Day 181 (Month 6, End of Study [EOS]), at least 800 participants per substudy cohort were to attend an in-person clinic visit for sample collection. All remaining participants were to have a safety follow-up call.

In the pivotal phase 3 study, the safety data were mainly presented by two age cohorts separately. However, data from participants ⩾50 years of age in Cohort A and Cohort B in Study mRNA-1083-P301 who received mRNA- 1083 were also pooled for unsolicited AEs, SAEs, AESIs, and SMQs and a descriptive analysis was performed.

5.4.2. Patient exposure

The safety and tolerability of the mRNA-1083 vaccine have been assessed using an overall safety database of over 8000 participants. In Studies mRNA-1083-P101 and mRNA-1083-P301 combined, a total of 4132 participants ⩾50 years have received mRNA-1083 at 30 µg, 40 µg, or 60 µg, including 4004 participants in Study mRNA-1083-P301 (=completed) who have received mRNA-1083 40 µg (tables below).

Table 27 Study mRNA-1083-P301: Summary of Exposure and Follow-Up Duration (Safety Set)

	≥65 Years (Cohort A)		≥50 to <65 (Cohort B)	
	mRNA-1083 40 µg + Placebo	**Fluzone HD + Spikevax**	**mRNA-1083 40 µg + Placebo**	**Fluarix + Spikevax**
Follow-up duration from injection (days)				
N	2011	2006	1993	2005
Mean (SD)	171.0 (17.47)	171.3 (16.46)	171.0 (18.34)	170.4 (20.67)
Median	171.0	171.0	171.0	170.0
Min, max	1, 201	1, 203	3, 197	1, 201

Numbers were based on actual study intervention group and percentages were based on the number of participants (n) in the Safety Set. Source: Study mRNA-1083-P301 CSR Table 14.1.3.1a (01 Jul 2024), Table 14.1.3.1b (01 Jul 2024), Table 14.1.7.1a, and Table 14.1.7.1b.

Table 28 Study mRNA-1083-P101: Summary of Exposure and Follow-Up Duration After Study Injection (Days) (Safety Set)

	Fluarix	**Fluzone HD**	**mRNA-1273.222 50 µg**	**mRNA-1083 30 µg**	**mRNA-1083 60 µg**
≥65 to <80 years (Cohort A), n	54	53	54	51	33
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
≥50 to <65 years (Cohort B), n	26	-	27	28	16
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

Numbers were based on actual study intervention group and percentages were based on the number of participants (n) in the Safety Set. 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.

5.4.3. Adverse events

Solicited adverse reactions in Study mRNA-1083-P301

Table 29 Study mRNA-1083-P301: Summary of Participants With Solicited Adverse Reactions Within 7 Days After Injection by Grade (Solicited Safety Set)

	≥65 Years (Cohort A)		≥50 to <65 Years (Cohort B)	
	mRNA-1083 40 µg + Placebo (N=2011) n (%)	**Fluzone HD + Spikevax (N=2001) n (%)**	**mRNA-1083 40 µg + Placebo (N=1993) n (%)**	**Fluarix + Spikevax (N=2004) n (%)**
Solicited adverse reactions - N1	2011	2001	1993	2004
Any	1681 (83.6)	1565 (78.2)	1698 (85.2)	1640 (81.8)
95% CI	81.9, 85.2	76.3, 80.0	83.6, 86.7	80.1, 83.5
Grade 1	687 (34.2)	808 (40.4)	551 (27.6)	748 (37.3)
Grade 2	811 (40.3)	673 (33.6)	901 (45.2)	765 (38.2)
Grade 3	181 (9.0)	83 (4.1)	244 (12.2)	126 (6.3)
Grade 4	2 (<0.1)	1 (<0.1)	2 (0.1)	1 (<0.1)
Grade 3 or Grade 4	183 (9.1)	84 (4.2)	246 (12.3)	127 (6.3)
Solicited local adverse reactions - N1	2011	2000	1993	2004
Any	1524 (75.8)	1401 (70.1)	1579 (79.2)	1527 (76.2)
95% CI	73.8, 77.6	68.0, 72.1	77.4, 81.0	74.3, 78.0
Grade 1	923 (45.9)	941 (47.1)	790 (39.6)	903 (45.1)
Grade 2	544 (27.1)	429 (21.5)	721 (36.2)	580 (28.9)
Grade 3	57 (2.8)	31 (1.6)	68 (3.4)	44 (2.2)
Grade 4	0	0	0	0
Grade 3 or Grade 4	57 (2.8)	31 (1.6)	68 (3.4)	44 (2.2)
Pain - N1	2011	2000	1993	2004
Any	1480 (73.6)	1362 (68.1)	1554 (78.0)	1500 (74.9)
Grade 1	933 (46.4)	966 (48.3)	817 (41.0)	925 (46.2)
Grade 2	510 (25.4)	375 (18.8)	690 (34.6)	538 (26.8)
Grade 3	37 (1.8)	21 (1.1)	47 (2.4)	37 (1.8)
Grade 4	0	0	0	0
Grade 3 or Grade 4	37 (1.8)	21 (1.1)	47 (2.4)	37 (1.8)
Erythema (redness) - N1	2010	1999	1993	2003
Any	105 (5.2)	97 (4.9)	106 (5.3)	92 (4.6)
Grade 1	45 (2.2)	46 (2.3)	51 (2.6)	50 (2.5)
Grade 2	51 (2.5)	46 (2.3)	43 (2.2)	40 (2.0)
Grade 3	9 (0.4)	5 (0.3)	12 (0.6)	2 (<0.1)
Grade 4	0	0	0	0
Grade 3 or Grade 4	9 (0.4)	5 (0.3)	12 (0.6)	2 (<0.1)

	≥65 Years (Cohort A)		≥50 to <65 Years (Cohort B)	
	mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2001) n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2004) n (%)
Swelling (hardness) - N1	2010	1999	1993	2003
Any	124 (6.2)	110 (5.5)	134 (6.7)	116 (5.8)
Grade 1	70 (3.5)	66 (3.3)	76 (3.8)	67 (3.3)
Grade 2	47 (2.3)	40 (2.0)	50 (2.5)	46 (2.3)
Grade 3	7 (0.3)	4 (0.2)	8 (0.4)	3 (0.1)
Grade 4	0	0	0	0
Grade 3 or Grade 4	7 (0.3)	4 (0.2)	8 (0.4)	3 (0.1)
Axillary swelling or tenderness - N1	2011	1999	1993	2003
Any	414 (20.6)	318 (15.9)	487 (24.4)	420 (21.0)
Grade 1	303 (15.1)	242 (12.1)	316 (15.9)	307 (15.3)
Grade 2	95 (4.7)	67 (3.4)	159 (8.0)	102 (5.1)
Grade 3	16 (0.8)	9 (0.5)	12 (0.6)	11 (0.5)
Grade 4	0	0	0	0
Grade 3 or Grade 4	16 (0.8)	9 (0.5)	12 (0.6)	11 (0.5)
Solicited systemic adverse reactions - N1	2011	2000	1993	2003
Any	1410 (70.1)	1263 (63.2)	1495 (75.0)	1346 (67.2)
95% CI	68.1, 72.1	61.0, 65.3	73.1, 76.9	65.1, 69.3
Grade 1	557 (27.7)	649 (32.5)	486 (24.4)	626 (31.3)
Grade 2	699 (34.8)	546 (27.3)	795 (39.9)	610 (30.5)
Grade 3	152 (7.6)	67 (3.4)	212 (10.6)	109 (5.4)
Grade 4	2 (<0.1)	1 (<0.1)	2 (0.1)	1 (<0.1)
Grade 3 or Grade 4	154 (7.7)	68 (3.4)	214 (10.7)	110 (5.5)
Fever - N1	2008	1999	1992	2001
Any	239 (11.9)	87 (4.4)	288 (14.5)	124 (6.2)
Grade 1	139 (6.9)	58 (2.9)	162 (8.1)	84 (4.2)
Grade 2	76 (3.8)	21 (1.1)	90 (4.5)	29 (1.4)
Grade 3	22 (1.1)	7 (0.4)	34 (1.7)	10 (0.5)
Grade 4	2 (<0.1)	1 (<0.1)	2 (0.1)	1 (<0.1)
Grade 3 or Grade 4	24 (1.2)	8 (0.4)	36 (1.8)	11 (0.5)
Headache - N1	2010	1999	1993	2003
Any	875 (43.5)	726 (36.3)	1025 (51.4)	859 (42.9)
Grade 1	473 (23.5)	465 (23.3)	457 (22.9)	486 (24.3)
Grade 2	351 (17.5)	235 (11.8)	490 (24.6)	334 (16.7)

	≥65 Years (Cohort A)		≥50 to <65 Years (Cohort B)	
	mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2001) n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2004) n (%)
Grade 3	51 (2.5)	26 (1.3)	78 (3.9)	39 (1.9)
Grade 4	0	0	0	0
Grade 3 or Grade 4	51 (2.5)	26 (1.3)	78 (3.9)	39 (1.9)
Fatigue - N1	2011	2000	1993	2003
Any	1064 (52.9)	886 (44.3)	1174 (58.9)	979 (48.9)
Grade 1	449 (22.3)	462 (23.1)	420 (21.1)	502 (25.1)
Grade 2	521 (25.9)	379 (19.0)	622 (31.2)	410 (20.5)
Grade 3	94 (4.7)	45 (2.3)	132 (6.6)	67 (3.3)
Grade 4	0	0	0	0
Grade 3 or Grade 4	94 (4.7)	45 (2.3)	132 (6.6)	67 (3.3)
Myalgia - N1	2011	2000	1993	2003
Any	1030 (51.2)	859 (43.0)	1163 (58.4)	942 (47.0)
Grade 1	469 (23.3)	501 (25.1)	439 (22.0)	479 (23.9)
Grade 2	481 (23.9)	320 (16.0)	598 (30.0)	402 (20.1)
Grade 3	80 (4.0)	38 (1.9)	126 (6.3)	61 (3.0)
Grade 4	0	0	0	0
Grade 3 or Grade 4	80 (4.0)	38 (1.9)	126 (6.3)	61 (3.0)
Arthralgia - N1	2010	2000	1993	2003
Any	849 (42.2)	714 (35.7)	937 (47.0)	720 (35.9)
Grade 1	427 (21.2)	430 (21.5)	390 (19.6)	403 (20.1)
Grade 2	365 (18.2)	258 (12.9)	460 (23.1)	284 (14.2)
Grade 3	57 (2.8)	26 (1.3)	87 (4.4)	33 (1.6)
Grade 4	0	0	0	0
Grade 3 or Grade 4	57 (2.8)	26 (1.3)	87 (4.4)	33 (1.6)
Nausea/vomiting - N1	2010	1999	1993	2003
Any	269 (13.4)	177 (8.9)	361 (18.1)	256 (12.8)
Grade 1	168 (8.4)	128 (6.4)	237 (11.9)	187 (9.3)
Grade 2	96 (4.8)	49 (2.5)	124 (6.2)	66 (3.3)
Grade 3	5 (0.2)	0	0	3 (0.1)
Grade 4	0	0	0	0
Grade 3 or Grade 4	5 (0.2)	0	0	3 (0.1)
Chills - N1	2010	2000	1993	2003
Any	699 (34.8)	427 (21.4)	829 (41.6)	559 (27.9)
Grade 1	326 (16.2)	260 (13.0)	346 (17.4)	301 (15.0)

	≥65 Years (Cohort A)		≥50 to <65 Years (Cohort B)	
	mRNA-1083 40 µg + Placebo (N=2011) n (%)	**Fluzone HD + Spikevax (N=2001) n (%)**	**mRNA-1083 40 µg + Placebo (N=1993) n (%)**	**Fluarix + Spikevax (N=2004) n (%)**
Grade 2	356 (17.7)	165 (8.3)	471 (23.6)	252 (12.6)
Grade 3	17 (0.8)	2 (0.1)	12 (0.6)	6 (0.3)
Grade 4	0	0	0	0
Grade 3 or Grade 4	17 (0.8)	2 (0.1)	12 (0.6)	6 (0.3)

Table 30 Onset and duration of solicited ARs (Study mRNA-1083-P301), Cohort A (top) and B (bottom)

Solicited Adverse Reaction Category Statistic	mRNA-1083 40 µg + Placebo (N=2011)	Fluzone HD + Spikevax (N=2001)
Solicited Local Adverse Reactions - N1	2011	2000
Any, n (%)	1524 (75.8)	1401 (70.1)
Day of Onset		
n	1524	1401
Mean (SD)	1.8 (0.77)	1.7 (0.77)
Median	2.0	2.0
Q1, Q3	1.0, 2.0	1.0, 2.0
Min, Max	1, 7	1, 7
Duration (Days)		
n	1524	1401
Mean (SD)	3.2 (6.35)	3.2 (4.85)
Median	3.0	2.0
Q1, Q3	1.0, 4.0	1.0, 4.0
Min, Max	1, 179	1, 102
Persisted Beyond 7 Days, n (%)	24 (1.2)	33 (1.7)
Solicited Systemic Adverse Reactions - N1	2011	2000
Any, n (%)	1410 (70.1)	1263 (63.2)
Day of Onset		
n	1410	1263
Mean (SD)	2.0 (0.95)	2.0 (1.03)
Median	2.0	2.0
Q1, Q3	2.0, 2.0	1.0, 2.0
Min, Max	1, 7	1, 7
Duration (Days)		
n	1410	1263
Mean (SD)	3.2 (3.42)	3.3 (4.63)
Median	2.0	2.0
Q1, Q3	1.0, 5.0	1.0, 5.0
Min, Max	1, 93	1, 129
Persisted Beyond 7 Days, n (%)	31 (1.5)	29 (1.5)

Solicited Adverse Reaction Category Statistic	mRNA-1083 40 µg + Placebo (N=1993)	Fluarix + Spikevax (N=2004)
Solicited Local Adverse Reactions - N1	1993	2004
Any, n (%)	1579 (79.2)	1527 (76.2)
Day of Onset		
n	1579	1527
Mean (SD)	1.7 (0.77)	1.7 (0.74)
Median	2.0	2.0
Q1, Q3	1.0, 2.0	1.0, 2.0
Min, Max	1, 7	1, 7
Duration (Days)		
n	1579	1527
Mean (SD)	3.3 (2.46)	3.1 (2.04)
Median	3.0	3.0
Q1, Q3	2.0, 4.0	2.0, 4.0
Min, Max	1, 64	1, 28
Persisted Beyond 7 Days, n (%)	40 (2.0)	22 (1.1)
Solicited Systemic Adverse Reactions - N1	1993	2003
Any, n (%)	1495 (75.0)	1346 (67.2)
Day of Onset		
n	1495	1346
Mean (SD)	2.0 (0.89)	2.0 (0.99)
Median	2.0	2.0
Q1, Q3	1.0, 2.0	1.0, 2.0
Min, Max	1, 7	1, 7
Duration (Days)		
n	1495	1346
Mean (SD)	3.3 (2.83)	3.4 (4.73)
Median	3.0	2.0
Q1, Q3	1.0, 5.0	1.0, 5.0
Min, Max	1, 42	1, 116
Persisted Beyond 7 Days, n (%)	38 (1.9)	32 (1.6)

Source: Table 14.3.1.4.1a and Table 14.3.1.4.1b (modified)

In the pooled cohort, across the study, 4004 participants received mRNA-1083. The most commonly reported adverse reactions were injection site pain (75.8%), fatigue (55.9%), myalgia (54.8%), headache (47.5%), arthralgia (44.6%), chills (38.2%), lymphadenopathy (22.5%), nausea/vomiting (15.7%) and pyrexia (13.2%). The median time to onset for solicited adverse reactions was Day 2, with median duration of 3 days.

Solicited ARs persisting beyond 7 days after injection were reported at comparable rates in Cohort A (mRNA-1083: 2.3%, control: 2.6%) but at a slightly higher frequency for mRNA-1083 in Cohort B (mRNA-1083: 3.4%, control: 2.4%).

Table 31 Summary of Daily Medication Taken to Prevent or Treat Pain/Fever Within 7 Days After Injection — Cohort A, Solicited Safety Set, mRNA-1083-P301

	mRNA-1083 + Placebo (N=2011)	Fluzone HD + Spikevax (N=2001)	Overall (N=4012)
Any Medications Taken for Fever/Pain	779 (38.7%)	620 (31.0%)	1399 (34.9%)
Any Medication Taken to Treat Fever/Pain	716 (35.6%)	553 (27.6%)	1269 (31.6%)
Any Medication Taken to Prevent Fever/Pain	165 (8.2%)	153 (7.6%)	318 (7.9%)

Source: Table 14.1.6.4a

Table 32 Summary of Daily Medication Taken to Prevent or Treat Pain/Fever Within 7 Days After Injection — Cohort B, Solicited Safety Set, mRNA-1083-P301

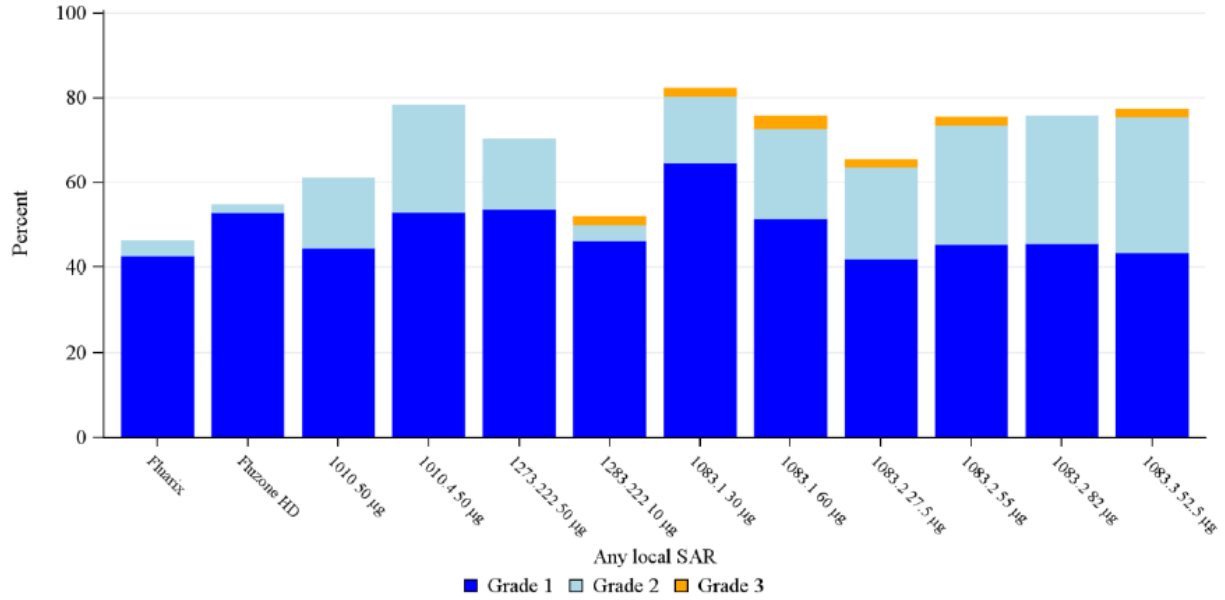
	mRNA-1083 + Placebo (N=1993)	Fluarix HD + Spikevax (N=2004)	Overall (N=3997)
Any Medications Taken for Fever/Pain	967 (48.5%)	752 (37.5%)	1719 (43.0%)
Any Medication Taken to Treat Fever/Pain	902 (45.3%)	687 (34.3%)	1589 (39.8%)
Any Medication Taken to Prevent Fever/Pain	225 (11.3%)	166 (8.3%)	391 (9.8%)

Source: Table 14.1.6.4b

Use of medication to treat fever/pain peaked on Day 2 after injection in both cohorts and both treatment groups.

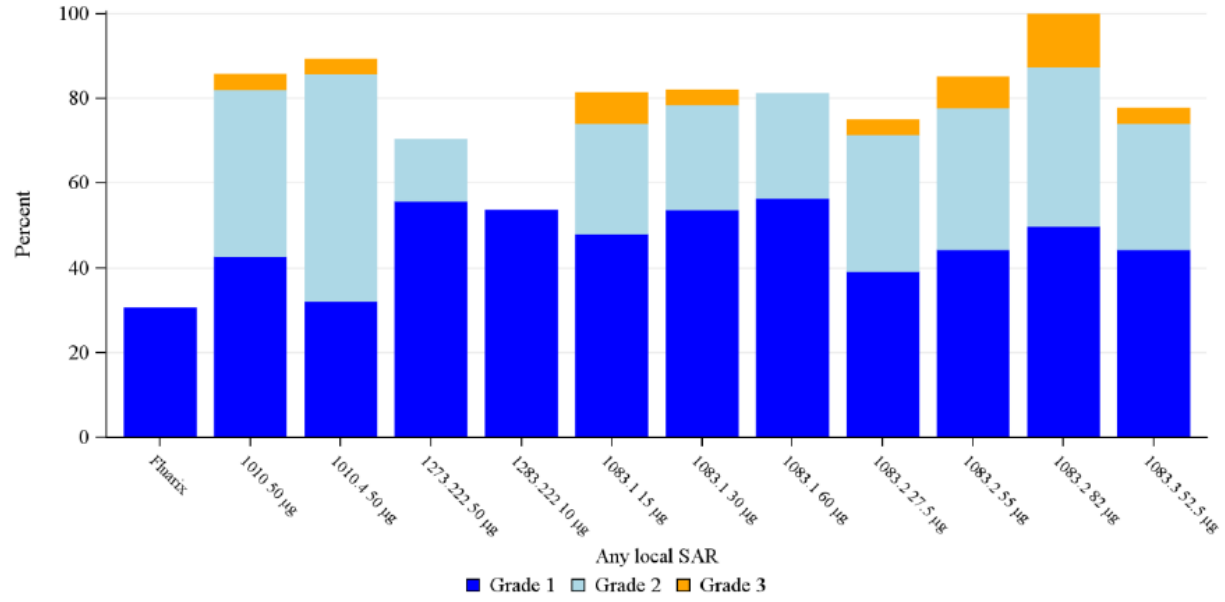
Solicited adverse reactions in Study mRNA-1083-P101

Figure 28 Summary of solicited local ARs within 7 days after injection by toxicity grade – Cohort A: ⩾ 65 to <80 years (Solicited Safety Set)



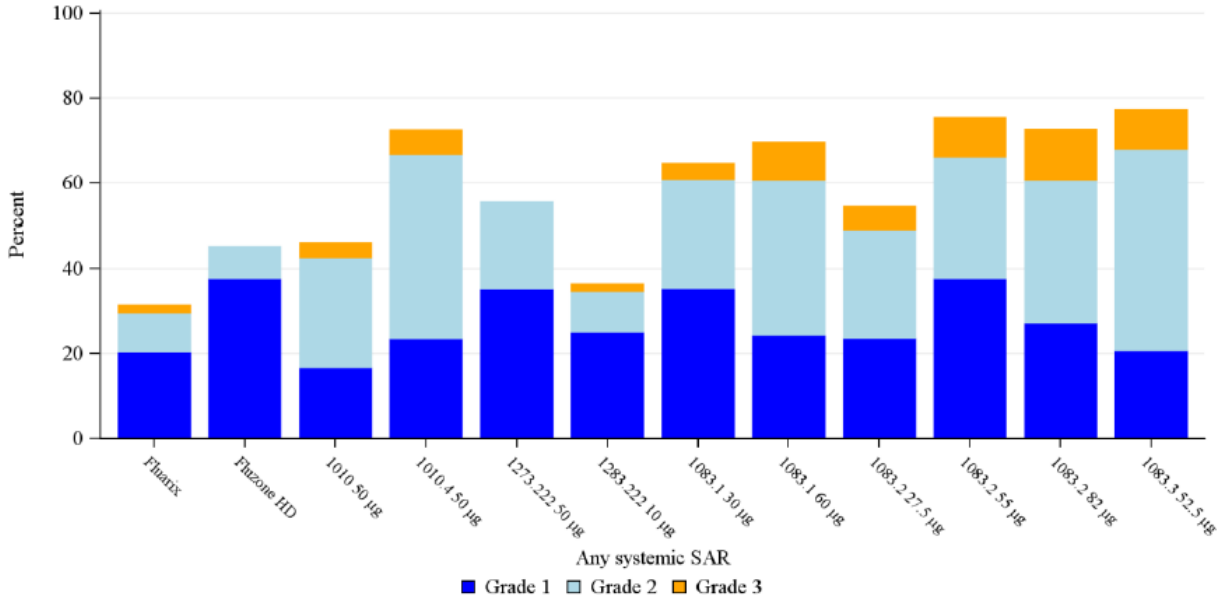
Source: Figure 14.3.1.1 (CSR)

Figure 29 Summary of solicited local ARs within 7 days after injection by toxicity grade – Cohort B: ⩾ 50 to <65 years (Solicited Safety Set)



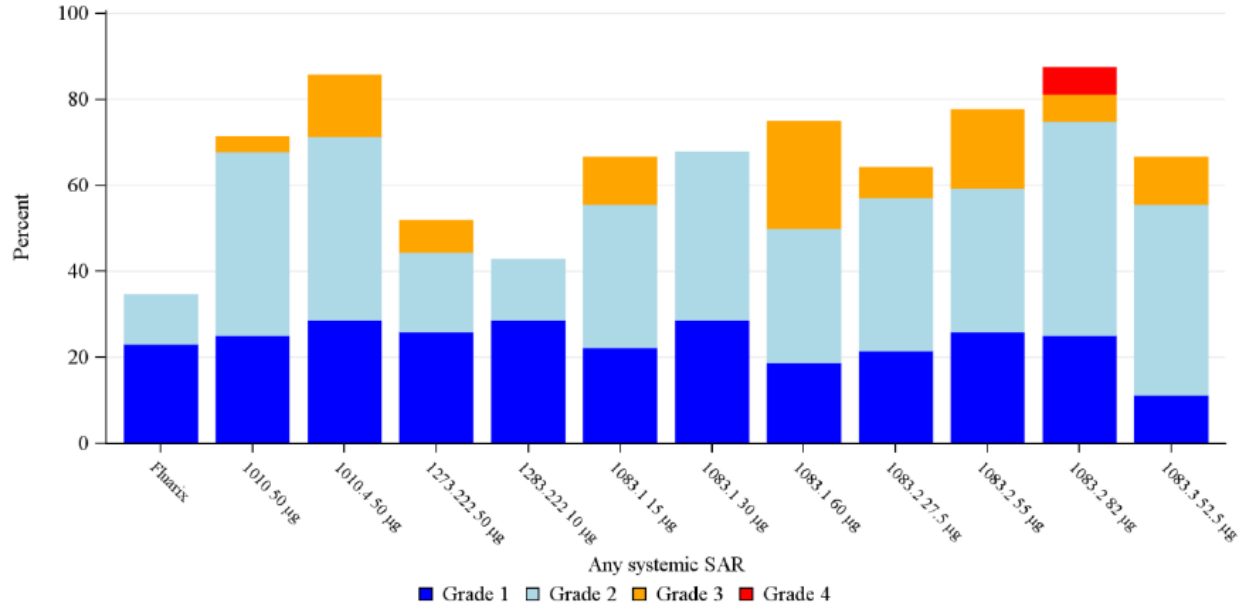
Source: Figure 14.3.1.2 (CSR)

Figure 30 Summary of solicited systemic ARs within 7 days after injection by toxicity grade – Cohort A: ⩾65 to <80 years (Solicited Safety Set)



Source: Figure 14.3.1.1 (CSR)

Figure 31 Summary of solicited systemic ARs within 7 days after injection by toxicity grade – Cohort B: ⩾50 to <65 years (Solicited Safety Set)



Source: 14.3.1.2 (CSR)

Unsolicited adverse reactions in Study mRNA-1083-P301

Table 33 Study mRNA-1083-P301: Overall Summary of Unsolicited AEs Up to 28 Days After Injection (Safety Set)

Unsolicited AEs Up to 28 Days After Injection	Pooled mRNA-1083 Cohort (N=4004) n (%)	≥65 Years (Cohort A)		≥50 to <65 Years (Cohort B)	
		mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)
Regardless of relationship to study injection					
All	434 (10.8)	239 (11.9)	250 (12.5)	195 (9.8)	191 (9.5)
Serious	28 (0.7)	18 (0.9)	15 (0.7)	10 (0.5)	5 (0.2)
Fatal	0	0	1 (<0.1)	0	0
Medically attended	238 (5.9)	138 (6.9)	144 (7.2)	100 (5.0)	101 (5.0)
Leading to study discontinuation	0	0	0	0	0
Severe (≥Grade 3)	23 (0.6)	15 (0.7)	12 (0.6)	8 (0.4)	4 (0.2)
AE of special interest	4 (<0.1)	2 (<0.1)	4 (0.2)	2 (0.1)	2 (<0.1)
Related to study injection					
All	34 (0.8)	16 (0.8)	20 (1.0)	18 (0.9)	25 (1.2)
Serious	0	0	0	0	0
Fatal	0	0	0	0	0
Medically attended	5 (0.1)	3 (0.1)	5 (0.2)	2 (0.1)	3 (0.1)
Leading to study discontinuation	0	0	0	0	0
Severe (≥Grade 3)	1 (<0.1)	0	0	1 (<0.1)	0
AE of special interest	1 (<0.1)	1 (<0.1)	0	0	0

Source: Study mRNA-1083-P301 CSR Table 14.3.2.1.3.

Table 34 Study mRNA-1083-P301: Overall Summary of Unsolicited AEs Up to EOS/Day 181 (Safety Set)

Unsolicited AEs Up to EOS	Pooled mRNA-1083 Cohort (N=4004) n (%)	≥65 Years (Cohort A)		≥50 to <65 Years (Cohort B)	
		mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)
Regardless of relationship to study injection					
All	880 (22.0)	503 (25.0)	500 (24.9)	377 (18.9)	376 (18.8)
Serious	99 (2.5)	70 (3.5)	52 (2.6)	29 (1.5)	27 (1.3)
Fatal	4 (<0.1)	2 (<0.1)	1 (<0.1)	2 (0.1)	2 (<0.1)

Unsolicited AEs Up to EOS	Pooled mRNA-1083 Cohort (N=4004) n (%)	≥65 Years (Cohort A)		≥50 to <65 Years (Cohort B)	
		mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)
Medically attended	727 (18.2)	426 (21.2)	428 (21.3)	301 (15.1)	304 (15.2)
Leading to study discontinuation	1 (<0.1)	0	0	1 (<0.1)	0
Severe (≥Grade 3)	94 (2.3)	69 (3.4)	46 (2.3)	25 (1.3)	20 (1.0)
AE of special interest	22 (0.5)	18 (0.9)	13 (0.6)	4 (0.2)	9 (0.4)
Related to study injection					
All	34 (0.8)	16 (0.8)	20 (1.0)	18 (0.9)	25 (1.2)
Serious	0	0	0	0	0
Fatal	0	0	0	0	0
Medically attended	5 (0.1)	3 (0.1)	5 (0.2)	2 (0.1)	3 (0.1)
Leading to study discontinuation	0	0	0	0	0
Severe (≥Grade 3)	1 (<0.1)	0	0	1 (<0.1)	0
AE of special interest	1 (<0.1)	1 (<0.1)	0	0	0

Source: Study mRNA-1083-P301 CSR Table 14.3.2.1.3.

Table 35 Participant incidence of unsolicited treatment-related AEs up to 28 days after injection by severity, SOC, and PT – Cohort A (Safety Set)

	mRNA-1083 40 µg + Placebo (N=2011) n (%)				Fluzone HD + Spikevax (N=2006) n (%)			
System Organ Class Preferred Term	Any Severity/ Grade	Mild/ Grade 1	Moderate/ Grade 2	Severe/ ≥Grade 3	Any Severity/ Grade	Mild/ Grade 1	Moderate/ Grade 2	Severe/ ≥Grade 3
Number of participants reporting unsolicited AEs	16 (0.8)	12 (0.6)	4 (0.2)	0	20 (1.0)	17 (0.8)	3 (0.1)	0
Number of unsolicited AEs	19	14	5	0	21	18	3	0
Infections and infestations	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Herpes zoster	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Blood and lymphatic system disorders	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Lymphadenopathy	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Metabolism and nutrition disorders	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Decreased appetite	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Psychiatric disorders	2 (<0.1)	1 (<0.1)	1 (<0.1)	0	0	0	0	0
Confusional state	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Insomnia	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Nervous system disorders	1 (<0.1)	1 (<0.1)	0	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	0
Paresthesia	1 (<0.1)	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)	0	0
Dizziness	0	0	0	0	1 (<0.1)	0	1 (<0.1)	0
Eye disorders	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Eye pain	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Ear and labyrinth disorders	0	0	0	0	2 (<0.1)	2 (<0.1)	0	0
Tinnitus	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Vertigo	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Vascular disorders	0	0	0	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	0
Hypertension	0	0	0	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	0
Respiratory, thoracic and mediastinal disorders	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Cough	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Nasal congestion	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Gastrointestinal disorders	2 (<0.1)	1 (<0.1)	1 (<0.1)	0	0	0	0	0
Diarrhea	2 (<0.1)	2 (<0.1)	0	0	0	0	0	0
Constipation	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	4 (0.2)	4 (0.2)	0	0
Dermatitis contact	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Rash	0	0	0	0	2 (<0.1)	2 (<0.1)	0	0
Rash papular	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Musculoskeletal and connective tissue disorders	4 (0.2)	4 (0.2)	0	0	2 (<0.1)	2 (<0.1)	0	0
Pain in extremity	2 (<0.1)	2 (<0.1)	0	0	0	0	0	0
Limb discomfort	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Muscular weakness	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Muscle spasms	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Neck pain	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
General disorders and administration site conditions	4 (0.2)	4 (0.2)	0	0	4 (0.2)	4 (0.2)	0	0
Injection site pain	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Injection site pruritus	1 (<0.1)	1 (<0.1)	0	0	4 (0.2)	4 (0.2)	0	0
Injection site swelling	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Pain	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Swelling	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Skin abrasion	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0

Source: Table 14.3.2.5.5a

Table 36 Participant incidence of unsolicited treatment-related AEs up to 28 days after injection by severity, SOC and PT – Cohort B (Safety Set)

	mRNA-1083 40 µg + Placebo (N=1993) n (%)				Fluarix + Spikevax (N=2005) n (%)			
System Organ Class Preferred Term	Any Severity/ Grade	Mild/ Grade 1	Moderate/ Grade 2	Severe/ ≥Grade 3	Any Severity/ Grade	Mild/ Grade 1	Moderate/ Grade 2	Severe/ ≥Grade 3
Number of participants reporting unsolicited AEs	18 (0.9)	13 (0.7)	4 (0.2)	1 (<0.1)	25 (1.2)	21 (1.0)	4 (0.2)	0
Number of unsolicited AEs	21	14	6	0	38	31	7	0
Infections and infestations	2 (0.1)	2 (0.1)	0	0	4 (0.2)	3 (0.1)	1 (<0.1)	0
Oral herpes	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Viral rash	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Bronchitis	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Nasopharyngitis	0	0	0	0	1(<0.1)	1 (<0.1)	0	0
Upper respiratory tract infection	0	0	0	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	0
Blood and lymphatic system disorders	2 (0.1)	1 (<0.1)	1 (<0.1)	0	0	0	0	0
Lymphadenopathy	2 (0.1)	1 (<0.1)	1 (<0.1)	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Dehydration	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Psychiatric disorders	3 (0.2)	3 (0.2)	0	0	1 (<0.1)	1 (<0.1)	0	0
Immunization stress-related response	2 (0.1)	2 (0.1)	0	0	0	0	0	0
Irritability	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Insomnia	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Nervous system disorders	0	0	0	0	2 (<0.1)	2 (<0.1)	0	0
Dizziness	0	0	0	0	2 (<0.1)	2 (<0.1)	0	0
Ear and labyrinth disorders	0	0	0	0	2 (<0.1)	2 (<0.1)	0	0
Ear congestion	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Tinnitus	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	4 (0.2)	3 (0.1)	1 (<0.1)	0
Cough	0	0	0	0	3 (0.1)	2 (<0.1)	1 (<0.1)	0
Dysphonia	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Nasal congestion	0	0	0	0	2 (<0.1)	2 (<0.1)	0	0
Rhinorrhea	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Sinus pain	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Gastrointestinal disorders	4 (0.2)	3 (0.2)	1 (<0.1)	0	6 (0.3)	4 (0.2)	2 (<0.1)	0
Constipation	2 (0.1)	1 (<0.1)	1 (<0.1)	0	0	0	0	0
Feces discolored	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Nausea	1 (<0.1)	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)	0	0
Abdominal pain upper	0	0	0	0	1 (<0.1)	0	1 (<0.1)	0
Aphthous ulcer	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Defecation urgency	0	0	0	0	1 (<0.1)	0	1 (<0.1)	0
Diarrhea	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0

System Organ Class Preferred Term	mRNA-1083 40 µg + Placebo (N=1993) n (%) Any Severity/ Grade	Mild/ Grade 1	Moderate/ Grade 2	Severe/ ≥Grade 3	Fluarix + Spikevax (N=2005) n (%) Any Severity/ Grade	Mild/ Grade 1	Moderate/ Grade 2	Severe/ ≥Grade 3
Gastrointestinal tract irritation	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Skin and subcutaneous tissue disorders	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)	0	0
Dermatitis allergic	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Pruritus	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Musculoskeletal and connective tissue disorders	1 (<0.1)	0	1 (<0.1)	0	4 (0.2)	3 (0.1)	1 (<0.1)	0
Arthralgia	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Myalgia	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Back pain	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Muscle swelling	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Pain in extremity	0	0	0	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	0
Renal and urinary disorders	0	0	0	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	0
Micturition urgency	0	0	0	0	1 (<0.1)	0	1 (<0.1)	0
Polyuria	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
General disorders and administration site conditions	7 (0.4)	5 (0.3)	1 (<0.1)	1 (<0.1)	3 (0.1)	3 (0.1)	0	0
Injection site pruritus	3 (0.2)	3 (0.2)	0	0	2 (<0.1)	2 (<0.1)	0	0
Axillary pain	1 (<0.1)	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)	0	0
Fatigue	1 (<0.1)	0	0	1 (<0.1)	0	0	0	0
Influenza like illness	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0
Peripheral swelling	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0
Investigations	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Blood pressure increased	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Injury, poisoning and procedural complications	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0
Epicondylitis	0	0	0	0	1 (<0.1)	1 (<0.1)	0	0

Source: Table 14.3.2.5.5b.

Medically attended adverse events in Study mRNA-1083-P301

MAAEs up to 28 days after injection

≥65 years (Cohort A)

Participant incidences of MAAEs up to 28 days after injection with occurrence in ≥3 participants ≥65 years (Cohort A) in any group are presented in Table 37 (by SOC and PT).

MAAEs that were assessed as related to the study injection by the Investigator were reported by 0.1% (3/2011) of participants in the mRNA-1083 group and 0.2% (5/2006) of participants in the active comparator group):

- mRNA-1083: herpes zoster and eye pain, which resolved, and paraesthesia, which did not resolve (each reported by <0.1% [1/2011] of participants).
- Fluzone HD + Spikevax: hypertension (reported by <0.1% [2/2006] of participants) and herpes zoster, rash, and papular rash (each reported by <0.1% [1/2006] of participants), all of

which resolved (including 1 MAAE of hypertension which resolved with sequelae of ongoing medication).

None of the MAAEs assessed as related to study injection by the Investigator were SAEs. All MAAEs assessed as related to study injection by the Investigator were mild or moderate in intensity.

≥50 to <65 years (Cohort B)

Participant incidences of MAAEs up to 28 days after injection with occurrence in ≥3 participants ≥50 to <65 years (Cohort B) in any group are presented in Table 38 (by SOC and PT).

Up to 28 days after injection, MAAEs that were assessed as related to the study injection by the Investigator were reported by 0.1% (2/1993) of participants in the mRNA-1083 group and 0.1% (3/2005) of participants in the active comparator group:

- mRNA-1083: lymphadenopathy and dermatitis allergic (each reported by <0.1% [1/1993] of participants), which resolved.
- Fluarix + Spikevax: upper respiratory tract infection, bronchitis, and blood pressure increased (each reported by <0.1% [1/2005] of participants), all of which resolved.

None of the MAAEs assessed as related to study injection by the Investigator were SAEs. All MAAEs assessed as related to study injection by the Investigator were of mild or moderate intensity and all resolved.

Table 37 Study mRNA-1083-P301: Participant incidence of MAAEs up to 28 days after injection with occurrence in ⩾3 participants ⩾65 years (Cohort A) in any group by SOC and PT

	≥65 Years (Cohort A)	
System Organ Class Preferred Term	**mRNA-1083 40 µg + Placebo (N=2011) n (%)**	**Fluzone HD + Spikevax (N=2006) n (%)**
Number of participants reporting unsolicited AEs	138 (6.9)	144 (7.2)
Number of unsolicited AEs	181	194
Infections and infestations	57 (2.8)	59 (2.9)
COVID-19	7 (0.3)	10 (0.5)
Bronchitis	5 (0.2)	9 (0.4)
Upper respiratory tract infection	5 (0.2)	11 (0.5)
Diverticulitis	4 (0.2)	1 (<0.1)
Acute sinusitis	3 (0.1)	1 (<0.1)
Conjunctivitis	3 (0.1)	2 (<0.1)
Herpes zoster	3 (0.1)	1 (<0.1)
Sinusitis	3 (0.1)	3 (0.1)
Tooth abscess	3 (0.1)	0
Viral upper respiratory tract infection	3 (0.1)	1 (<0.1)
Pneumonia	1 (<0.1)	3 (0.1)
Urinary tract infection	1 (<0.1)	7 (0.3)
Metabolism and nutrition disorders	8 (0.4)	12 (0.6)
Type 2 diabetes mellitus	3 (0.1)	2 (<0.1)

System Organ Class Preferred Term	≥65 Years (Cohort A) mRNA-1083 40 µg + Placebo (N=2011) n (%)	≥65 Years (Cohort A) Fluzone HD + Spikevax (N=2006) n (%)
Nervous system disorders	7 (0.3)	7 (0.3)
Syncope	1 (<0.1)	4 (0.2)
Cardiac disorders	3 (0.1)	7 (0.3)
Atrial fibrillation	1 (<0.1)	4 (0.2)
Vascular disorders	9 (0.4)	7 (0.3)
Hypertension	8 (0.4)	5 (0.2)
Musculoskeletal and connective tissue disorders	10 (0.5)	12 (0.6)
Back pain	2 (<0.1)	3 (0.1)
Osteoarthritis	2 (<0.1)	4 (0.2)
Injury, poisoning and procedural complications	16 (0.8)	16 (0.8)
Fall	5 (0.2)	1 (<0.1)

Source: Study mRNA-1083-P301 CSR Table 14.3.2.8.1a.

Table 38 Study mRNA-1083-P301: Participant incidence of MAAEs up to 28 days after injection with occurrence in ⩾3 participants ⩾50 to <65 years (Cohort B) in any group by SOC and PT (Safety Set)

System Organ Class Preferred Term	≥50 to <65 (Cohort B) mRNA-1083 40 µg + Placebo (N=1993) n (%)	≥50 to <65 (Cohort B) Fluarix + Spikevax (N=2005) n (%)
Number of participants reporting unsolicited AEs	100 (5.0)	101 (5.0)
Number of unsolicited AEs	123	128
Infections and infestations	44 (2.2)	45 (2.2)
Sinusitis	7 (0.4)	5 (0.2)
Upper respiratory tract infection	7 (0.4)	12 (0.6)
Urinary tract infection	4 (0.2)	1 (<0.1)
Ear infection	3 (0.2)	5 (0.2)
Influenza	3 (0.2)	4 (0.2)
Tooth abscess	3 (0.2)	1 (<0.1)
Bronchitis	2 (0.1)	3 (0.1)
COVID-19	2 (0.1)	7 (0.3)
Nasopharyngitis	2 (0.1)	3 (0.1)
Psychiatric disorders	5 (0.3)	7 (0.3)
Depression	1 (<0.1)	3 (0.1)
Vascular disorders	9 (0.5)	8 (0.4)
Hypertension	7 (0.4)	7 (0.3)

Source: Study mRNA-1083-P301 CSR Table 14.3.2.8.1b.

MAAEs up to EOS/Day 181

Among participants ≥65 years (Cohort A) up to EOS/Day 181, 21.2% (426/2011) of participants in the mRNA-1083 group and 21.3% (428/2006) of participants in the Fluzone HD + Spikevax group experienced at least 1 MAAE.

MAAEs were most frequently reported in the SOC infections and infestations (9.2% [186/2011] of participants in the mRNA-1083 group vs 8.5% [171/2006] of participants in the active comparator group); injury, poisoning, and procedural complications (2.6% [53/2011] vs 2.8% [57/2006]); musculoskeletal and connective tissue disorders (2.6% [52/2011] vs 2.8% [56/2006]); metabolism and nutrition disorders (1.9% [39/2011] vs 2.1% [43/2006]); and respiratory, thoracic, and mediastinal disorders (1.9% [38/2011] vs 1.0% [20/2006]). By PT, MAAEs occurring in ≥1% of participants in either group were COVID-19 (1.5% [30/2011] of participants in the mRNA-1083 group vs 2.5% [51/2006] of participants in the active comparator group), upper respiratory tract infection (1.2% [24/2011] and 1.1% [22/2006]), and hypertension (1.2% [24/2011] and 1.0% [21/2006]).

No additional MAAEs assessed as related to study injection by the Investigator were reported beyond 28 days after injection up to EOS/Day 181.

Among participants ≥50 to <65 years (Cohort B) up to EOS/Day 181, 15.1% (301/1993) of participants in the mRNA-1083 group and 15.2% (304/2005) of participants in the Fluarix + Spikevax group experienced at least 1 MAAE.

MAAEs were most frequently reported in the SOC infections and infestations (6.1% [122/1993] of participants in the mRNA-1083 group vs 7.1% [142/2005] of participants in the active comparator group); injury, poisoning, and procedural complications (1.6% [31/1993] vs 1.7% [35/2005]); and metabolism and nutrition disorders (1.6% [31/1993] vs 1.4% [29/2005]). By PT, MAAEs occurring in ≥ 1% of participants in either group were COVID-19 (1.1% [22/1993] of participants in the mRNA-1083 group vs 1.1% [23/2005] of participants in the active comparator group), upper respiratory tract infection (1.1% [22/1993] vs 1.2% [25/2005]), and hypertension (1.0% [20/1993] vs 1.0% [20/2005]).

No additional MAAEs assessed as related to study injection by the Investigator were reported beyond 28 days after injection up to EOS/Day 181.

Unsolicited Adverse Events in Study mRNA-1083-P101

Only the 5 most relevant (out of 12) treatment groups are described.

≥65 to <80 years (Cohort A)

Among participants ≥65 to <80 years (Cohort A), unsolicited AEs **within 28 days** after mRNA-1083 injection were reported for 13.7% (7/51) of participants in the mRNA-1083 30-µg group and 6.1% (2/33) of participants in the mRNA-1083 60-µg group. Additionally, in the Fluarix, Fluzone HD, and mRNA-1273 groups, the proportions of unsolicited AEs were 9.3% (5/54), 17.0% (9/53), and 13.0% (7/54), respectively. One participant each in the mRNA-1083 30-µg, Fluzone HD, and mRNA-1273 groups experienced SAEs.

The incidence of unsolicited AEs that were assessed by the Investigator as **related** to study injection were 5.9% (3/51) of participants in the mRNA-1083 30-µg group and none in the mRNA-1083 60-µg group. Additionally, in the Fluarix, Fluzone HD, and mRNA-1273 groups, the proportions of unsolicited AEs assessed by the Investigator as related to study injection were 1.9% (1/54), 5.7% (3/53), and 5.6% (3/54), respectively. There was no PT for which more than 1 participant had an unsolicited AE that was assessed as related. The following unsolicited AEs by PT were assessed by the Investigator

as related to the study injection in the mRNA-1083 30-µg group: bronchitis, diarrhoea, urinary incontinence, thrombocytopenia, and white blood cell count decreased. Unsolicited AEs assessed as related to study injection by the Investigator in the comparator groups included thrombocytopenia in the Fluarix group; decreased appetite, alanine aminotransferase increased, and hepatic enzyme increased in the Fluzone HD group; and thrombocytopenia, dizziness, and syncope in the mRNA-1273 group.

Among participants ≥65 to <80 years (Cohort A), unsolicited AEs **up to EOS/Day 181** were reported for 27.5% (14/51) of participants in the mRNA-1083 30-µg group, 15.2% (5/33) of participants in the mRNA-1083 60-µg group, 25.9% (14/54) of participants in the Fluarix group, 43.4% (23/53) of participants in the Fluzone HD group, and 25.9% (14/54) of participants in the mRNA-1273 group, including 2 participants each in the mRNA-1083 30-µg, Fluarix, Fluzone HD, and mRNA-1273 groups with at least 1 SAE.

No unsolicited AEs beyond 28 days after injection were assessed as related to study injection by the Investigator in the mRNA-1083, Fluarix, Fluzone HD, or mRNA-1273 groups.

≥50 to <65 years (Cohort B)

Among participants ≥50 to <65 years (Cohort B), unsolicited AEs **within 28 days** after mRNA-1083 injection were reported for 3.6% (1/28) of participants in the mRNA-1083 30-µg group and 12.5% (2/16) of participants in the mRNA-1083 60-µg group. In the Fluarix, and mRNA-1273 groups, the proportions of unsolicited AEs were 3.8% (1/26) and 14.8% (4/27). No severe AEs or SAEs were reported in the mRNA-1083, Fluarix, or mRNA-1273 groups.

Unsolicited AEs in the mRNA-1083 30-µg group included nasal congestion, which was assessed by the Investigator as **related** to study. Unsolicited AEs in the mRNA-1083 60-µg group included depression and ulna fracture, each in 1 participant, and were assessed as **not** related to study injection.

In the Fluarix group, no unsolicited AEs were assessed as related to study injection by the Investigator. One unsolicited AE assessed as related to study injection by the Investigator in the mRNA-1273 group was hepatic enzyme increased, which was assessed as related to study injection by the Investigator.

Among participants ≥50 to <65 years (Cohort B), unsolicited AEs **up to EOS/Day 181** were reported for 17.9% (5/28) of participants in the mRNA-1083 30-µg group and 25.0% (4/16) of participants in the mRNA-1083 60-µg group.

In the Fluarix group, 19.2% (5/26) of participants experienced unsolicited AEs up to EOS/Day 181; none were assessed as related to study injection by the Investigator. In the mRNA-1273 group, 37.0% (10/27) of participants experienced unsolicited AEs up to EOS/Day 181.

No additional participants experienced unsolicited AEs beyond 28 days after injection that were assessed as related to study injection by the Investigator.

Adverse drug reactions

Adverse reactions reported are listed according to the following frequency convention: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data).

Table 39 Adverse reactions proposed for inclusion by the applicant in the SmPC

MedDRA system organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very common	Axillary swelling or tenderness

MedDRA system organ class	Frequency	Adverse reaction
Nervous system disorders	Very common	Headache
Gastrointestinal disorders	Common	Nausea/vomiting
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills
	Common	Pyrexia
	Common	Injection site swelling Injection site erythema

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest (AESI) in Study mRNA-1083-P301

An AESI was defined as an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program for which ongoing monitoring and immediate notification by the Investigator to the Sponsor was required and documentation was in the form of a case narrative. The Investigator's medical judgment was applied to assess an event as an AESI, as most AESIs are based on medical concepts.

The table below does not provide a comprehensive list of terms. The table describes events/medical concepts that are of interest in COVID-19 vaccine safety surveillance. Some are specific to vaccines; however, some are of interest due to their occurrence in the context of concurrent or recent COVID-19. Events falling into the descriptions below should be reported as AESIs, per protocol, even when they occur during/following COVID-19 infection

Table 40 Adverse Events of Special Interest in this Summary of Clinical Safety

Anosmia, ageusia	Subacute thyroiditis
Acute pancreatitis	Appendicitis
Rhabdomyolysis	ARDS
Coagulation disorders	Acute cardiovascular injury
Acute kidney injury	Acute liver injury
Dermatologic findings	Systemic inflammatory syndromes
Thrombocytopenia	Acute aseptic arthritis
New onset of or worsening of neurologic disease	Anaphylaxis
Other syndromes (detailed in the protocol)	

Abbreviation: ARDS = acute respiratory distress syndrome. Source: Modified from Study P301 Protocol Amendment 1 Section 10.6.

*Table 41 Study mRNA-1083-P301: Participant Incidence of **AESIs** as Assessed by Investigator Up to EOS/Day 181 by SOC and PT (Safety Set)*

	Pooled Cohort	≥65 Years (Cohort A)		≥50 to <65 (Cohort B)	
	mRNA-1083 40 µg + Placebo (N=4004) n (%)	mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)
Number of participants reporting unsolicited AEs	22 (0.5)	18 (0.9)	13 (0.6)	4 (0.2)	9 (0.4)
Number of unsolicited AEs	23	18	13	5	10
Infections and infestations	1 (<0.1)	1 (<0.1)	1 (<0.1)	0	1 (<0.1)
Appendicitis	1 (<0.1)	1 (<0.1)	1 (<0.1)	0	1 (<0.1)
Psychiatric disorders	1 (<0.1)	1 (<0.1)	0	0	0
Confusional state	1 (<0.1)	1 (<0.1)	0	0	0
Nervous system disorders	6 (0.1)	4 (0.2)	1 (<0.1)	2 (0.1)	2 (<0.1)
Anosmia	2 (<0.1)	0	0	2 (0.1)	1 (<0.1)
Cerebrovascular accident	2 (<0.1)	2 (<0.1)	0	0	0
Ageusia	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)
Bell's palsy	1 (<0.1)	1 (<0.1)	0	0	1 (<0.1)
Transient ischaemic attack	1 (<0.1)	1 (<0.1)	0	0	0
Ischaemic stroke	0	0	1 (<0.1)	0	0
Cardiac disorders	6 (0.1)	4 (0.2)	8 (0.4)	2 (0.1)	5 (0.2)
Atrial fibrillation	2 (<0.1)	2 (<0.1)	2 (<0.1)	0	1 (<0.1)
Acute myocardial infarction	1 (<0.1)	1 (<0.1)	1 (<0.1)	0	0
Coronary artery disease	1 (<0.1)	0	0	1 (<0.1)	0
Myocardial infarction	1 (<0.1)	1 (<0.1)	1 (<0.1)	0	2 (<0.1)
Pericarditis	1 (<0.1)	0	0	1 (<0.1)	0
Acute coronary syndrome	0	0	2 (<0.1)	0	0
Cardiac arrest	0	0	0	0	1 (<0.1)
Cardiac failure acute	0	0	2 (<0.1)	0	0
Pericardial effusion	0	0	0	0	1 (<0.1)
Vascular disorders	3 (<0.1)	3 (0.1)	2 (<0.1)	0	0
Deep vein thrombosis	2 (<0.1)	2 (<0.1)	2 (<0.1)	0	0
Superficial vein thrombosis	1 (<0.1)	1 (<0.1)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (<0.1)	0	1 (<0.1)
Pulmonary embolism	0	0	1 (<0.1)	0	1 (<0.1)
Gastrointestinal disorders	1 (<0.1)	1 (<0.1)	0	0	0
Pancreatitis acute	1 (<0.1)	1 (<0.1)	0	0	0
Renal and urinary disorders	4 (<0.1)	4 (0.2)	0	0	0
Acute kidney injury	4 (<0.1)	4 (0.2)	0	0	0

Source: Study mRNA-1083-P301 CSR Table 14.3.2.10.2a, Table 14.3.2.10.2b, and Table 14.3.2.10.4.

Serious adverse events in Study mRNA-1083-P301

*Table 42 Participant Incidence of Unsolicited **SAE** Throughout the Study by System Organ Class and Preferred Term — **Cohort A** Safety Set*

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=2011 n (%)	Fluzone HD + Spikevax N=2006 n (%)
Number of Participants Reporting Unsolicited SAEs	70 (3.5)	52 (2.6)
Number of Unsolicited SAEs	96	84
Infections and infestations	12 (0.6)	13 (0.6)
Cellulitis	2 (<0.1)	1 (<0.1)
Appendicitis	1 (<0.1)	1 (<0.1)
COVID-19	1 (<0.1)	0
Diabetic foot infection	1 (<0.1)	0
Extradural abscess	1 (<0.1)	0
Gastroenteritis	1 (<0.1)	0
Pneumonia	1 (<0.1)	3 (0.1)
Sepsis	1 (<0.1)	1 (<0.1)
Streptococcal abscess	1 (<0.1)	0
Urinary tract infection	1 (<0.1)	1 (<0.1)
Urosepsis	1 (<0.1)	0
Vulval cellulitis	1 (<0.1)	0
Abdominal sepsis	0	1 (<0.1)
Abscess limb	0	1 (<0.1)
Bacterial sepsis	0	1 (<0.1)
Diverticulitis	0	1 (<0.1)
Diverticulitis intestinal perforated	0	1 (<0.1)
Infected bite	0	1 (<0.1)
Peritonitis	0	1 (<0.1)
Respiratory syncytial virus infection	0	1 (<0.1)
Septic shock	0	1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.3)	6 (0.3)
Bladder cancer	1 (<0.1)	0
Bladder transitional cell carcinoma	1 (<0.1)	0
Colon cancer	1 (<0.1)	0

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=2011 n (%)	Fluzone HD + Spikevax N=2006 n (%)
Gastrointestinal adenocarcinoma	1 (<0.1)	0
Neoplasm malignant	1 (<0.1)	0
Plasma cell myeloma	1 (<0.1)	0
Prostate cancer	1 (<0.1)	1 (<0.1)
Benign abdominal neoplasm	0	1 (<0.1)
Breast cancer	0	1 (<0.1)
Colorectal cancer metastatic	0	1 (<0.1)
Lung adenocarcinoma	0	1 (<0.1)
Squamous cell carcinoma of skin	0	1 (<0.1)
Blood and lymphatic system disorders	0	1 (<0.1)
Anaemia	0	1 (<0.1)
Metabolism and nutrition disorders	5 (0.2)	4 (0.2)
Hyperkalaemia	2 (<0.1)	0
Hypoglycaemia	2 (<0.1)	0
Diabetes mellitus	1 (<0.1)	0
Diabetic ketoacidosis	0	2 (<0.1)
Hypovolaemia	0	1 (<0.1)
Lactic acidosis	0	1 (<0.1)
Psychiatric disorders	5 (0.2)	1 (<0.1)
Alcohol withdrawal syndrome	1 (<0.1)	0
Bipolar disorder	1 (<0.1)	0
Major depression	1 (<0.1)	1 (<0.1)
Mental status changes	1 (<0.1)	0
Suicidal ideation	1 (<0.1)	0
Nervous system disorders	11 (0.5)	4 (0.2)
Cerebrovascular accident	3 (0.1)	0
Metabolic encephalopathy	2 (<0.1)	0
Aphasia	1 (<0.1)	0
Haemorrhage intracranial	1 (<0.1)	0
Headache	1 (<0.1)	0
Hepatic encephalopathy	1 (<0.1)	0
Lumbar radiculopathy	1 (<0.1)	0
Transient global amnesia	1 (<0.1)	0
Transient ischaemic attack	1 (<0.1)	1 (<0.1)
Ischaemic stroke	0	1 (<0.1)
Subarachnoid haemorrhage	0	1 (<0.1)
Syncope	0	2 (<0.1)

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=2011 n (%)	Fluzone HD + Spikevax N=2006 n (%)
Cardiac disorders	8 (0.4)	14 (0.7)
Atrial fibrillation	2 (<0.1)	3 (0.1)
Coronary artery disease	2 (<0.1)	0
Acute myocardial infarction	1 (<0.1)	1 (<0.1)
Angina pectoris	1 (<0.1)	1 (<0.1)
Bradycardia	1 (<0.1)	0
Cardiac failure congestive	1 (<0.1)	0
Mitral valve incompetence	1 (<0.1)	0
Myocardial infarction	1 (<0.1)	1 (<0.1)
Acute coronary syndrome	0	2 (<0.1)
Cardiac arrest	0	2 (<0.1)
Cardiac failure acute	0	2 (<0.1)
Coronary artery stenosis	0	1 (<0.1)
Pericardial effusion	0	1 (<0.1)
Vascular disorders	2 (<0.1)	2 (<0.1)
Hypertension	1 (<0.1)	0
Orthostatic hypotension	1 (<0.1)	0
Deep vein thrombosis	0	2 (<0.1)
Respiratory, thoracic and mediastinal disorders	9 (0.4)	4 (0.2)
Acute respiratory failure	4 (0.2)	2 (<0.1)
Chronic obstructive pulmonary disease	2 (<0.1)	1 (<0.1)
Hypoxia	1 (<0.1)	0
Pulmonary embolism	1 (<0.1)	1 (<0.1)
Pulmonary oedema	1 (<0.1)	0
Gastrointestinal disorders	4 (0.2)	7 (0.3)
Haemoperitoneum	1 (<0.1)	0
Hiatus hernia	1 (<0.1)	0
Intestinal perforation	1 (<0.1)	0
Intra-abdominal fluid collection	1 (<0.1)	0
Pancreatitis acute	1 (<0.1)	1 (<0.1)
Abdominal adhesions	0	1 (<0.1)
Colitis	0	1 (<0.1)
Internal hernia	0	1 (<0.1)
Intestinal obstruction	0	2 (<0.1)
Nausea	0	1 (<0.1)
Small intestinal obstruction	0	2 (<0.1)
Vomiting	0	1 (<0.1)
Hepatobiliary disorders	2 (<0.1)	2 (<0.1)
Cholelithiasis	2 (<0.1)	0

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=2011 n (%)	Fluzone HD + Spikevax N=2006 n (%)
Cholecystitis acute	0	1 (<0.1)
Cholecystitis chronic	0	1 (<0.1)
Skin and subcutaneous tissue disorders	1 (<0.1)	0
Angioedema	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	5 (0.2)	3 (0.1)
Arthralgia	1 (<0.1)	0
Back pain	1 (<0.1)	0
Intervertebral disc degeneration	1 (<0.1)	0
Pain in extremity	1 (<0.1)	0
Rhabdomyolysis	1 (<0.1)	0
Fracture nonunion	0	1 (<0.1)
Musculoskeletal chest pain	0	1 (<0.1)
Osteoarthritis	0	1 (<0.1)
Renal and urinary disorders	3 (0.1)	1 (<0.1)
Urinary retention	2 (<0.1)	0
Acute kidney injury	1 (<0.1)	1 (<0.1)
Nephrolithiasis	1 (<0.1)	0
Reproductive system and breast disorders	0	1 (<0.1)
Benign prostatic hyperplasia	0	1 (<0.1)
Congenital, familial and genetic disorders	1 (<0.1)	0
Janus kinase 2 mutation	1 (<0.1)	0
General disorders and administration site conditions	4 (0.2)	2 (<0.1)
Non-cardiac chest pain	3 (0.1)	0
Death	1 (<0.1)	0
Asthenia	0	1 (<0.1)
Chest pain	0	1 (<0.1)
Investigations	1 (<0.1)	1 (<0.1)
Electrocardiogram abnormal	1 (<0.1)	0
Fibrin D dimer increased	0	1 (<0.1)
Injury, poisoning and procedural complications	6 (0.3)	6 (0.3)
Femur fracture	2 (<0.1)	0
Accidental overdose	1 (<0.1)	0
Hip fracture	1 (<0.1)	0
Pelvic fracture	1 (<0.1)	0
Post procedural haemorrhage	1 (<0.1)	0

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=2011 n (%)	Fluzone HD + Spikevax N=2006 n (%)
Road traffic accident	1 (<0.1)	0
Splenic rupture	1 (<0.1)	0
Fall	0	1 (<0.1)
Head injury	0	2 (<0.1)
Postoperative ileus	0	1 (<0.1)
Radial head dislocation	0	1 (<0.1)
Rib fracture	0	1 (<0.1)
Subdural haematoma	0	2 (<0.1)
Ulna fracture	0	1 (<0.1)

Source: mRNA-1083-P301 CSR Table 14.3.2.6.6.a

*Table 43 Participant Incidence of Unsolicited **SAE** Throughout the Study by System Organ Class and Preferred Term (**Cohort B**; Safety Set)*

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=1993 Any n (%)	Fluarix + Spikevax N=2005 Any n (%)
Number of Participants Reporting Unsolicited SAEs	29 (1.5)	27 (1.3)
Number of Unsolicited SAEs	33	33
Infections and infestations	5 (0.3)	7 (0.3)
Bronchitis	1 (<0.1)	1 (<0.1)
COVID-19	1 (<0.1)	0
Cellulitis	1 (<0.1)	0
Pneumonia	1 (<0.1)	3 (0.1)
Urosepsis	1 (<0.1)	0
Appendicitis	0	1 (<0.1)
Helicobacter infection	0	1 (<0.1)
Influenza	0	1 (<0.1)
Sepsis	0	1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.3)	4 (0.2)
Colon cancer	3 (0.2)	0
Invasive ductal breast carcinoma	1 (<0.1)	0
Lung neoplasm malignant	1 (<0.1)	0
Breast cancer	0	1 (<0.1)
Papillary thyroid cancer	0	1 (<0.1)
Prostate cancer	0	1 (<0.1)
Renal cancer	0	1 (<0.1)
Metabolism and nutrition disorders	1 (<0.1)	1 (<0.1)

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=1993 Any n (%)	Fluarix + Spikevax N=2005 Any n (%)
Diabetic ketoacidosis	1 (<0.1)	0
Dehydration	0	1 (<0.1)
Psychiatric disorders	3 (0.2)	1 (<0.1)
Post-traumatic stress disorder	2 (0.1)	0
Alcohol abuse	1 (<0.1)	0
Suicidal ideation	0	1 (<0.1)
Nervous system disorders	1 (<0.1)	2 (<0.1)
Metabolic encephalopathy	1 (<0.1)	0
Hydrocephalus	0	1 (<0.1)
Psychogenic seizure	0	1 (<0.1)
Cardiac disorders	4 (0.2)	5 (0.2)
Cardiac arrest	1 (<0.1)	2 (<0.1)
Cardiac failure acute	1 (<0.1)	0
Coronary artery disease	1 (<0.1)	0
Pericarditis	1 (<0.1)	0
Atrial fibrillation	0	1 (<0.1)
Myocardial infarction	0	1 (<0.1)
Pericardial effusion	0	1 (<0.1)
Vascular disorders	0	2 (<0.1)
Hypertensive urgency	0	2 (<0.1)
Respiratory, thoracic and mediastinal disorders	2 (0.1)	4 (0.2)
Chronic obstructive pulmonary disease	2 (0.1)	2 (<0.1)
Acute respiratory failure	0	1 (<0.1)
Pulmonary embolism	0	1 (<0.1)
Gastrointestinal disorders	3 (0.2)	1 (<0.1)
Abdominal pain	1 (<0.1)	0
Enterovesical fistula	1 (<0.1)	0
Volvulus	1 (<0.1)	0
Small intestinal obstruction	0	1 (<0.1)
Hepatobiliary disorders	1 (<0.1)	1 (<0.1)
Cholecystitis acute	1 (<0.1)	1 (<0.1)
Skin and subcutaneous tissue disorders	1 (<0.1)	0
Ecchymosis	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	1 (<0.1)	0
Costochondritis	1 (<0.1)	0
Renal and urinary disorders	0	1 (<0.1)
Nephrolithiasis	0	1 (<0.1)
Reproductive system and breast disorders	0	1 (<0.1)

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=1993 Any n (%)	Fluarix + Spikevax N=2005 Any n (%)
Benign prostatic hyperplasia	0	1 (<0.1)
General disorders and administration site conditions	2 (0.1)	1 (<0.1)
Non-cardiac chest pain	1 (<0.1)	0
Oedema peripheral	1 (<0.1)	0
Death	0	1 (<0.1)
Injury, poisoning and procedural complications	4 (0.2)	1 (<0.1)
Radius fracture	1 (<0.1)	0
Spinal compression fracture	1 (<0.1)	0
Thermal burn	1 (<0.1)	0
Wrist fracture	1 (<0.1)	0
Meniscus injury	0	1 (<0.1)

Source: mRNA-1083-P301 CSR Table 14.3.2.6.6.b

Deaths in Study mRNA-1083-P301

*Table 44 Participant Incidence of Unsolicited AE Leading to **Death** Throughout the Study by System Organ Class and Preferred Term (**Cohort A**; Safety Set)*

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=2011 n (%)	Fluzone HD + Spikevax N=2006 n (%)
Number of Participants Reporting Unsolicited AEs Leading to Death	2 (<0.1)	1 (<0.1)
Number of Unsolicited AEs Leading to Death	2	1
Cardiac disorders	0	1 (<0.1)
Cardiac arrest	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	1 (<0.1)	0
Pulmonary embolism	1 (<0.1)	0
General disorders and administration site conditions	1 (<0.1)	0
Death	1 (<0.1)	0

Source: mRNA-1083-P301 CSR Table 14.3.2.15.2a

*Table 45 Participant Incidence of Unsolicited AE Leading to **Death** Throughout the Study by System Organ Class and Preferred Term (**Cohort B**; Safety Set)*

System Organ Class Preferred Term	mRNA-1083 40 μg + Placebo N=1993 n (%)	Fluarix + Spikevax N=2005 n (%)
Number of Participants Reporting Unsolicited AEs Leading to Death	2 (0.1)	2 (<0.1)
Number of Unsolicited AEs Leading to Death	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	0
Lung neoplasm malignant	1 (<0.1)	0
Cardiac disorders	1 (<0.1)	1 (<0.1)
Cardiac arrest	1 (<0.1)	1 (<0.1)
General disorders and administration site conditions	0	1 (<0.1)
Death	0	1 (<0.1)

Source: mRNA-1083-P301 CSR Table 14.3.2.15.2.b

Table 46 Study mRNA-1083-P301: Summary of Unsolicited AEs by SMQ and PT Up to EOS/Day 181 (Safety Set)

	Pooled Cohort	≥65 Years (Cohort A)		≥50 to <65 (Cohort B)	
SMQ	mRNA-1083 40 µg + Placebo (N=4004) n (%)	mRNA-1083 40 µg + Placebo (N=2011) n (%)	Fluzone HD + Spikevax (N=2006) n (%)	mRNA-1083 40 µg + Placebo (N=1993) n (%)	Fluarix + Spikevax (N=2005) n (%)
Anaphylactic reaction	0	0	0	0	0
Angioedema	3 (<0.1)	2 (<0.1)	2 (<0.1)	1 (<0.1)	2 (<0.1)
Arthritis	26 (0.6)	16 (0.8)	23 (1.1)	10 (0.5)	6 (0.3)
Cardiac arrhythmias	14 (0.3)	11 (0.5)	8 (0.4)	3 (0.2)	2 (<0.1)
Cardiac failure	6 (0.1)	4 (0.2)	3 (0.1)	2 (0.1)	1 (<0.1)
Cardiomyopathy	0	0	0	0	0
Central nervous system vascular disorder	5 (0.1)	5 (0.2)	5 (0.2)	0	0
Convulsions	1 (<0.1)	1 (<0.1)	0	0	0
Demyelination	0	0	0	0	0
Embolic and thrombotic events	10 (0.2)	10 (0.5)	10 (0.5)	0	3 (0.1)
Guillain-Barré syndrome	0	0	0	0	0
Hematopoietic cytopenias	0	0	0	0	0
Hearing and vestibular disorders	8 (0.2)	6 (0.3)	10 (0.5)	2 (0.1)	5 (0.2)
Hypersensitivity	25 (0.6)	15 (0.7)	17 (0.8)	10 (0.5)	6 (0.3)

Immune-mediated/autoimmune disorders	1 (<0.1)	1 (<0.1)	2 (<0.1)	0	2 (<0.1)
Ischemic heart disease	8 (0.2)	6 (0.3)	9 (0.4)	2 (0.1)	4 (0.2)
Noninfectious myocarditis/pericarditis	1 (<0.1)	0	0	1 (<0.1)	0
Peripheral neuropathy	4 (<0.1)	3 (0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Thrombophlebitis	0	0	0	0	0
Vasculitis	1 (<0.1)	1 (<0.1)	0	0	0

SMQ = standardized MedDRA query. Source: Study mRNA-1083-P301 CSR Table 14.3.2.11.1a, Table 14.3.2.11.1b, and Table 14.3.2.11.4.

AESIs, SAEs, and deaths in Study mRNA-1083-P101

Among participants ≥65 to <80 years (Cohort A) up to 28 days after injection, 1 participant in the mRNA-1083 30-µg group experienced an **AESI** (thrombocytopenia, assessed related by the Investigator). No participants in the mRNA-1083 60-µg group experienced an AESI. Additionally, one participant each in the mRNA-1273 and Fluarix groups experienced an AESI of thrombocytopenia, and one participant in the Fluzone HD group experienced hepatic enzyme increased; all were assessed as related to study injection by the Investigator. One participant in the Fluarix group experienced decreased platelet count, which was assessed as not related to study injection by the Investigator.

Cumulatively among participants ≥65 to <80 years (Cohort A), 1 additional participant in the mRNA-1083 30-µg group beyond 28 days after injection experienced an AESI (thrombocytopenia) up to EOS/Day 181. No AESIs were reported in the mRNA-1083 60-µg group. In the Fluarix group, 1 additional AESI beyond 28 days after injection was reported: acute myocardial infarction. In the mRNA-1273 group, 1 additional AESI beyond 28 days after injection (appendicitis) was reported. In the Fluzone HD group, no additional AESIs beyond 28 days after injection were reported. In all mRNA-1083 and comparator groups, no additional AESIs beyond 28 days after injection were assessed as related to study injection by the Investigator.

Among participants ≥50 to <65 years (Cohort B), no participants in the mRNA-1083 30-µg or 60-µg, Fluarix, or mRNA-1273 groups experienced AESIs up to 28 days after injection.

Cumulatively among participants ≥50 to <65 years (Cohort B), no participants in the mRNA-1083 30-µg or 60-µg, Fluarix, or mRNA-1273 groups experienced AESIs up to EOS/Day 181.

Until 28 days after injection, among participants ≥65 to <80 years (Cohort A), an **SAE** of carotid artery stenosis (verbatim term: worsening of right carotid artery stenosis [severe]) was reported in 1 participant in the mRNA-1083 30-µg group. No additional SAEs were reported in the mRNA-1083 30-µg or 60-µg groups up to 28 days after injection. Other SAEs reported among participants ≥65 to <80 years (Cohort A) was hepatic enzyme increased in the Fluzone HD group and angina pectoris and urinary tract infection in the mRNA 1273 group. The event of hepatic enzyme increased was also an AESI.

Among participants ≥65 to <80 years (Cohort A), 1 additional participant in the mRNA-1083 30 µg group experienced an SAE beyond 28 days after injection up to EOS/Day 181: invasive breast carcinoma. No PT was reported as an SAE in more than 1 participant in either mRNA-1083 30 µg or 60 µg group during the study. No SAEs were assessed as related to mRNA-1083 by the Investigator. In the mRNA-1273 group, 1 additional SAE, non-cardiac chest pain, was reported beyond 28 days. In the Fluzone HD group, 1 additional SAE, incarcerated inguinal hernia, was reported beyond 28 days

after injection. In the Fluarix group, 2 participants experienced SAEs beyond 28 days after injection up to EOS/Day 181, one myocardial infarction (also considered as an AESI) and one haemoglobin decreased. All of the aforementioned SAEs were assessed as not related to study injection by the Investigator.

No SAEs were reported in Cohort B within 28 days after injection in the mRNA-1083 30-µg or 60-µg, Fluarix, Fluzone HD, or mRNA-1273 groups.

Among participants ≥50 to <65 years (Cohort B), 1 participant in the mRNA-1083 60-µg group experienced an SAE up to EOS/Day 181: renal pseudoaneurysm (assessed as not related to study injection by the Investigator). No PT was reported as an SAE in more than 1 participant in either group during the study. No SAEs were reported in the mRNA-1083 30-µg, Fluarix, or mRNA 1273 groups.

No **deaths** were reported in any study intervention group of Study mRNA-1083-P101.

5.4.5. Discontinuation due to adverse events

Study mRNA-1083-P301: The only reported AE leading to discontinuation was one fatal case of lung neoplasm. However, there were other fatal cases, which are described in the section above.

Study mRNA-1083-P101: No discontinuations due to AEs were reported in any study intervention group through EOS/Day 181.

5.4.6. Safety in special populations

In both studies, the frequency and severity of solicited ARs were numerically lower among older participants than among younger participants in the mRNA-1083 and comparator groups. Median times to onset were generally later and median durations were generally shorter among older participants than among younger participants in Study mRNA-1083-P101. In Study mRNA-1083-P301, median durations were generally shorter among older participants than among younger participants; no differences in median times to onset were observed based on age cohorts.

In Study mRNA-1083-P301, reporting of any solicited ARs was numerically higher among White participants than among participants in other racial groups and numerically higher among female participants than among male participants. As with age-based differences, these differences were observed in both the mRNA-1083 and comparator groups. No differences in reactogenicity were observed for subgroups based on BMI category (<30 kg/m2 or ⩾30 kg/m2).

Among participants ⩾50 to <65 years (Cohort B), a higher percentage of participants reporting solicited ARs was observed among those with negative Baseline SARS-CoV-2 status in the mRNA-1083 group (N=393) as compared to the overall percentage of participants reporting solicited ARs. Subgroups for sex, race, and BMI were not summarized for Study mRNA-1083-P101.

No studies have been conducted of the effects of mRNA-1083 on pregnancy and lactation. Up to EOS/Day 181, no pregnancies were reported in Study mRNA-1083-P301. In Study mRNA-1083 P101, 3 pregnancies were reported in participants of Cohort B, which also included younger adults. One pregnancy resulted in a live birth without congenital anomalies at 37 weeks 4 days in a participant who received mRNA-1083.2 27.5 µg, 1 pregnancy resulted in an elective termination without reported congenital anomalies in a participant who received mRNA-1083 15 µg, and 1 pregnancy outcome was reported as term birth at 39 weeks (vaginal with no complications) in a participant who received mRNA-1083 30 µg.

5.4.7. Immunological events

Not applicable

5.4.8. Safety related to drug-drug interactions and other interactions

Not applicable

5.4.9. Vital signs and laboratory findings

Clinical laboratory tests performed in **Study mRNA-1083-P101** did not identify a safety concern.

Shifts from baseline <Grade 2 to postbaseline ≥Grade 2 results in laboratory test results within 7 days after injection were reported for all treatment groups, including the authorised influenza vaccine comparators. Analysis of vital signs from pre- to at least 60 minutes postinjection did not raise safety concerns for mRNA-1083. Mean and median changes in vital signs from before injection to at least 60 minutes after injection were minor and not medically relevant in any study intervention group.

Routine clinical laboratory evaluations were not performed in **Study mRNA-1083-P301**. Analysis of vital signs (diastolic and systolic blood pressure, heart rate, respiratory rate) before and after injection at Day 1 did not raise safety concerns for mRNA-1083. Mean and median changes in vital signs were minor and not medically relevant in any study intervention group. No relevant differences were observed between the groups. Unsolicited AEs reported up to 7 days after the injection that could indicate vital sign changes were as follows:

In the mRNA-1083 group, 4 (0.2%) participants experienced hypertension and 2 (<0.1%) participants experienced increased blood pressure, none of which were assessed as related to the study injection by the Investigator. Three of these participants had ongoing medical conditions of hypertension or essential hypertension.

In the Fluzone HD + Spikevax group, 4 (0.2%) participants experienced hypertension, 2 (<0.1%) participants experienced increased blood pressure, 1 (<0.1%) participant experienced increased systolic blood pressure, and 1 (<0.1%) participant experienced dizziness. Two events of hypertension and the event of dizziness were assessed as related to the study injection by the Investigator. Six of these participants had ongoing medical condition of hypertension.

5.4.10. Post marketing experience

Not applicable

5.4.11. Supportive studies

Supportive study mRNA-1010-P301

Study mRNA-1010-P301 was a global, multicentre phase 3, randomised, stratified, observer-blind, active-controlled study to evaluate the immunogenicity and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years and older. The study was conducted at 53 centres in Argentina, Australia, Colombia, Panama, and the Philippines.

Participants were randomly assigned in a 1:1 ratio to receive a single dose of 50 µg mRNA-1010 or a single dose of an authorised seasonal influenza vaccine as an active comparator (Fluarix Tetra 60 µg; hereafter referred to as Fluarix), with stratification based on age categories (18 to <50 years, ≥50 to

<65 years, or ≥65 years, such that at least 50% of enrollees were ≥50 years and approximately 20% were ≥65 years) and influenza vaccine status in the prior 12 months (received or did not receive).

Participants were enrolled in the study and followed for 12 months after administration of study injection. The median age of participants was 50 years. The median safety follow-up was 355 days.

Participants were issued eDiaries for daily reporting of solicited adverse reactions (ARs) reflective of reactogenicity occurring within 7 days after study injection. SAEs, MAAEs, AESIs, and AEs leading to discontinuation were collected through Day 361 (Month 12)/end of study (EOS) or withdrawal from the study. Unsolicited nonserious AEs that did not meet criteria for the preceding categories were collected through 28 days after injection.

A total of 6083 participants received an injection: 3035 participants in the mRNA-1010 group and 3048 participants in the Fluarix group.

The study enrolled medically stable adults at least 18 years of age at the time of consent. Female participants of childbearing potential were included if they had a negative pregnancy test. In addition, female participants were required to practice adequate contraception.

Key exclusion criteria included immunocompromising conditions; use of systemic immunosuppressants; history of anaphylaxis or hypersensitivity to mRNA or influenza vaccines; receipt of an influenza vaccine or positive test for influenza within 180 days before study injection and receipt of any authorised vaccine within 28 days before study injection (or plans to receive within 28 days after study injection).

Adverse events:

Solicited ARs were reported by 2137/3035 participants (70.4%) in the mRNA-1010 group and 1463/3046 participants (48.0%) in the Fluarix group. Grade 3 solicited ARs were reported by 10.3% of participants in the mRNA-1010 group vs 3.1% of participants in the Fluarix group.

Solicited local ARs were reported by 1912/3035 participants (63.0%) in the mRNA-1010 group and 1106/3046 participants (36.3%) in the Fluarix group. The most frequently reported solicited local ARs (>20% of participants in the mRNA-1010 group) were injection site pain (60.4% in the mRNA-1010 group vs 34.5% in the Fluarix group) and axillary swelling or tenderness (25.1% vs 11.8%). Grade 3 solicited local ARs were reported by 4.3% of participants in the mRNA-1010 group vs 1.2% of participants in the Fluarix group.

Solicited systemic ARs were reported by 1676/3035 participants (55.2%) in the mRNA-1010 group and 1073/3046 participants (35.2%) in the Fluarix group. The most frequently reported solicited systemic ARs (>20% in the mRNA-1010 group) were myalgia (37.8% of participants in the mRNA-1010 group vs 16.6% of participants in the Fluarix group), headache (37.1% vs 23.1%), fatigue (32.5% vs 18.6%), arthralgia (27.3% vs 12.7%), and chills (23.9% vs 7.7%). Grade 3 solicited systemic ARs were reported by 7.6% of participants in the mRNA-1010 group and 2.2% of participants in the Fluarix group.

Grade 4 solicited systemic ARs were reported by 6 participants (0.2%) in the mRNA-1010 group and 10 participants (0.3%) in the Fluarix group. All Grade 4 solicited systemic ARs were fever, except for 1 Grade 4 headache in the Fluarix group. Two of the 6 participants in the mRNA-1010 group took medication to treat the event. This included 1 participant with fever from Day 1 to 2, who had no temperature reported and had a concurrent MAAE of severe herpes zoster (Day 1 to 22), which was assessed as not related to study injection by the Investigator.

Unsolicited AEs up to 28 days after injection were reported for 26.4% (n=800/3035) of participants in the mRNA-1010 group, compared to 24.6% (n=749/3048) in the Fluarix group, with related unsolicited AEs reported in 0.7% (n=22/3035) vs 1% (n=29/3048), respectively.

Unsolicited AEs up to 28 days after injection most frequently mapped to the primary SOCs of infections and infestations (15.1% in the mRNA-1010 group vs 13.8% in the Fluarix group) and respiratory, thoracic, and mediastinal disorders (4.8% vs 3.7%). All other SOCs were reported for <3% of participants in both groups.

By PT, the most frequently reported (≥1% in either group) unsolicited AEs were generally consistent with infections or their signs and symptoms, including COVID-19 (3.4% in both groups), viral upper respiratory tract infection (2.2% in mRNA-1010 group vs 2.0% in Fluarix group), upper respiratory tract infection (2.0% in both groups), influenza-like illness (1.7% in both groups), nasopharyngitis (1.9% vs 1.2%), nasal congestion (1.5% vs 1.1%), rhinorrhoea (1.1% vs 0.6%), and rhinovirus infection (1.1% vs 0.9%).

Supportive study mRNA-1010-P303

Study mRNA-1010-P303 was a Phase 3, randomised, stratified, observer-blind, active-controlled study to evaluate the immunogenicity, reactogenicity and safety of mRNA-1010 seasonal influenza vaccine in adults 18 years and older. The study was conducted in the US. The study consisted of 3 parts.

Part A (no data included in the dossier) was the first evaluation of the optimized mRNA-1010 compared to a standard dose (SD) seasonal influenza vaccine (Fluarix Quadrivalent influenza vaccine [QIV]; hereafter referred to as "SD Authorised QIV comparator") conducted in adults ≥18 years old. Based on data from Part A, Parts B and C were conducted as described below.

Part B of this study evaluated mRNA-1010 compared to a SD authorised QIV comparator in adults ≥18 to <65 years old, to establish immunogenicity and obtain additional safety data in support of authorisation.

Part C of this study was conducted to establish immunogenicity and safety of mRNA-1010 versus a authorised high dose (HD) seasonal influenza vaccine (Fluzone HD QIV; hereafter referred to as "HD authorised QIV comparator), in adults ≥65 years old.

Medically stable adults were randomly assigned to treatment in a 1:1 ratio to receive a single dose of mRNA-1010 or a single dose of SD authorised QIV comparator (Part B) or a single dose of HD authorised QIV comparator (Part C) on Day 1. Randomisation was stratified by the previous influenza season (since Sep 2022) vaccination status (received or not received; if received, was it from prior participation in the mRNA-1010-P302 study).

Solicited adverse reactions (ARs) were collected daily from Day 1 to Day 8 (via electronic diary [eDiary]). All unsolicited AEs were collected at study visits from Day 1 to Day 29, and collection of SAEs, MAAEs, AESIs, and AEs leading to discontinuation continued through EOS/Day 181 (Month 6).

In Part B, study injection was administered to 2988 participants, including 1498 participants in the mRNA-1010 group and 1490 participants in the SD authorised QIV comparator group. The median age in Part B was 49 years. The median duration of follow-up after injection was 171 days.

In Part C, study injection was administered to 2996 participants, of whom 1504 participants were in the mRNA-1010 group and 1492 participants were in the HD authorised QIV comparator group. The median age in Part C was 70 years. The median duration of follow-up after injection was 171 days.

Adverse events:

Adverse events in Part B:

Solicited local ARs were reported in 1069/1492 participants (71.6%) in the mRNA-1010 group vs 606/1488 participants (40.7%) in the SD authorised QIV comparator group. The most frequently reported solicited local AR was injection site pain (69.6% vs 39.2%, respectively), followed by axillary swelling or tenderness (28.6% vs 9.6%, respectively). Grade 3 solicited local ARs were reported by 5.2% of participants in the mRNA-1010 group vs 0.3% of participants in the SD authorised QIV comparator group, primarily consisting of injection site pain (4.6% vs 0.2%, respectively).

Solicited systemic ARs were reported by 1044/1492 participants (70.0%) in the mRNA-1010 group vs 555/1488 participants (37.3%) in the SD authorised QIV comparator group. The most frequently reported solicited systemic ARs were fatigue (53.5% vs 23.1%, respectively), headache (52.2% vs 23.8%, respectively), and myalgia (52.0% vs 16.1%, respectively). Grade 3 solicited systemic ARs were reported by 13.6% of participants in the mRNA-1010 group vs 1.8% of participants in the SD authorised QIV comparator group, and most frequently (>5% of participant in the mRNA-1010 group) involved reports of fatigue (7.6% vs 1.1%), myalgia (7.5% vs 0.8%), headache (5.9% vs 0.9%), and arthralgia (5.5% vs 0.4%).

Grade 4 solicited systemic ARs were reported by 2 participants (0.1%) in each group, including fever in the mRNA-1010 participants and nausea/vomiting, chills, and fever in the SD authorised QIV comparator group.

Unsolicited AEs up to 28 days after injection were reported for 9.9% (n=147/1492) of participants in the mRNA-1010 group, compared to 9% (n=134/1488) in the SD authorised QIV comparator group, with related unsolicited AEs reported in 0.7% (n=10/1492) vs 0.1% (n=2/1488), respectively. AEs were most frequently reported within the SOC of infections and infestations (mRNA-1010: 5%; SD authorised QIV comparator: 4.2%), mainly due to upper respiratory infections.

Adverse events in Part C:

Solicited local ARs were reported by 993/1502 participants (66.1%) in the mRNA-1010 group vs 580/1490 participants (38.9%) in the HD authorised QIV comparator group. The most frequently reported solicited local AR was injection site pain (64.6% vs 36.7%, respectively) followed by axillary swelling or tenderness (16.8% vs 8.6%, respectively). Grade 3 solicited local ARs were reported by 2.4% of participants in the mRNA-1010 group vs 0.8% of participants in the HD authorised QIV comparator group, primarily consisting of injection site pain (1.5% vs 0.4%, respectively) and axillary swelling or tenderness (0.5% vs 0.4%, respectively).

Solicited systemic ARs were reported by 920/1502 participants (61.3%) in the mRNA-1010 group vs 490/1489 participants (32.9%) in the HD authorised QIV comparator group. The most frequently reported solicited systemic ARs were fatigue (44.5% vs 19.7%, respectively), myalgia (41.7% vs 16.1%, respectively), headache (39.4% vs 17.3%, respectively), and arthralgia (35.2% vs 14.1%, respectively). Grade 3 solicited systemic ARs were reported by 6.7% of participants in the mRNA-1010 group and 1.7% of participants in the HD authorised QIV comparator group, and most frequently involved reports of fatigue (3.5% vs 0.8%, respectively) and myalgia (3.2% vs 0.7%, respectively).

Grade 4 solicited systemic ARs were reported by 2 participants (0.1%) in the mRNA-1010 group (fever in both cases) vs 0 in the HD authorised QIV comparator group.

Unsolicited AEs up to 28 days after injection were reported for 10.3% (n=155/1502) of participants in the mRNA-1010 group, compared to 9.2% (n=137/1490) in the HD authorised QIV comparator group, with related unsolicited AEs reported in 0.5% (n=8/1502) vs 0.2% (n=3/1490), respectively. Similar to Part B, AEs were most frequently reported within the SOC of infections and infestations (mRNA-1010: 4.5%; HD authorised QIV comparator: 4.4%), mainly due to upper respiratory infections.

Supportive study mRNA-1010-P304

Study mRNA-1010-P304 is a randomised, observer-blind, active-controlled, case-driven Phase 3 study to investigate the safety, efficacy, and immunogenicity of mRNA-1010 candidate seasonal influenza vaccine compared with an authorised inactivated seasonal influenza vaccine in adults ≥50 years of age. This multicentre study was conducted at 301 sites in 11 countries in North America, Europe, and East Asia.

Participants were randomised in a 1:1 ratio to receive a single injection of either mRNA-1010 or SD comparator. Randomisation was stratified by age category at Screening and influenza vaccine status in the previous influenza season. Approximately 50% of enrolled participants were to be ≥65 years of age at Screening, including approximately 10% who were ≥75 years of age at Screening.

Study P304 collected solicited adverse reactions (ARs) for 7 days postinjection from the Reactogenicity Subset of approximately 6000 participants who were assigned via the interactive response technology. All unsolicited adverse events (AEs) were collected up to 28 days, SAEs, MAAEs, AEs leading to discontinuation, and AESI from all participants up to Day 181.

Participants who received an authorised seasonal influenza vaccine within 180 days (or planned anytime during study) or any vaccine approved by a local health agency within 28 days prior to Day 1 (Baseline) or any planned vaccine within 14 days after Day 1 were excluded.

The Safety Set included a total of 40,703 adults with a median (range) age of 64.0 years (50 to 97 years). As of the data cut off, the median (range) duration of follow-up after injection was 181.0 days (1 to 227 days) for each group.

Adverse events:

Solicited local ARs were more frequently reported by participants in the mRNA-1010 group (2034/3015 [67.5%]) vs participants in the SD comparator group (961/2997 [32.1%]). The most frequently reported solicited local AR in both groups was injection site pain (65.8% vs 29.8%). Grade 3 solicited local ARs were more frequently reported by participants in the mRNA-1010 group (52 [1.7%]) vs the SD comparator group (4 [0.1%]).

Solicited systemic ARs were more frequently reported by participants in the mRNA-1010 group (1750/3015 [58.0%]) vs participants in the SD comparator group (970/2997 [32.4%]). The most frequently reported solicited systemic ARs were fatigue (45.1% vs 20.3%), headache (37.8% vs 18.0%), and myalgia (35.4% vs 11.6%). Grade 3 solicited systemic ARs were more frequently reported by participants in the mRNA-1010 group (167 ([5.5%]) vs participants in the comparator groups (27 [0.9%]). No Grade 4 solicited systemic ARs were reported in either group.

Overall, the proportion of participants with unsolicited AEs up to 28 days after injection was generally balanced between the groups (mRNA-1010: 1204/20350 [5.9%]; SD comparator: 1165/20353 [5.7%]). AEs assessed as related to study injection by the Investigator were reported in 100/20350 (0.5%) participants in the mRNA-1010 group vs 48/20353 (0.2%) participants in the SD comparator group. In both groups, the most frequently reported unsolicited AEs up to 28 days after injection were in the following SOCs: infections and infestations (1.4% in each group), musculoskeletal and connective tissue disorders (0.8% vs 0.7%), injury, poisoning and procedural complications (0.7% in each group), and gastrointestinal disorders (0.6% in each group).

Supportive study mRNA-1283-P301

Study mRNA-1283-P301 was a randomised, observer-blind, active-controlled Phase 3 study to investigate the safety, immunogenicity, and relative vaccine efficacy of mRNA-1283 compared with mRNA-1273 in participants aged ≥12 years for the prevention of COVID-19. The study was conducted in the US, UK, and Canada.

mRNA-1283 is a COVID-19 vaccine that encodes for the 2 key subdomains of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike glycoprotein, the Receptor Binding Domain (RBD) and N-terminal Domain (NTD), which are linked with a 7-amino acid flexible linker. For comparison, mRNA-1273 (Spikevax) encodes the full-length spike of SARS-CoV-2. mRNA-1283 focuses the immune response to the key neutralisation and T-cell epitopes of the NTD and RBD regions of the Spike protein, which are known to elicit protective immune responses.

Participants were randomised 1:1 to receive mRNA-1283.222 10 µg (original SARS-CoV-2: Omicron BA.4/BA5) or mRNA-1273.222 50 µg (original SARS-CoV-2: Omicron BA.4/BA5) as a single dose. The study vaccines aligned with the 2022/2023 variant formulation recommended by the United States FDA and by the WHO (original Omicron BA.4/BA.5 bivalent) because study enrolment occurred Mar through Aug 2023. Randomisation was stratified by age groups (adolescents, 12 to <18, 18 to <65, and ≥65 years), with the goal to enrol approximately 1000 adolescents (12 to <18 years) and approximately 30% of participants to be in the ≥65 age group.

All participants needed to be medically stable for study entry.

Local and systemic adverse reactions within 7 days following vaccination were solicited and recorded daily by participants using eDiaries. In addition, all unsolicited AEs were recorded within 28 days postvaccination and SAEs, AESIs, and MAAEs were recorded throughout the study.

A total of 11,417 participants were dosed, of which 5706 participants were in the mRNA-1283.222 group and 5711 participants were in the mRNA-1273.222 group.

The planned follow-up time for all participants is 12 months and the primary study analysis presented in this report includes at least 6 months of follow-up time for all participants. As of the data cutoff date, the median (range) duration of follow-up after study vaccination was 8.77 months in both groups. The median age of participants was 56 years.

Demographics and baseline characteristics were balanced between the 2 vaccine groups, including age, race, prior SARS-CoV-2 infection, and COVID-19 vaccination history.

Adverse events:

The incidence of all solicited local ARs was lower in the mRNA-1283.222 group (4007/5701 [70.3%] participants) compared to the mRNA-1273.222 group (4473/5705 [78.4%] participants). In both groups, the most frequently reported solicited local AR was injection site pain (3905/5701 [68.5%] participants in the mRNA-1283.222 group and 4419/5705 [77.5%] participants in the mRNA-1273.222 group), followed by axillary swelling or tenderness (1123/5701 [19.7%] participants in the mRNA-1283.222 group and 1047/5705 [18.4%] participants in the mRNA-1273.222 group). The incidence of Grade 3 solicited local ARs was also lower in the mRNA-1283.222 group (92/5701 [1.6%] participants) compared to the mRNA-1273.222 group (122/5705 [2.1%] participants). No Grade 4 solicited local ARs were reported.

The incidence of solicited systemic ARs was similar in the mRNA-1283.222 group (3672/5702 [64.4%] participants) and the mRNA-1273.222 group (3664/5706 [64.2%] participants). In both groups, the most frequently reported solicited systemic ARs were fatigue (2876/5701 [50.4%] participants in the mRNA-1283.222 group and 2798/5705 [49.0%] participants in the mRNA-1273.222 group) followed by headache (2519/5702 [44.2%] participants in the mRNA-1283.222 group and 2349/5705 [41.2%] participants in the mRNA-1273.222 group). The incidence of Grade 3 solicited local ARs was higher in the mRNA-1283.222 group compared to mRNA-1273.22 (408/5702 [7.2%] participants in the mRNA-1283.222 group and 329/5706 [5.8%] participants in the mRNA-1273.222 group). No Grade 4 solicited ARs were reported in the mRNA-1283.222 group and 1 Grade 4 solicited systemic AR (fever) was reported in the mRNA-1273.222 group on Day 2 that resolved the same day.

Up to the data cutoff date (including events up to 28 days), the incidence of all unsolicited AEs was similar between groups (2100/5706 [36.8%] participants in the mRNA-1283.222 group, and 2046/5711 [35.8%] participants in the mRNA-1273.222 group. The incidence of unsolicited AEs up to the data cutoff date that were assessed as related to study vaccine by the Investigator was similar between the groups (48/5706 [0.8%] and 52/571 [1.0%] participants in the mRNA-1283.222 and mRNA-1273.222 groups, respectively). In both groups, the most frequently reported unsolicited AEs up to 28 days after study vaccination by PT were in the infections and infestations SOC. Upper respiratory tract infection (81/5706 [1.4%] participants in the mRNA-1283.222 group; 88/5711 [1.5%] participants in the mRNA-1273.222 group) was the most frequently reported PT, and the only PT reported in more than 1% of participants in either group.

5.4.12. Overall discussion and conclusions on clinical safety

Discussion

Overall assessment of available safety data

The submission comprises data from two clinical trials which investigated the safety of mRNA-1083.

The completed **pivotal phase 3 study mRNA-1083-P301** was a randomised, stratified, observer-blind, active-control study conducted in healthy adults in two independent substudies: Cohort A (≥65 years) and Cohort B (≥50 to <65 years). Participants were to receive two injections on Day 1, either mRNA-1083 and placebo or Spikevax and an authorised influenza vaccine (Cohort: Fluzone HD, Cohort B: Fluarix). Both blinded injections were administered in the deltoid muscle (one in each arm). A total of 4,004 participants received mRNA1083 + placebo and 4,011 received the control vaccines. The study allowed for the inclusion of participants with stable common comorbidities, while **pregnant women and immunocompromised individuals were excluded**.

The total mRNA dose of mRNA-1083 given in this study was 40 µg and consisted of mRNA for four influenza strains (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) recommended by WHO for the 2023/2024 season and one SARS-CoV-2 variant (XBB.1.5). Importantly, the **actual drug product** only contains **a total of ~31.7 µg**, because the initially included B/Yamagata influenza strain was removed from the vaccine in line with a recommendation by ETF (EMA/123036/2024). Both Rapporteurs agreed in a presubmission meeting that the data collected with a quadrivalent influenza component could in principle support authorisation of a (with respect to influenza) trivalent composition. From a safety perspective, the reduction of the total dose could be considered beneficial for the safety profile of the vaccine, but the actual extent is unknown and cannot be estimated.

Study mRNA-1083-P101 is an ongoing 2-part study. Part 1 was a Phase 1/2 randomised, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 compositions and dose levels in two cohorts of healthy adults (Cohort A: ≥65 to <80 years, Cohort B: ≥50 to <65 years). Each cohort consisted of 12 treatment groups to investigate different formulations of mRNA-1083 but also mRNA-1010 (Influenza-only vaccine), mRNA-1283.222 (bivalent COVID-only vaccine), mRNA-1273.222 (bivalent authorised Spikevax), and the authorised influenza vaccines Fluarix and/or Fluzone HD. The detailed compositions are indicated in the efficacy section. The Summary of Clinical Safety (Module 2) describes data for the mRNA-1083 30-µg and 60-µg doses (compared to Fluarix, Fluzone HD and Spikevax) because the applicant considered these 2 groups to be most relevant for dose selection. Considering that the Influenza to SARS-CoV-2 mRNA ratio (5:1) for these two dose levels was closest to the ratio actually included in the drug product

(24.9 µg : 6.7 µg or 1:3.7), the assessment will also focus on the 30 µg and 60 µg dose levels. Part 2 will investigate different compositions of mRNA-1083 in healthy adults (no data available).

The dossier further includes CSRs of four phase 3 studies which either investigated an influenza-only (mRNA-1010; Studies mRNA-1010-P301, mRNA-1010-P303 and mRNA-1010-P304) or a SARS-CoV-2-only (mRNA-1283; Study mRNA-1283-P301) vaccine. Of note, the phase 3 data for the COVID-only vaccine were evaluated in frame of a recently concluded MA procedure (positive CHMP opinion for mRNA-1283 in December 2025). Due to the differences in antigen content the main safety information from these trials which is relevant for the combination vaccine concern the (possibly related) SAEs and AESIs. These supportive data are only briefly described on a high level.

Pivotal phase 3 Study mRNA-1083-P301

Safety data collection

Participants were instructed to report a defined list of solicited local and systemic adverse reactions (ARs) via eDiary during the 7 days following injection (i.e., the day of injection and 6 subsequent days). The chosen list of local and systemic ARs (see results) is considered reasonable. Solicited ARs ongoing beyond Day 7 were to be reviewed during the next scheduled safety call or at the next study site visit. Severity grading of ARs was clearly defined and followed (modified) FDA guidance (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, DHHS 2007) and occurred automatically based on participant entry into the eDiary. All solicited ARs were assessed as causally related to dosing per-protocol definition, which is endorsed.

All unsolicited adverse events until 28 days after vaccination (visit 3) were documented. SAEs, MAAEs, AESIs and AEs leading to discontinuation were reported from Day 1 through the end of the Study (Day 181, visit 5). This is a usual approach for vaccine trials and acceptable. The study protocol included guidance for the Investigators on how to assess severity and relatedness of unsolicited adverse events (including SAEs, AESIs, MAAEs). Severity (intensity) grading for unsolicited events (mild, moderate, severe) was based on the extent to which it interferes with usual activities and/or requires therapeutic intervention and is not objected.

As indicated in the protocol, safety monitoring included an unblinded Drug Safety Monitoring Board (DSMB), which conducted reviews of related SAEs at regular intervals. There was also an independent Cardiac Event Adjudication Committee to review any suspected cases of myocarditis, pericarditis, and myopericarditis.

Safety data is descriptive which is acceptable. Safety data is presented for all participants who were randomised and received study intervention, except for solicited reactions which are presented only for those who contributed solicited AR data. Relevantly, 99.9 % (8009/8015) of the safety set contributed to the solicited AR data. Safety analyses were performed separately on each cohort, which is acceptable since different authorised influenza vaccines were administered. The dossier also includes pooled safety analyses that combined the mRNA-1083 group from the 2 cohorts, and these data are the basis for the ADR table in section 4.8 of the SmPC.

Overall, the collection of safety data appears suitably reliable. The strategy for assessment of severity/relatedness of AEs is acceptable, based on instructions described in the study protocol.

Patient exposure

The study was conducted at 146 enrolling centres in the US and a total of 4,004 participants were exposed to mRNA-1083 + placebo, while 2006 participants received Fluzone HD + Spikevax and 2005 participants received Fluarix + Spikevax. The median safety follow-up was 170 days after injection.

The median age in Cohort A was 70 years and 20.7% of participants were ≥75 years of age. Most participants were female (54.2%) and White (78.2%; Black or African American: 18.4%). Based on the Edmonton Frail Scale, 74% of participants were considered fit at baseline, 18% were vulnerable, and 7.6% were frail. A high proportion of participants were obese (45.3% with BMI ≥30 kg/m^2).

In Cohort B, the median age was 58 years, and the majority of participants were female (58.8%), White (68%; Black or African American: 26.7%), and obese (52.4% with BMI ≥30 kg/m^2).

In both cohorts, demographic variables and medical history conditions were sufficiently well balanced between the groups.

The size of the safety database and the overall length of the safety follow-up are considered sufficient for an evaluation of the B/R profile.

Adverse events

For interpretation of the safety results, it has to be considered that to the knowledge of the CHMP, there are no large randomised controlled trials which compared the combinations used as active controls (either Fluzone HD + Spikevax or Fluarix + Spikevax) vs. placebo. This consideration is especially relevant for interpretation of potential imbalances of unsolicited adverse events.

In both cohorts, the incidence of participants with **any solicited local adverse reactions (ARs)** was higher in the mRNA-1083+placebo group (Cohort A: 75.8%, Cohort B: 79.2%), compared to the control group (Cohort A: 70.1%, Cohort B: 76.2%). In both cohorts, most local ARs were mild or moderate in severity. Grade 3 solicited local ARs were reported at numerically higher frequencies in the mRNA-1083+placebo group (Cohort A: 2.8%, Cohort B: 3.4%), compared to the active comparator group (Cohort A: 1.6%, Cohort B: 2.2%).

Also, with respect to **any solicited systemic ARs**, higher incidences were reported in the mRNA-1083 group (Cohort A: 70.1%, Cohort B: 75%), compared to the control group (Cohort A: 63.2%, Cohort B: 67.2%). For all individual solicited systemic ARs, clearly higher frequencies were reported for the mRNA-1083 group, compared to the active control group.

In Cohort A, the following frequencies were reported: fever (mRNA-1083: 11.9%, control: 4.4%), headache (mRNA-1083: 43.5%, control: 36.3%), fatigue (mRNA-1083: 52.9%, control: 44.3%), myalgia (mRNA-1083: 51.2%, control: 43%), arthralgia (mRNA-1083: 42.2%, control: 35.7%), nausea/vomiting (mRNA-1083: 13.4%, control: 8.9%), and chills (mRNA-1083: 34.8%, control: 21.4%). Grade ≥3 systemic ARs were reported in 7.7% of participants in the mRNA-1083 group, compared to 3.4% in the active control group.

A very similar pattern is noted in the younger Cohort B, with overall further increased frequencies for fever (mRNA-1083: 14.5%, control: 6.2%), headache (mRNA-1083: 51.4%, control: 42.9%), fatigue (mRNA-1083: 58.9%, control: 48.9%), myalgia (mRNA-1083: 58.4%, control: 47%), arthralgia (mRNA-1083: 47%, control: 35.9%), nausea/vomiting (mRNA-1083: 18.1%, control: 12.8%), and chills (mRNA-1083: 41.6%, control: 27.9%). Grade ≥3 systemic ARs were reported in 10.7% of participants in the mRNA-1083 group, compared to 5.5% in the active control group.

A total of 4 participants in the RNA-1083 groups (2 in each cohort) and 2 participants in the active comparator groups (1 per cohort) reported grade 4 events of fever (defined as >40.0°C).

In both cohorts, the median onset of solicited local and systemic reactions was on Day 2.

In Cohort A, the median **duration** of any solicited local AR was 3 days in the mRNA-1083 group and 2 days in the Fluzone HD + Spikevax group, and the median duration of any solicited systemic AR was 2 days in both groups. In Cohort B, the median duration of any solicited local AR was 3 days in both

groups, and the median duration of any solicited systemic AR was 3 days in the mRNA-1083 group and 2 days in the Fluarix + Spikevax group.

Solicited ARs persisting beyond 7 days after injection were reported at comparable rates in Cohort A (mRNA-1083: 2.3%, control: 2.6%) but at a slightly higher frequency for mRNA-1083 in Cohort B (mRNA-1083: 3.4%, control: 2.4%).

Use of medication to treat or prevent pain and/or fever was reported by 43.6% (1746/4004) of participants in the mRNA-1083 group and 34.3% (1372/4005) of participants in the combined comparator groups of both cohorts. Medication was mostly taken for treatment rather than prevention(at roughly 4-fold higher rates for treatment in both groups of both cohorts). Use of medication to treat fever/pain peaked on Day 2 after injection in both cohorts and both treatment groups.

Overall, the phase 3 data suggest a clearly more pronounced reactogenicity for mRNA-1083 compared to the active control groups. The differences between the treatment groups with respect to incidence of solicited systemic ARs can be considered clinically significant (i.e., when comparing incidences of each queried systemic AR between the groups), also due to the observed **2- to nearly 3-fold increased rates of fever** or the **2-fold higher frequency of any grade 3 systemic ARs**. For interpretation of these data, it needs to be considered that Spikevax alone can already be considered reactogenic in comparison to other standard vaccines and that co-administration with influenza vaccines in the control group can be expected to further increase reactogenicity. However, the CHMP considered the reactogenicity profile manageable and a lesser burden than the potential clinical illness burden of individuals who experience severe disease caused by infection with COVID-19 or influenza. This application concerns individuals aged 50 years of age and above and especially older and elderly adults are at increased risk of developing severe disease caused by infection with COVID-19 or influenza.

The incidences of solicited local and systemic ARs were higher in female and White participants. The reactogenicity tended to decrease with increasing age, which is not an unusual finding for vaccines. A lower percentage of participants reporting solicited ARs was observed among those who had not received influenza or COVID-19 vaccine in the prior season. Finally, an increase in reporting of solicited ADRs was observed in younger adults who were baseline SARS-CoV-2 negative.

Where observed, differences between subgroups are small (~5-10%). No placebo arm is included and similar differences between subgroups in the reporting of solicited ADRs were also observed in the comparator groups. Therefore, it is unclear whether the differences are due to differences in reporting behaviour between subgroups – where relevant - or whether indeed the use of the vaccines is associated with reduced or increased reactogenicity in certain subgroups. The clinical relevance of observed differences is likely limited. Moreover, whilst the reasons behind the observed differences may be scientifically of interest it should not impact the use of the vaccine.

Until up to 28 days after injection, overall incidences of all unsolicited AEs, SAEs, MAAEs, and AESIs considered related to study injection (by the Investigator) were comparable between the groups for both age cohorts. The incidences of unsolicited AEs were slightly higher in the older age Cohort A, compared to younger participants, which is not unexpected.

Until end of study (EOS), the incidences of the above-mentioned adverse events remained comparable between the groups, except for numerical imbalances for SAEs (mRNA-1083: 3.5%, control: 2.6%) in the older age Cohort A. SAEs are described further below.

Unsolicited AEs were reported mostly in the SOC of infections and infestations; most frequent PT reported in study mRNA-1083-P301 was upper respiratory tract infection. There was no clear imbalance in AEs between study arms, and no apparent trend in reporting of AEs that is of concern.

In **Cohort A**, up to 28 days after study injection, 19 unsolicited AEs in 16 (0.8%) participants were **considered related by the Investigator**, compared to 21 AEs in 20 (1.0%) participants in the active control group. Until up to 28 days after injection, treatment-related AEs as judged by the Investigator that were reported by at least 2 participants were diarrhoea and pain in extremity (each reported by 2 participants) in the mRNA-1083 group and injection site pruritus (4 participants), rash and hypertension (each reported by 2 participants) in the control group. The remaining treatment-related AEs in the mRNA-1083 group were herpes zoster, confusional state, insomnia, paraesthesia, eye pain, cough, nasal congestion, constipation, limb discomfort, muscular weakness, injection site pain, injection site pruritus, injection site swelling, pain, and swelling (each reported by 1 participant). Of note, one treatment related event of herpes zoster was also reported in the active control group. Other single cases of related events in the control group were shown.

In **Cohort B**, up to 28 days after study injection, 21 unsolicited AEs in 18 (0.9%) participants were **considered related by the Investigator**, compared to 38 AEs in 25 (1.2%) participants in the active control group. By PT, unsolicited AEs assessed as related to study injection that were reported by ≥2 participants in either group were injection site pruritus (3x), lymphadenopathy (2x), immunization stress-related response (2x), and constipation (2x) in the mRNA-1083 group, and upper respiratory tract infection, dizziness, cough, nasal congestion, injection site pruritus, and pain in extremity in the active comparator group. The remaining treatment-related AEs in Cohort B were oral herpes, viral rash, irritability, faeces discoloured, nausea, dermatitis allergic, arthralgia, myalgia, axillary pain, fatigue, influenza like illness, and peripheral swelling. Other single cases of related events in the control group are shown in this report.

As diarrhoea is a known ADR for mRNA-1273, Fluarix and Fluzone HD and has been reported in both mRNA-1083-P101 as mRNA-1083-P301 following mRNA-1083 in rates similar to the comparator group. It was reported for 17/4004 (0.4%) participants in the pooled mRNA-1083 group, the comparator authorised vaccine groups reported 13 cases of diarrhoea: 7/2006 (0.3%). Furthermore, causality was judged likely by the investigator for two events following mRNA-1083. Therefore 'diarrhoea' was included as an ADR for mRNA-1083 with the frequency 'uncommon'**.**

There were 4 injection site pruritus events reported in the mRNA-1083 group which were considered related to study intervention by the Investigator with a time to onset of 1 to 2 days and resolved in 3 to 14 days. Injection site pruritus was included in section 4.8 with the frequency 'uncommon'.

Amongst the medically attended adverse events, there was an event of paraesthesia which was considered related by the investigator to mRNA-1083. Paraesthesia is listed as an ADR for mRNA-1273. The applicant provided an overview of all cases of paraesthesia reported within 28 days of administration of mRNA-1083 (any formulation) within clinical trials. The Applicant identified 3 cases of paraesthesia in persons exposed to mRNA-1083. The cases were mild in intensity. Relatedness was unclear due to concomitant medications and/or limited information and do not provide evidence that would be suggestive that mRNA-1083 may trigger paraesthesia. The Applicant confirmed that all reports of paraesthesia and other similar terms will be reviewed using routine surveillance and that periodic safety updates will be provided in the corresponding PSUR reporting periods.

Beyond 28 days after vaccination (until EOS), unsolicited AEs were collected if they were medically attended (**MAAEs**) and none of these events were considered related by the Investigator. In Cohort A, MAAEs (until EOS) were most frequently reported in the SOC infections and infestations (9.2% of participants in the mRNA-1083 group vs 8.5% of participants in the active comparator group); injury, poisoning, and procedural complications (2.6% vs 2.8%); and musculoskeletal and connective tissue

disorders (2.6% vs 2.8%). MAAEs (by PT) reported in ≥1% of participants in either group were COVID-19 (1.5% in the mRNA-1083 group vs 2.5% in the control), upper respiratory tract infection (1.2% vs. 1.1%), and hypertension (1.2% vs. 1.0%). Similarly, in Cohort B, MAAEs (until EOS) were most frequently reported in the SOC infections and infestations (6.1% of participants in the mRNA-1083 group vs 7.1% of participants in the active comparator group); and injury, poisoning, and procedural complications (1.6% vs 1.7%). MAAEs (by PT) reported in ≥1% of participants in either group were COVID-19 (1.1% of participants in the mRNA-1083 group vs 1.1% of participants in the active comparator group), upper respiratory tract infection (1.1% vs 1.2%), and hypertension (1.0% vs 1.0%). (Source: Tables 14.3.2.8.2a and 14.3.2.8.2b in the CSR; not shown in this AR due to size).

The applicant identified 14 herpes-related events in the mRNA-1083 group versus 7 in the comparator groups, with several herpes zoster (n=4) and all oral herpes (n=6) cases in the mRNA-1083 arm occurring within the first month after vaccination. While a few events in both groups were considered related by investigators, overall herpes zoster rates were within expected annual background levels, although a clustering of four early post-vaccination cases was noted in the mRNA-1083 group. The applicant confirmed that all herpes zoster reports will continue to be monitored through routine post-marketing surveillance and included in future PSUR updates.

Up to 28 days after vaccination, the documented **AESIs** in the mRNA-1083 group (both cohorts) were myocardial infarction, confusional state, anosmia, and coronary artery disease (in 1 participant each). In the active control group of Cohort A (Fluzone HD + Spikevax), reported AESIs up to 28 days after vaccination were acute coronary syndrome, atrial fibrillation, cardiac failure acute, and deep vein thrombosis in 1 participant each. In the active control group of Cohort B (Fluarix + Spikevax), AESIs up to 28 days included appendicitis, anosmia, and ageusia in 1 participant each.

The AESI (SAE) of myocardial infarction in the mRNA-1083 group occurred on Day 5 after vaccination in a 66-year-old female participant. The ongoing medical history included but was not limited to essential hypertension, overweight, depression, renal hypoplasia, CKD stage 3a, and osteoporosis. The Investigator assessed the event of myocardial infarction as not related. In the view of the Rapporteur, a potential contribution of vaccination cannot be excluded due to the close temporal relationship, although the medical history of the participant is noted.

No event of anaphylaxis was reported throughout the study.

Myocarditis and pericarditis have been identified as adverse reactions to mRNA-1273 (Spikevax), hence may be expected to be adverse reactions to mRNA-1083 as well. The Applicant suggests that differences between mRNA-1083 and mRNA-1273, specifically the absence of the furin cleavage site present in the full-length spike protein, would potentially limit circulating antigen and therefore maybe reduce the risk of vaccine-related myocarditis/pericarditis. Whilst the hypothesis is acknowledged, it is a hypothesis and the actual impact of the changes made remains to be established.

There was one event of pericarditis on Day 148 in the mRNA-1083 group in a 59-year-old male participant. The CEAC adjudicated the diagnosis of the event as acute pericarditis. The event resolved on Day 158. The Investigator assessed the event of pericarditis as not related to study vaccine, which is not objected based on the late onset of the event and the available background information. One case of related "mild transient possible myocarditis" in a 29-year-old female participant of the phase 1 study is described further below under Study mRNA-1083-P101. This event was not considered as a charter-defined cardiac event by the CEAC.

Based on the currently available data, there is no ground for inclusion of myocarditis and pericarditis in section 4.8 as a specific ADR for mRNA-1083. Nonetheless, due to the similarities of mRNA-1083 with mRNA-1273 and the known risk of myocarditis and pericarditis with the latter, it was included as a warning in the SmPC.

Among all AESIs in the phase 3 trial, one event of confusional state (Day 23 to Day 35) in an elderly participant (tested positive for COVID-19 on Day 24) was considered related by the Investigator. Due to confounding by COVID-19 infection, elderly age of the participant and the single occurrence, relatedness of this case is unclear.

Two cases of Bell's palsy occurred in mRNA-1083 recipients, both with long onset times (84 and 161 days) and considered unrelated to vaccination. Supportive mRNA-1010 and mRNA-1283 studies reported three additional early-onset facial paralysis events but with insufficient information to assess causality, and no imbalance was observed across groups. While peripherical facial paralysis is listed as an ADR for mRNA-1273 based on clinical trial data, post-authorisation safety studies have so far not provided clear evidence of an increased risk of acute peripheral facial paralysis following vaccination mRNA-1273 as results have been inconsistent. Therefore, the occurrence of acute peripheral facial paralysis will be monitored through the PSURs. Four mRNA-1083 participants experienced acute kidney injury with onset between Days 44–120 and relatedness to vaccination is unlikely due to clear alternative causes. Finally, supportive studies reported two urticaria events (one acute and one chronic) related to mRNA-1010 or mRNA-1283, but no cases occurred near vaccination with mRNA-1083; given urticaria (including more debilitating chronic urticaria), is a known ADR for both Spikevax and mRESVIA, the Applicant will monitor all urticaria types in PSURs.

In Cohort A, the number of **SAEs until EOS/Day 181** was numerically slightly higher in the mRNA-1083 group (96 SAEs in 70 [3.5%] participants), compared to the Fluzone HD + Spikevax group (84 SAEs in 52 [2.6%] participants), with imbalances noted in the SOCs of Nervous system disorders (0.5% vs. 0.2%) and Respiratory, thoracic and mediastinal disorders (0.4% vs. 0.2%). In Cohort B, the numbers of SAEs were balanced between the groups (mRNA-1083: 33 SAEs in 29 [1.5%] participants; Fluarix + Spikevax: 33 SAEs in 27 [1.3%] participants). The above-described imbalances in the SOCs of Nervous system disorders and Respiratory, thoracic and mediastinal disorders were not observed in Cohort B and the numbers of events were slightly higher in the control group.

During the assessment a CSR Addendum for P301 was submitting describing two new SAEs (hepatic cirrhosis and worsening chronic kidney disease) which the Investigator deemed related to study injection. These events occurred in a 78-year-old participant with a relevant medical history of obesity, hypercholesterolemia, hypertension, type 2 diabetes, mixed hyperlipidaemia, nephropathy, Stage 3 chronic kidney disease, hypertensive kidney disease, low potassium, hypothyroidism, sleep apnoea, and vitamin D deficiency (among others). The event of hepatic cirrhosis was initially reported as a grade 2 MAAE on Day 43 and considered unrelated. The participant developed hepatic cirrhosis and related complications including ascites, oesophageal varices, and hepatorenal syndrome, which required paracentesis, repeated endoscopic treatment of varices, and renal dialysis. The Investigator reassessed both events as serious and related after review of medical records from a hepatologist.

Of note, the **non-clinical** section describes hepatic alterations and corresponding changes in clinical chemistry (statistically significant increases in ALT, AST, ALP, bilirubin) in rats at the highest tested dose in the pivotal toxicity study.

In the **clinical** phase 3 trial, adverse events in the SOC of hepatobiliary disorders up to 28 days after vaccination in the mRNA-1083 group included one event of transaminitis (grade 2, Day 148 to Day 151) and cholecystitis acute (grade 2, Day 3 to Day 5). With respect to MAAEs throughout the study, there was one event of hepatic steatosis (grade 2, Day 146 – ongoing) and 6 events of cholelithiasis. Of note, the events of cholelithiasis were reported during month 2 after vaccination or later, the event in closest temporal relationship was on Day 32 (beside the above-described case of acute cholecystitis). The only hepatic event (MAAE) in the SOC of Investigations was one case of hepatic enzyme increased (verbatim: due to statin therapy; grade 1, Day 150 – ongoing). Considering the relatively large trial, these events do not raise a concern.

Post-vaccination laboratory tests were only performed in the phase 1 study (on Day 8), which did not show any findings with respect to alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin. Slightly increased values compared to baseline were only noted for the Fluzone HD group, for which two AEs with the PTs of elevated alanine transaminase and elevated liver enzymes were observed.

Upon request, the Applicant summarized and discussed data from clinical trials, literature and postmarketing (GSDB, Moderna global safety database) for Spikevax using the high-level term of Hepatic fibrosis and cirrhosis. The Applicant pointed out the PRAC assessment for autoimmune hepatitis (Procedure no.: EMEA/H/C/ PSUSA/00010897/202206) which concluded that there was insufficient data for a causal association between AIH and SPIKEVAX despite any temporal association.

Overall, besides non-clinical findings at the highest dose and the one SAE of hepatic cirrhosis in the phase 3 trial which was considered related to study injection by the Investigator, the available clinical data from over 4,000 participants who received mRNA-1083 do not indicate a hepatic safety risk.

Throughout the study, there was one **AE leading to discontinuation** (mRNA-1083 group, lung neoplasm on Day 133, fatal, assessed as not related by the Investigator).

Throughout the study, there were 4 fatal events in the mRNA-1083 group (both cohorts combined), 1 fatal event in the Fluzone HD + Spikevax group (Cohort A), and 2 events in the Fluarix + Spikevax group (Cohort B).The events were considered not related to vaccination by the Investigator.

The applicant performed different SMQ (standardized MedDRA Queries) analyses, which did not reveal notable imbalances between the groups.

Of note, for the supportive study mRNA-1283-P301, the applicant performed an SMQ analysis for immune-mediated/autoimmune disorders, which revealed three events which were considered related by the Investigator (lichen planus exacerbation, hypoparathyroidism, acute aseptic arthritis). A similar analysis for Study mRNA-1083-P301 identified two events within the first 7 days after vaccination (worsening of microscopic colitis, worsening of sensory neuropathy), and four events (anosmia, dermatitis, new onset of diabetes mellitus, worsening of hypothyroidism) within 8-28 days post-injection. None of these events was considered related by the Investigator.

For interpretation of the data, it needs to be considered that only certain immune-mediated conditions that were stable and well-controlled as well as those that did not require systemic immunosuppressants were permitted at the discretion of the Investigator and that this population was likely rather small (the exact proportion difficult to determine from the medical history data, as currently presented). As also acknowledged by the Applicant, there are theoretical concerns regarding post-vaccination exacerbation of autoimmune or inflammatory disease flares. The very pronounced reactogenicity of mRNA-1083 raises the question whether individuals affected by immune-mediated disorders might be at an increased risk for such exacerbations, compared to other less reactogenic vaccines. Although some uncertainty remains because the phase 3 study did not focus on a population with immune-mediated or autoimmune disorders, the currently available data from the phase 3 study do not indicate a particularly increased risk for onset or exacerbation of such disorders.

Individuals with unstable medical conditions were excluded from the trial. Based on the Edmonton Frail Scale, 7.6% of participants of the phase 3 trial were considered frail. There were no differences with respect to solicited and unsolicited events between participants who were classified as fit, vulnerable or frail. However, the majority of frail patients were mildly frail, which limits the interpretability and meaningfulness of the data for individuals with severe frailty.

The Applicant committed to closely monitor exacerbations/flare ups of autoimmune or immune-mediated disorders and use in very elderly and unstable frail individuals in the Periodic Safety Update

Reports (PSURs) due to the observed reactogenicity of mRNA-1083 and the limited amount or absence of data in these populations.

Considering that this vaccine may be administered with other vaccines such as RSV or herpes zoster vaccines, and due to the pronounced reactogenicity of mRNA-1083 (and a potential impact on immunogenicity), it was considered of value to collect data on co-administration. The Applicant confirmed to monitor co-administration with other vaccines through routine pharmacovigilance (PSURS).

Study mRNA-1083-P101

Above-described methods for data collection were also applied for the phase 1 study. The median safety follow-up duration was ~170 days for each treatment group. The baseline characteristics were not always perfectly (in terms of sex, race, BMI, prior COVID-19/influenza vaccination status) but sufficiently well balanced for this small study.

The smaller sample sizes, especially in Cohort B, need to be considered for interpretation of the results of this phase 1 study. All 12 treatment groups are shown in Figures indicating any solicited local and systemic ARs. It should be noted that Cohort B of the phase 1 study also included individuals from 18 to 50 years of age. These data were not included in the Summary of Clinical Safety and consequently also not in this report, also due to the small number of participants in this age group. However, these data were reviewed based on the CSR.

In both age cohorts, the incidences of solicited local and systemic ARs were authorised clearly higher in the mRNA-1083 (described as mRNA-1083.1 within the CSR) groups vs. the authorised influenza vaccines (Fluarix and/or Fluzone HD) and numerically slightly higher vs. the mRNA-1273.222 group (detailed tables only included in the CSR).

When comparing any solicited local and systemic ARs of different formulations (i.e., different influenza to SARS-CoV-2 mRNA-ratios) and dose levels of mRNA-1083, no clear differences are noted, but there was a tendency for lower incidences with mRNA-1083.2.27.5 µg and higher incidences with mRNA-1083.2.82 µg, but this was not very consistent for both age cohorts. Both formulations had a different influenza to SARS-CoV-2 mRNA ratio compared to mRNA-1083.1.

In participants 50 years of age and older, unsolicited AEs in the mRNA-1083 30-µg or 60 µg groups considered **related** by the Investigator were bronchitis, diarrhoea, urinary incontinence, thrombocytopenia, white blood cell count decreased and nasal congestion. In adults from ≥18 to <50 years of age, treatment-related AEs (by PT) included increased platelet count (2 events), thrombocytosis, dizziness, **myocarditis**, exertional dyspnoea, and anaemia.

The case of **myocarditis** (verbatim: *mild transient possible myocarditis*) occurred in a 29-year-old female participant in the mRNA-1083 30-µg group. This grade 2 AESI occurred on Day 10 and was considered resolved on Day 73. The participant reported fatigue, exertional dyspnoea, elevated pulse while walking, and worsening of pre-existing head tremor. On Day 14, the participant denied chest pain, cough, lightheadedness, dizziness, presyncope or syncope, fevers, chills, SOB at rest, sore throat, abdominal pain, nausea, vomiting, and diarrhoea. The CEAC Cardiac Event Adjudication Committee reviewed the participant's records and determined that a charter-defined cardiac event (myocarditis or pericarditis) did not occur. Investigations by a cardiologist (48-hour holter monitoring from Day 58, a functional stress test on Day 70, transthoracic echocardiography on Day 71) were unremarkable.

There were no cases of death or AEs leading to discontinuation in the phase 1 study P101.

Thrombocytopenia/ decreased platelet count was the most commonly reported AESI in study P101. Events of thrombocytopenia and decreased platelet count were observed in a similar frequency in all

treatment groups, with no clear imbalance between the arms. Events were identified through scheduled safety labs. No AESIs of thrombocytopenia or decreased platelet count were reported in the phase 3 trial, likely as no blood laboratory values were determined in this study.

From a safety perspective alone, the choice of the dose level for the phase 3 trial (40 µg) is not completely clear, because the overall incidences of solicited ARs were comparable between the 30 µg and 60 µg dose levels of mRNA-1083. The incidences of fever (Cohort A: 5.9% in the 30 µg group, 21.2% in the 60 µg group; Cohort B: 7.1% in the 30 µg group, 37.5% in the 60 µg group) were much higher in the 60 µg group. Grade 3 systemic ARs were also more frequent in the 60 µg group. However, it needs to be pointed out that these incidences are based on few events in small treatment groups, which limits the interpretability.

Organ transplant

As raised in the assessment of mRNA-1283 (mNEXSPIKE), there were no confirmed safety concerns that mRNA COVID-19 vaccines can cause organ rejection in transplant recipients. Ongoing safety monitoring continues, with extra attention for people who are recently transplanted, have known donor-specific antibodies, or are on higher levels of immunosuppression. Decisions about vaccination should always be made in partnership with the patient's transplant team.

Pregnancy

No pregnancies were reported for the phase 3 trial. In the phase 1 study, three pregnancies occurred in the younger subpopulation of Cohort B. There was one elective induced abortion, and two pregnancies resulted in live term births. The SmPC advises that due to the limited data in pregnant women, as a precautionary measure, it is preferrable to avoid the use of mCOMBRIAX during pregnancy.

Supportive studies

The safety data from supportive studies confirm the known safety profile of mRNA vaccines, which are more reactogenic than inactivated influenza vaccines. Overall, the data are reassuring regarding the occurrence of adverse events of special interest and serious adverse events. Some events of interest are described in sections further above.

Adverse drug reactions in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 5.4.3.1 above.

Ta: ADRs proposed for inclusion in the SmPC by the CHMP

MedDRA system organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Nervous system disorders	Very common	Headache
Gastrointestinal disorders	Very common	Nausea/vomiting
	Uncommon	Diarrhoea
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills
	Very common	Pyrexia
	Common	Injection site swelling Injection site erythema

	Uncommon	Injection site pruritus

** Lymphadenopathy included mainly axillary (underarm) swelling or tenderness ipsilateral to the side of injection and other associated terms including lymphadenitis, lymph node pain, and lymph node involvement in other locations (e.g., cervical, supraclavicular).*

Differences between mRNA-1273 and mRNA-1283 (the SARS-CoV-2 component of mRNA-1083) may result in a slightly different safety profile, and it is recognised that mRNA-1083 is intended only as a single dose booster vaccine for older adults aged 50 years and older. Therefore, it is accepted that not all safety information may be directly translatable to mRNA-1083.

Upon request, axillary swelling or tenderness was labelled as lymphadenopathy. The frequencies for nausea/vomiting and pyrexia were amended based on the events reported.

Conclusions on clinical safety

mRNA-1083 was more reactogenic than the combinations of authorised active comparators in both study cohorts, not only with respect to incidences of all solicited systemic adverse reactions, but also in terms of severity. However, the CHMP considered the reactogenicity profile manageable, and the transient adverse reactions following vaccination are a lesser burden than the potential clinical illness in individuals who experience COVID-19 or influenza. From the clinical safety perspective mCOMBRIAX is approvable.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Important identified risks	None
Important potential risks	Myocarditis Pericarditis
Missing information	None

6.1.2. Discussion on proposed safety specification

The potential risks of **myocarditis and pericarditis** have been suggested by the applicant and supported. The summary of safety concerns for this newly developed mRNA combination vaccine largely corresponds to those of approved mRNA vaccines. Myocarditis and pericarditis are classified as 'important identified risks' for the approved COVID-19 mRNA vaccine Spikevax due to their occurrence after vaccination, especially in younger men and after the second dose. However, for the proposed RMP, myocarditis and pericarditis are considered important potential risks. Unlike current mRNA vaccines, the new vaccine lacks a furin cleavage site, potentially reducing the risk of myocarditis and pericarditis by limiting the circulating spike protein. One case of myocarditis in a participant in the mRNA-1083 30-µg group in study mRNA-1083-P101 was considered related to study vaccine by the Investigator. However, this singular event does not change the assessment at this point, but further monitoring is necessary in the upcoming PSURs.

Module SVII.1.2 of the RMP includes the respective justification for inclusion of myocarditis and pericarditis as important potential risks.

The Applicant confirmed continued monitoring of myocarditis and pericarditis as important potential risks via PSURs, including case characterisation and data from post-marketing sources.

Myocarditis and pericarditis will be further assessed through the planned post-authorisation safety study mRNA-1083-P907 (further discussed in Part III).

In addition, the Applicant committed to closely monitor, through the PSURs, risks not listed as safety concerns, including exacerbations or flare-ups of autoimmune disorders, frail individuals, and concomitant administration with other vaccines. These aspects are addressed in the overall discussion and conclusion on clinical safety.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities consisting of adverse reaction collecting and reporting and signal detection will be employed according to the applicant as per all appropriate local pharmacovigilance requirements.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Traceability - mCOMBRIAX SmPC includes instructions for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability. An identification code (Datamatrix) will be printed on the carton of the vaccine. In addition, the MAH will provide single or double peel-off stickers to facilitate record keeping at the point of care in the countries where this will be required.

Additional pharmacovigilance activities

Table 47: 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

6.2.2. Discussion on the Pharmacovigilance Plan

Routine pharmacovigilance activities

Routine pharmacovigilance is considered sufficient, and additional activities are warranted. The measures put in place by the MAH, a scannable barcode encoding the lot number and product ID, and 2 stickers with the lot number/dose and product ID per patient, where required, are considered acceptable to ensure proper traceability in countries with different availabilities of electronic equipment.

Additional pharmacovigilance activities

The RMP includes an EU PASS (mRNA-1083-P907) using European data. This study aims to evaluate whether the important potential risk of myocarditis, pericarditis, and other safety topics of interest among individuals vaccinated with mRNA-1083 is higher than the risk in an unexposed reference population. This study will include a feasibility assessment through monitoring the distribution and uptake in Europe, identifying fit-for-purpose data sources, and characterizing the recipients of mRNA-1083.

The final study protocol and statistical analysis plan (SAP) will be submitted for review prior to initiation of data collection. Furthermore, the Applicant confirms that both the study protocol and the final study report will be registered in the HMA–EMA Catalogue of Real-World Data Studies, and that the required registration information will be reflected in the full study protocol.

6.3. Plans for post-authorisation efficacy studies

Not applicable, as there are no imposed post-authorisation efficacy studies.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 48: Planned routine risk minimisation measures

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

The applicant did not propose any additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

Routine risk minimisation measures

Routine risk minimisation activities as proposed by the applicant are considered sufficient.

Additional risk minimisation measures

The applicant did not propose any additional risk minimisation measures, which is acceptable**.**

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.0 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list, and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The indication is aligned with the population studied in the pivotal clinical trials. The wording is aligned with the other seasonal influenza and COVID-19 vaccines.

8.2. Labelling

8.2.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.2.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

the Group granted a labelling exemption to replace the full excipient name (IUPAC name) "heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate" with the acronym "SM-102" on the outer carton due to space constraints.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, mCOMBRIAX (influenza and COVID-19, mRNA vaccine) is included in the additional monitoring list since as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, therapeutic indication

The agreed indication is "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."

Both influenza and COVID-19 primarily manifest respiratory symptoms, such as cough and nasal congestion, and systemic symptoms, such as fever and chills; symptoms may be mild to severe. Influenza can manifest a mild to moderate illness, such as sinusitis or otitis media, or as a severe disease, including pneumonia, multi-organ failure, and hyperinflammatory responses. The clinical manifestations of COVID-19 may also include loss of taste or smell, and the spectrum of illness from SARS-CoV-2 can range from asymptomatic infection to severe pneumonia, acute respiratory distress syndrome, respiratory failure, septic shock, multiple organ dysfunction or failure, and death. While COVID-19 is primarily a pulmonary disease, it can also lead to cardiac, dermatologic, haematologic, hepatic, neurologic, renal, and other complications, including thromboembolic events and peri- and myocarditis.

In the EU/EEA, seasonal influenza is responsible for up to 50 million symptomatic cases and 15,000 to 70,000 deaths annually. In Europe, as of 8 February 2026, 281,735,665 COVID-19 cases and 2,282,775 deaths had been reported. COVID-19 was among the top 4 leading causes of death in Europe in 2022, the last year with available data.

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. Age has been identified as a key risk factor for severe COVID-19 disease outcome, and adults ⩾50 years are more likely than younger people to have hospitalisation or die due to SARS-CoV-2 infection. Adults ⩾65 years are at highest risk of COVID-19 and severe COVID-19 outcomes including death.

9.1.2. Available therapies and unmet medical need

The most important way to prevent the flu and COVID-19 caused by SARS-CoV-2 is active immunisation through prophylactic vaccination. Other interventions include specific antiviral compounds, monoclonal antibodies and supportive care.

There are currently several efficacious vaccines approved separately for influenza and COVID-19 that are updated on an annual or periodic basis to match the identified circulating viral strains to maximise protection.

Several different technologies have been utilized to create and administer vaccines for influenza and SARS-CoV-2. For influenza, vaccines may be based on egg- or cell-culture growth, live attenuated or recombinant HA and may be delivered IM, or intranasally. In addition, higher dose and adjuvanted compositions of influenza vaccines are available for older adults at increased risk for complications from influenza. For SARS-CoV-2, mRNA-based as well as protein-based vaccines are available, all as IM injections. In addition, co-administration of influenza and COVID-19 vaccines to different injection sites is possible. For instance, the SmPC of the COVID-19 comparator vaccine used in the clinical studies of this MAA states that "Spikevax (including variant formulations) can be concomitantly administered with influenza vaccines (standard and high-dose)".

For both viruses, specific recommendations vary by country and region. Most EU countries do not have universal vaccination recommendations for influenza or COVID-19 but instead focus on young children 6 through 59 months, adults ≥60 years, and high-risk groups, such as individuals with specific chronic medical conditions (including immunocompromise), healthcare workers, and pregnant women.

An unmet medical need is not fulfilled.

9.2. Main clinical studies

Study mRNA-1083-P301 is a Phase 3, randomised, stratified, observer-blind, active-control study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1083 40 µg in healthy adults ⩾50 years. Participants ⩾65 years (Cohort A) received mRNA-1083 40 µg + placebo (referred to as mRNA-1083 group) or coadministered Fluzone HD + Spikevax. Participants ⩾50 to <65 years (Cohort B) received mRNA-1083 40 µg + placebo (referred to as mRNA-1083 group) or coadministered Fluarix + Spikevax. Approximately 2000 subjects were dosed in each group. Each participant was to receive 2 injections on Day 1. The mRNA-1083 composition included the influenza strains recommended by the WHO for the NH 2023/2024 season in an equivalent mass ratio and a SARS-CoV-2 mRNA sequence that encodes the NTD and RBD of the SARS-CoV-2 Spike glycoprotein of the 2023/2024 Omicron XBB.1.5 variant.

9.3. Favourable effects

The non-inferiority criteria for all 10 co-primary immunogenicity endpoints were met in Cohort A (≥65 years of age) and Cohort B (≥50 to <65 years of age):

Cohort A

- Influenza Day 29 GMRs (mRNA-1083 group vs Fluzone HD + Spikevax) were 1.155 (97.5% CI: 1.086, 1.229) for A/H1N1, 1.063 (97.5% CI: 0.999, 1.130) for A/H3N2, 1.118 (97.5% CI: 1.063, 1.175) for B/Victoria, and 1.007 (97.5% CI: 0.969, 1.047) for B/Yamagata.
- The Day 29 SCR differences were 5.4 (97.5% CI: 1.9, 8.8) for A/H1N1, 4.0 (97.5% CI: 0.5,

7.6) for A/H3N2, 4.5 (97.5% CI: 1.5, 7.5) for B/Victoria, and -1.4 (97.5% CI: -3.6, 0.7) for B/Yamagata.
- SARS-CoV-2 Day 29 GMR was 1.641 (97.5% CI: 1.510, 1.783) for the SARS-CoV-2 Omicron XBB.1.5.
- The Day 29 SRR difference was 12.8 (97.5% CI: 9.6, 15.9) for the SARS CoV-2 Omicron XBB.1.5.

Cohort B

- Influenza Day 29 GMRs (mRNA-1083 vs Fluarix + Spikevax) were 1.414 (97.5% CI: 1.322, 1.513) for A/H1N1, 1.380 (97.5% CI: 1.300, 1.465) for A/H3N2, 1.216 (97.5% CI: 1.156, 1.278) for B/Victoria, and 1.154 (97.5% CI: 1.109, 1.201) for B/Yamagata.
- The Day 29 SCR differences were 17.9 (97.5% CI: 14.3, 21.4) for A/H1N1, 14.6 (97.5% CI: 11.1, 18.0) for A/H3N2, 8.6 (97.5% CI: 5.6, 11.6) for B/Victoria, and 2.7 (97.5% CI: 0.3, 5.0) for B/Yamagata.
- SARS-CoV-2 Day 29 GMR was 1.308 (97.5% CI: 1.207, 1.418) for the SARS-CoV-2 Omicron XBB.1.5.
- The SRR difference was 8.1 (97.5% CI: 5.2, 11.0) for the SARS-CoV-2 Omicron XBB.1.5.

Immunogenicity for influenza was also assessed using a multicycle neutralisation assay (MN-CPE) which may capture neutralising capacity against additional antiviral effects, beyond anti-HA. Results indicated comparable neutralising capacity between mRNA-1083 and the inactivated influenza vaccine comparators.

The principle of immunobridging the influenza component of mRNA-1083 with an inactivated influenza vaccine is supported by efficacy and immunogenicity data from the mRNA-1010 vaccine that is based on the same influenza antigen constructs from study mRNA-1010-P304. In adults 50 years of age and older, a single dose of mRNA-1010 showed higher efficacy than the inactivated comparator vaccine in the prevention of RT-PCR-confirmed influenza-like illness. The rVE was 26.6% (95% CI: 16.7, 35.4).

9.3.1. Uncertainties and limitations about favourable effects

No correlates of protection for influenza or COVID-19 exist. The main study for mRNA-1083 solely relies on immunogenicity data.

Although efficacy has been demonstrated for mRNA-1010, this has a higher dose of mRNA encoding for influenza. Differences in the influenza correlate of protection relationship hamper a direct interpretation of relative immunogenicity results for mRNA-1083 and no inverse correlation between haemagglutinin inhibition titres and influenza-like illness risk could be demonstrated for influenza B/Victoria. The extent of protection of mRNA-1083 is therefore unclear.

9.4. Unfavourable effects

The clinical safety profile of mRNA-1083 was mainly derived from study P301 in which a total of 4004 participants received mRNA-1083 + Placebo (two age cohorts combined, one injection in each arm), 2006 participants in Cohort A (⩾65 years of age) received Fluzone HD + Spikevax as active control, and 2005 participants in Cohort B (50 to 65 years of age) received Fluarix + Spikevax as active control. The median safety follow-up was 171 days.

In the mRNA-1083 group, subject incidences of any solicited local adverse reactions (ARs) were 75.8% in Cohort A and 79.2% in Cohort B, vs. 70.1% in Cohort A and 76.2% in Cohort B of the

active control groups. Grade 3 solicited local ARs were reported by 2.8% (Cohort A) and 3.4% (Cohort B) of participants who received mRNA-1083, vs. 1.6% (Cohort A) and 2.2% (Cohort B) in the active control groups.

In Cohort A, the median duration of any solicited local AR was 3 days in the mRNA-1083 group and 2 days in the Fluzone HD + Spikevax group. In Cohort B, the median duration of any solicited local AR was 3 days in both groups.

Subject incidences of any solicited systemic ARs were 70.1% in Cohort A and 75% in Cohort B of the mRNA-1083 group, vs. 63.2% (Cohort A) and 67.2% (Cohort B) in the active control groups.

In Cohort A, the following frequencies were reported: fever (mRNA-1083: 11.9%, control: 4.4%), headache (mRNA-1083: 43.5%, control: 36.3%), fatigue (mRNA-1083: 52.9%, control: 44.3%), myalgia (mRNA-1083: 51.2%, control: 43%), arthralgia (mRNA-1083: 42.2%, control: 35.7%), nausea/vomiting (mRNA-1083: 13.4%, control: 8.9%), and chills (mRNA-1083: 34.8%, control: 21.4%). Grade ≥3 systemic ARs were reported in 7.7% of participants in the mRNA-1083 group, compared to 3.4% in the active control group.

In Cohort B, the following frequencies were reported: fever (mRNA-1083: 14.5%, control: 6.2%), headache (mRNA-1083: 51.4%, control: 42.9%), fatigue (mRNA-1083: 58.9%, control: 48.9%), myalgia (mRNA-1083: 58.4%, control: 47%), arthralgia (mRNA-1083: 47%, control: 35.9%), nausea/vomiting (mRNA-1083: 18.1%, control: 12.8%), and chills (mRNA-1083: 41.6%, control: 27.9%). Grade ≥3 systemic ARs were reported in 10.7% of participants in the mRNA-1083 group, compared to 5.5% in the active control group.

In Cohort A, the median duration of any solicited systemic AR was 2 days in both groups. In Cohort B, the median duration of any solicited systemic AR was 3 days in the mRNA-1083 group and 2 days in the Fluarix + Spikevax group.

The incidences of solicited ARs tended to be higher in female and younger participants.

Unsolicited AEs until 28 days after vaccination considered to be related (by the Investigator) were reported in 0.8% vs. 1.0% (Cohort A) and 0.9% vs. 1.2% (Cohort B) of participants in the mRNA-1083 group vs. the active control groups, respectively.

9.4.1. Uncertainties and limitations about unfavourable effects

The safety database of over 4000 vaccinated participants is in principle sufficient to detect uncommon AEs (occurring in between 1/100 and 1/1000 vaccinated individuals), but potential rare AEs (occurring in less than 1/1000 vaccinated individuals) might not have been detected. Information on rare but serious AEs should be collected post-authorisation.

Post-marketing data for Spikevax revealed ADRs, which were not detected in initial clinical trials. This includes rare cases of myocarditis/pericarditis, for which pharmacoepidemiological studies revealed the highest excess risk in younger males. It is not known whether there is a similar risk for cardiac inflammation with mRNA-1083 and whether this will be present in the targeted age group (>50 years of age), and in the context of a booster dose. As a result, the relevant warning in section 4.4 of the SmPC was included. The RMP includes myocarditis and pericarditis as important potential risks together with additional pharmacovigilance activities.

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9.5. Effects Table

Table 49: Effects Table for mCOMBRIAX Active immunisation for the prevention of influenza disease and COVID-19 caused by SARS-CoV-2 in individuals 50 years of age and older.

Effect (short description)		***Treatment vs Control***		***Uncertainties/ Strength of evidence***	***Ref***
Favourable Effects					
		Cohort A (≥65 years of age)	Cohort B (50 to <65 years of age)		
		mCOMBRIAX + placebo vs Fluzone HD + Spikevax	mCOMBRIAX + placebo vs Fluarix + Spikevax		
Influenza Day 29 Geometric Mean anti-HA antibody titre Ratio (97.5% CI) Non-inferiority (NI margin LB 2-sided 97.5% >0.667) demonstrated based on GMR for all four influenza strains at Day 29 after mRNA-1083 compared an inactivated influenza vaccine co-administered with Spikevax.	A/H1N1	1.155 (1.086, 1.229)	1.414 (1.322, 1.513)	**SoE:** NI criteria were met for all co-primary EP. **Uncertainty:** remains regarding HAI titres as a surrogate of protection for the immunobridging of influenza mRNA vaccines against inactivated vaccines. Supportive efficacy and immunogenicity data derive from the mRNA-1010 vaccine that is based on the same influenza antigen constructs.	P301
	A/H3N2	1.063 (0.999, 1.130)	1.380 (1.300, 1.465)		
	B/Victoria	1.118 (1.063, 1.175)	1.216 (1.156, 1.278)		
	B/Yamagata	1.007 (0.969, 1.047	1.154 (1.109, 1.201)		
SARS-CoV-2 Day 29 Geometric Mean neutralising antibody titre Ratio (97.5%CI) Non-inferiority (NI margin LB 2-sided 97.5% >0.667) demonstrated based on GMR for all four influenza strains at Day 29 after mRNA-1083 compared with Spikevax co-administered with an inactivated influenza vaccine.	XBB.1.5	1.641 (1.510, 1.783)	1.308 (1.207, 1.418)	**SoE:** Primary objective met	

Effect (short description)	***Treatment vs Control***		***Uncertainties/ Strength of evidence***	***Ref***
Unfavourable Effects				
	Cohort A	Cohort B		

Effect (short description)	Treatment vs Control				Uncertainties/ Strength of evidence	Ref
	mRNA-1083 40 µg + Placebo	Fluzone HD + Spikevax	mRNA-1083 40 µg + Placebo	Fluarix + Spikevax		P301
Any solicited local AR (%)	75.8	70.1	79.2	76.2		
Lymphadenopathy (%)	20.6	15.9	24.4	21.0		
Fever (%)	11.9	4.4	14.5	6.2		
Myalgia (%)	51.2	43	58.4	47		
Any Grade ≥3 systemic AR (%)	7.7	3.4	10.7	5.5		

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Extrapolation of clinical data from the formulation containing four influenza strains mRNA-1083 to mCOMBRIAX (with three influenza strains, without B/Yamagata) is supported by the shared manufacturing process and consistent antigen content for the retained strains, in line with WHO recommendations.

Efficacy

This application relies on establishing efficacy by inferring it from an immunogenicity comparison between mRNA-1083 and authorised COVID-19 and age-appropriate influenza vaccines. It is supported by efficacy data from the influenza only mRNA-1010 vaccine.

The humoral immune responses against 4 influenza strains and SARS-CoV-2 were non-inferior after vaccination with mRNA-1083 compared to responses induced by simultaneous vaccination with approved COVID-19 and influenza vaccines in individuals 50 years of age and older. Immunogenicity can be considered robust as 10 co-primary endpoints based on GMR and SCR/SRR against influenza and SARS-CoV-2 were met in two separately analysed age cohorts (≥50 to <65 years of age and ≥65 years of age). These findings are further supported by immune responses measured by the MN-CPE assay.

No correlates of protection for influenza or COVID-19 exist.

There are however several studies describing the key role of neutralising antibodies for protection against COVID-19 and it can be assumed that mRNA-1083 will elicit similar immune pathways as the approved comparator mRNA vaccine. Therefore, the immunobridging approach to infer efficacy for mRNA-1083 against COVID-19 can be accepted. This concept has also been applied previously for mRNA COVID-19 vaccines.

For influenza, data from a supportive study with mRNA-1010, which includes a higher dose of mRNA, indicated rVE for the influenza component of mRNA-1083. In addition, the results of the CoP report support surrogate properties of HAI titres against influenza A. Differences in the CoP relationship hamper a direct interpretation of relative immunogenicity results for mRNA-1083 and no inverse correlation between HAI titres and influenza-like illness risk could be demonstrated for influenza B/Victoria. However, rVE results for mRNA-1010 with respect to B/Victoria do still indicate rVE which

likely permit extrapolation of sufficient VE to mRNA-1083. While the immunobridging does not suffice as sole evidence for inferring efficacy to the flu component, the supportive data from the mRNA-1010 efficacy data allow to conclude on a protective effect of mRNA-1083. The extent of protection however remains unclear. Therefore, the applicant formally committed to conduct an effectiveness study for all included influenza strains and to submit the corresponding protocol before study initiation.

Mutations for influenza B HA proteins were introduced into the current versions of mRNA-1010 and mRNA-1083 following poor immunogenicity results with the original influenza B constructs. It is not entirely clear whether the stability of the influenza B antigen (and immunogenicity) will be affected with future strain updates. The applicant's proposal to evaluate protein structure/stability using in-silico analysis and in vitro relative protein expression assay (IVRPE) is in principle endorsed. However, additional functional testing is required, and a respective recommendation was agreed by BWP.

Safety

mRNA-1083 was clearly more reactogenic than the combinations of authorised active comparators in both study cohorts, not only with respect to incidences of all solicited systemic adverse reactions, but also in terms of severity. For interpretation of the available data, it is relevant to note that Spikevax alone can already be considered to have a pronounced reactogenicity in comparison to other standard vaccines and that co-administration with influenza vaccines may have further increased the incidences of solicited ARs in the active control group. However, the CHMP considered the reactogenicity profile manageable due to the transient nature of these adverse events. Importantly, the reactogenicity observed is considered lesser burden than the potential clinical illness burden of individuals who experience severe disease caused by infection with COVID-19 or influenza. This application concerns individuals aged 50 years of age and above and the elderly are at increased risk of developing severe disease caused by infection. It is important that the nature and relatively high frequency of ADRs is adequately communicated in order to allow well-informed decisions on vaccination.

The incidences of solicited ARs tended to be higher in female participants, which is not an unusual finding for vaccines.

Immunocompromised and immunodeficient individuals were excluded from the trial. Certain immune-mediated conditions that were stable and well-controlled as well as those that did not require systemic immunosuppressants were permitted at the discretion of the Investigator. The very pronounced reactogenicity of mRNA-1083 leads to a theoretical concern that patients affected by immune-mediated disorders might be at an increased risk for exacerbations of auto-immune or immune mediated disorders, compared to other less reactogenic vaccines. The currently available data from the phase 3 study do not indicate a particularly increased risk for onset or exacerbation of such disorders, but it needs to be considered that the study was not designed to investigate this issue based on the eligibility criteria.

For both age cohorts, the incidences of unsolicited AEs, MAAEs, AESIs and SAEs until 28 days after vaccination but also until end of study (Day 181) were comparable between the two study groups and no particular safety concern was detected. However, while the phase 3 study was sufficiently large for evaluation of the B/R, potential rare adverse drug reactions might not have been detected.

Although no AESIs of myocarditis or pericarditis were reported up to 28 days after vaccination, this is a recognised ADR for mRNA-1273 and considered a likely ADR also for mRNA-1083. The actual risk of myocarditis and pericarditis after mRNA-1083 when used for (annual) revaccination in adults aged 50 or older is however uncertain and should be characterised post-authorisation.

Individuals with unstable medical conditions were excluded from the trial. Based on the Edmonton Frail Scale, 7.6% of participants of the phase 3 trial were considered frail. There were no differences with respect to solicited and unsolicited events between participants who were classified as fit, vulnerable or frail. However, the majority of frail patients were mildly frail, which limits the interpretability and meaningfulness of the data for individuals with severe frailty.

The Applicant committed to closely monitor exacerbations/flare ups of autoimmune or immune-mediated disorders and use in very elderly and unstable frail individuals in the Periodic Safety Update Reports (PSURs) due to the reactogenicity of mRNA-1083 and the limited amount of data in these populations.

9.6.2. Balance of benefits and risks

In the main study, the co-primary immunogenicity endpoints were met indicating non-inferior immune response of mRNA-1083 to simultaneous vaccination with approved COVID-19 and influenza vaccines. Immunogenicity of the influenza component of mRNA-1083 was supported by efficacy and immunogenicity data from the influenza-only vaccine mRNA-1010.

The safety data reveal an increased reactogenicity of mRNA-1083 in terms of incidences and severity of solicited systemic adverse reactions compared to the control vaccines but is considered manageable in the sought indication.

Considering immunobridging results with mRNA-1083, supportive efficacy data with mRNA-1010 for influenza and mRNA-1283 for SARS-CoV-2 and an overall non-negligible but manageable safety profile, the benefit risk of mCOMBRIAX is positive.

9.7. Benefit-risk conclusions

The benefit/risk balance of mCOMBRIAX is positive.