Summary of the Risk Management Plan for COVID-19 Vaccine Moderna

This is a summary of the risk management plan (RMP) for COVID-19 Vaccine Moderna. The RMP details important risks of COVID-19 Vaccine Moderna, how these risks can be minimised, and how more information will be obtained about COVID-19 Vaccine Moderna risks and uncertainties (missing information).

The COVID-19 Vaccine Moderna's summary of product characteristics (SmPC) and its package leaflet provides essential information to healthcare professionals and patients on how COVID-19 Vaccine Moderna should be used.

This summary of the RMP for COVID-19 Vaccine Moderna should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the COVID-19 Vaccine Moderna RMP.

I The Medicine and What it is Used for

COVID-19 Vaccine Moderna is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The active substance in COVID-19 Vaccine Moderna is mRNA encoding the SARS-CoV-2 Spike protein embedded in lipid nanoparticles and it is given by intramuscular route.

Further information about the evaluation of COVID-19 Vaccine Moderna benefits can be found in the COVID-19 Vaccine Moderna EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: www.ema.europa.eu/medicines/human/EPAR/covid-19-vaccine-moderna

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

Important risks of COVID-19 Vaccine Moderna, together with measures to minimise such risks and the proposed studies for learning more about COVID-19 Vaccine Moderna risks, are outlined below.

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

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about Adverse Reactions (ARs) is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of COVID-19 Vaccine Moderna is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of COVID-19 Vaccine Moderna are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of COVID-19 Vaccine Moderna. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast-feeding Long-term safety Use in immunocompromised subjects Interaction with other vaccines Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders

II.B Summary of Important Risks

Table 2: Important Identified Risk: Anaphylaxis

Important Identified Risk: Anaphylaxis	
Evidence for linking the risk to the medicine	In the Phase 3 study P301, 2 cases of anaphylaxis have been reported; 1 case each in the placebo and the mRNA-1273 group. The cases happened 10 days after the first injection and 63 days after the second injection, respectively. Both cases were assessed unrelated per the investigators. After the data lock of the Phase 3 P301 study on 25 November 2020 and before the data lock point (DLP) of the risk management plan (RMP), a second case of

Important Identified Risk: Anaphylaxis	
	anaphylaxis was reported in the placebo group 60 days after the second injection. The case was non-serious and considered unrelated per the investigator. During emergency use authorisation, after the DLP of the RMP one case of anaphylaxis classified based on available information as a Level 2 according to Brighton Collaboration criteria was reported shortly after the intramuscular administration of mRNA-1273 vaccine.
Risk factors and risk groups	Any participant receiving the vaccine. However, participants with a known history of hypersensitivity to any component of the vaccine may be at risk of hypersensitivity reactions.
Risk minimisation measures	<u>Routine risk communication</u> : SmPC Sections 4.3 Contraindications 4.4 Special Warnings and Precautions for Use 4.8 Undesirable effects PL Sections 2 and 4 Ensure appropriate medical treatment and supervision to be always readily available in case of an anaphylactic reaction following administration of the vaccine. Recommendations for close observation for at least 15 minutes following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 vaccine Moderna (SmPC section 4.4). Patients to get urgent attention in case of signs and symptoms of allergic reactions is included in the Package Leaflet (PL) section 4. Contraindication in subjects with prior hypersensitivity to any component of the vaccine is included in section 4.3 and PL section 2. <u>Additional risk minimisation</u>: None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities</u>: Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US

Important Identified Risk: Anaphylaxis	
	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the European Union (EU) Phase 3 P301 Phase 2a P201 Phase 1 20-0003 Safety and Immunogenicity in Immunocompromised Adults See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 3: Important Potential Risk: Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD) Disease

Important Potential Risk: Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associatedEnhanced Respiratory Disease (VAERD)	
Evidence for linking the risk to the medicine	Research points to disease enhancement being triggered by one of two major mechanisms although other mechanisms may also contribute. The first and least well characterised is when priming by the initial infection results in a Th2 biased immune response mediated more by myeloid lineage cells, including neutrophils and eosinophils with immune complex formation and complement activation. This "Th2 biased" phenotype is most associated with enhanced disease as resulting from the formalin-inactivated measles and respiratory syncytial virus (RSV) vaccines. In these cases, post vaccination exposure of previously naïve vaccines resulted in an immune response characterised by high interleukin (IL) 4, 5 & 13 levels and localized tissue inflammation associated with neutrophil and eosinophil infiltration, immune complex deposition and pulmonary inflammation and obstruction. The second and far better characterised mechanism is antibody dependent enhancement (ADE). This results from the generation of binding but poorly neutralizing antibodies induced by heterologous antigens generated either by heterologous viral strains (eg, dengue), by chemically disrupted antigens (eg, formalin-inactivated RSV and measles) or by epitope altering mutations such as feline infectious peritonitis. These antibodies bind to but do not neutralize the virus and facilitate Fc receptor mediated entry

	of viable virus into macrophages. This can result in an accelerated and more marked viremia and more severe disease. This scenario is the one associated with dengue virus and its virus and vaccine-associated ADE. ADE for dengue can also result from sub-neutralizing concentrations of neutralizing antibodies, such as that seen in infants as maternal antibodies wane. It is likely that in many cases there are components of both mechanisms in enhanced disease. No evidence of harm has been identified in non-clinical studies nor from the Phase 3 P301 harm monitoring at the time of the data lock point for the risk management plan, where safety follow up is based on a median of 9 weeks of follow up post-second dose.
Risk factors and risk groups	This is a potential risk and no increased risk to mRNA-1273 has been established. Therefore, no risks groups or risks factors can be identified. However, the generation of binding but poorly neutralizing antibodies in individuals may result in an accelerated and more marked viremia and more severe disease.
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Phase 3 P301 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 4: Use in Pregnancy and While Breast-Feeding

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections

	4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the United States (US) Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Moderna mRNA-1273 Observational pregnancy outcome study See section II.C of this summary for an overview of the post-authorisation development plan.

Table 5: Long-Term Safety

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU • Phase 3 P301 • Phase 1 20-0003 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 6: Use in Immunocompromised Subjects

Risk minimisation measures	Routine risk minimisation measures:

	SmPC Section 4.4 Special Warnings and Precautions for Use PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. • Safety and Immunogenicity in Immunocompromised Adults See section II.C of this summary for an overview of the post-authorisation development plan.

Table 7: Interaction with Other Vaccines

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU See section II.C of this summary for an overview of the post-authorisation development plan.

Table 8: Use in Frail Subjects With Unstable Health Conditions and Co-morbidities (e.g. Chronic Obstructive Pulmonary Disease (COPD), Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Risk minimisation measures	Routine risk minimisation measures:

	SmPC Section 5.1 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU See section II.C of this summary for an overview of the post-authorisation development plan.

Table 9: Immunogenicity in Subjects With Autoimmune or Inflammatory Disorders

Risk minimisation measures	Routine risk minimisation measures: PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

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

Study Title and Number	**Purpose of the Study**
Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older (mRNA-1273-P301)	Long-term safety data and durability of vaccine effectiveness (VE).

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

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

Study Title and Number	**Purpose of the Study**
Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults (DMID Protocol No. 20-0003 [NCT04283461])	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses. Follow up period extended by an additional 12 months for 24 months follow up total after the second dose. Assessment of a booster dose.
A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ≥ 18 Years (mRNA-1273-P201)	Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster.
Study of the Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Immunocompromised Adults	Safety and reactogenicity and adverse events for 1 year after receiving 2 doses of SARS-CoV-2 mRNA-1273 vaccine. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.
Post Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity.	This study will monitor anaphylaxis, Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), and long-term safety. It will also monitor AESI and emerging validated safety signals.
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine, use in pregnancy and while breast-feeding, concomitant administration observed with non-COVID vaccines, use in frail participants with unstable health conditions and co-morbidities, and use in participants with autoimmune or inflammatory disorders.

Moderna mRNA-1273 Observational Pregnancy Outcome Study	Evaluate outcomes of pregnancies in females exposed to mRNA 1273 vaccine during pregnancy.
Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the U.S	Evaluate the real-world effectiveness and long-term effectiveness of mRNA-1273 in preventing COVID-19 and severe COVID-19 disease. Effectiveness stratified by age, sex, race/ethnicity, comorbid conditions. Effectiveness of two doses of vaccine in preventing COVID-19 among immunocompromised patients. Frail individuals and participants with autoimmune and inflammatory disorders will be evaluated to the extent that it is feasible. Considering current Advisory Committee on Immunization Practice recommendations to not co-administer other adult vaccines (eg, seasonal flu vaccine) in participants, Moderna will evaluate this schedule as possible. Durability of one or two doses of COVID19 Vaccine Moderna against COVID-19 and severe COVID-19 disease will also be assessed.