Date: 3 December 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Spikevax (previously COVID-19 Vaccine Moderna), dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified)

International non-proprietary name: CX-024414

Pharmaceutical form: Dispersion for injection, 0.20 mg/mL

Dosage strength: One dose (0.5 ml) contains 0.10 mg (100 µg) 5'-capped messenger RNA (mRNA), encoding the pre-fusion stabilised Spike (S) glycoprotein of 2019 novel Coronavirus (SARS-CoV-2) (embedded in lipid nanoparticles).

Route(s) of administration: Intramuscular injection

Marketing Authorisation Holder: Moderna Switzerland GmbH

Marketing Authorisation No.: 68267

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 12.01.2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AR	Adverse Reaction
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
bAbs	Binding antibodies
BP	Blood pressure
CDC	Center for Disease Control
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CMI	Cell-mediated immunity
COVID-19	Coronavirus disease caused by the SARS-CoV-2 virus
CYP	Cytochrome P450
ECMO	Extracorporeal membrane oxygenation
ERA	Environmental Risk Assessment
FIO2	Fraction of inspired oxygen
G-CSF	Granulocyte colony stimulating factor
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IL	Interleukin
INFγ	Interferon gamma
INN	International Nonproprietary Name
ITT	Intent to treat
LNP	Lipid nanoparticle
LLOQ	Lower limit of quantitation
LoQ	List of Questions
MAAE	Medically attended adverse event
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MIP-1	Macrophage inflammatory protein 1
mRNA	Messenger RNA
mRNA-1273	Original codename for COVID-19 Vaccine Moderna (Spikevax)
N/A	Not applicable
nAbs	Neutralising antibodies
NO(A)EL	No Observed (Adverse) Effect Level
PaO2	Partial pressure of oxygen
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK

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PP	Per protocol
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
RT-PCR	Real-time polymerase chain reaction
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SpO2	Percent saturation of oxygen in the blood
SwissPAR	Swiss Public Assessment Report
TNF-α	Tumour necrosis factor alpha
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
VE	Vaccine Efficacy
WHO	World Health Organisation
µg	Microgram

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance CX-024414 (single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2) of the medicinal product mentioned above.

Rolling authorisation procedure (FTP)
The applicant requested a rolling authorisation procedure. According to the Guidance document "Authorisation procedures for COVID-19 medicinal products during a pandemic, HMV4", for the exceptional case of a pandemic, and at the request of the applicant during a Presubmission Advice meeting, an authorisation application may be submitted as a "Rolling Submission". The "Rolling Submission" procedure represents a special form of a first authorisation procedure or a variation procedure.

Marketing authorisation for human medical products
The applicant requested a marketing authorisation in accordance with Art. 9a, para. 1 TPA. However, based on the submitted clinical data material and the results of the evaluation, Swissmedic granted a temporary authorisation in accordance with Art. 9a TPA and with regard to the guidance document "*Authorisation procedures for COVID-19 medicinal products during a pandemic, HMV4*"

OPEN project EMA
In the context of the EMA's OPEN project, Swissmedic has been participating in the meetings of the CHMP. Further information at: *EMA COVID-19 assessments 'OPEN' to non-EU regulators | European Medicines Agency (europa.eu).*

2.2 Indication and Dosage

2.2.1 Requested Indication

COVID-19 Vaccine Moderna is indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in individuals 18 years of age and older.
The use of this vaccine should be in accordance with official recommendations.

2.2.2 Approved Indication

COVID-19 Vaccine Moderna is indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in individuals 18 years of age and older.
The use of this vaccine should be in accordance with official recommendations.

2.2.3 Requested Dosage

COVID-19 Vaccine Moderna is a two-dose regimen. The second dose should be administered one month after the first dose (see Warnings and Precautions).
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

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2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	12 November 2020
Formal control completed	13 November 2020
List of Questions (LoQ)	Rolling List of Questions
Answers to LoQ	Rolling Answers to List of Questions
Predecision	11 January 2021
Answers to Predecision	11 January 2021
Labelling corrections	11 January 2021
Answers to Labelling corrections:	12 January 2021
Final Decision	12 January 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2).

The following link provides the number of cases and deaths globally and per country: WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data

As of 27 December 2020, as the Spikevax vaccine was under evaluation by Swissmedic, there had already been over 80,000,000 confirmed cases of SARS-CoV-2 infection globally with approximately 1.8 million deaths.

As of 27 February 2021, this had increased to 113,076,707 confirmed cases of COVID-19, including 2,512,272 deaths. By 22 September 2021, there were, cumulatively and worldwide, 229,373,963 confirmed cases and 4,705,111 deaths reported to WHO.

In Switzerland, COVID-19 data are collected by the Swiss Federal Office of Public Health (BAG, Bundesamt für Gesundheitswesen). On 23 December 2020, there had been 421,382 positive cases, 17,504 hospitalisations and 6,406 deaths since the beginning of the pandemic. Cumulatively, and up to February 21, 2021, there had been 550,066 confirmed cases of COVID-19 (6,391.6 per 100,000 inhabitants), 23,617 hospitalisations (274.4 per 100,000 inhabitants) and 9,204 deaths (106.9 per 100,000 inhabitants). By 23 September 2021, cumulatively, there were 831,880 confirmed cases, 32,570 hospitalisations, and 10,650 deaths. Link: COVID-19 Switzerland | Coronavirus | Dashboard (admin.ch)

While hospitalisations and deaths can occur in any age group, a majority occur in people aged 50 and over, with incidence increasing exponentially with age.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immunocompromised status, cancer and obesity are some of the risk factors for developing severe COVID-19.

People with COVID-19 have reported a wide range of symptoms, ranging from no, or mild, symptoms to severe illness and death. Symptoms may appear 2-14 days after exposure to the virus, and may include: fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhoea. Severe COVID-19 can cause dyspnoea, pneumonia and ARDS (Acute Respiratory Distress Syndrome), thromboembolism and other conditions that may require ICU care. In addition to respiratory sequelae, severe COVID-19 has been linked to severe health problems such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute renal injury, neurological complications such as encephalopathy and acute ischaemic stroke. Severely infected persons may develop post-acute COVID-19 syndrome and may need months of rehabilitation. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

There is no cure yet against COVID-19 and, in Switzerland, at the time of the evaluation of the vaccine, only one other vaccine had received a temporary authorisation, Pfizer's Comirnaty.

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4 Quality Aspects

4.1 Active Substance

CX-024414, the active substance of COVID-19 Vaccine Moderna, is a single-stranded, 5'-capped mRNA encoding the S1S2 full-length surface antigen from the SARS-CoV-2 virus. The S1S2 protein sequence includes an intrinsic signal peptide at the N-terminal end and two proline point mutations (K986P and V987P), resulting in a protein in the optimised prefusion conformation.
The RNA sequence contains common structural elements, such as 5'cap, 5' and 3' UTRs, poly(A) tail. Uridine in the full sequence is replaced by N-methyl pseudouridine.
The mRNA active substance is formulated with lipid nanoparticles to increase stability of the mRNA during storage and after administration, and to facilitate transfection into the host cells.
Upon uptake into the cells, the mRNA is released and translated in the cell to generate the encoded S1S2 protein antigen.

The mRNA active substance is manufactured in a cell-free system, by an *in vitro* transcription reaction using enzymatic reagents and utilising nucleotide triphosphates, a 5'-cap structure and linearised plasmid template as starting materials. The *in vitro* transcription reaction is followed by several purification steps.
Linearised plasmid is not a structural component of the active substance but serves as a template for the respective enzyme, thus defining the correct nucleotide sequence of the mRNA drug substance. The plasmid is produced by fermentation in established and characterised bacterial cell banks. For plasmid manufacture and control, sufficient information was provided.

Manufacturing process changes of the active substance during process development, including the transfer to the manufacturing site at Lonza, Visp, process changes and scale-up steps were adequately described, and supporting data from comparability studies between commercial and clinical batches were provided.
The active substance and its impurities were sufficiently characterised using state-of-the-art analytical methods.
Process performance qualification runs were performed, and the presented control strategy, validation data and extended characterisation results demonstrated that the manufacturing process is capable of producing active substance batches that consistently meet the predefined specifications.

The specification tests and acceptance criteria were provided and include e.g. identity test, purity and impurity testing. Analytical methods were described and non-compendial methods have been validated in accordance with ICH guidelines.

4.2 Finished Product

COVID-19 Vaccine Moderna is a white to off-white dispersion for injection containing 100 µg/0.5 mL of mRNA embedded in lipid nanoparticles (LNPs). LNPs consist of four lipids: cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), SM-102, and PEG2000 DMG (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000). Other ingredients are trometamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose, and water for injections. All excipients, with the exception of DSPC and the novel excipients SM-102 and PEG2000 DMG, comply with the pharmacopoeia.

A detailed description of the manufacturing process development and process characterisation studies was provided, and critical parameters were defined. The manufacturing history, including process changes and transfer to commercial facilities, was sufficiently described. Comparability of the

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material for emergency use and commercial supply with clinical batches has been demonstrated, based on the release testing and extended characterisation studies.
The manufacturing process validation is ongoing. The data from several GMP batches were provided prior to approval. A full process validation report, including extended characterisation and comparability studies of commercial drug product batches, will be submitted as one of the conditions of temporary authorisation.
The specification tests and acceptance criteria were provided and include a panel of analytical procedures to confirm identity, composition, purity, potency and safety. Analytical methods are described, and non-compendial methods have been validated in accordance with ICH requirements.

The finished product is supplied as a sterile, preservative-free, multidose presentation.
It is intended for intramuscular administration.

The finished product is supplied in a glass vial (glass type I or equivalent) sealed with a chlorobutyl rubber stopper and an aluminium seal. 10 doses of 0.5 mL can be withdrawn, each dose containing 100 µg of the active substance.
Vials are packaged in a carton containing a total of ten multi-dose vials per carton. The primary packaging materials comply with the requirements of the pharmacopoeia.

COVID-19 Vaccine Moderna is stored at -25 to -15 °C in the original container.
The proposed in-use shelf-life of the thawed finished product of 30 days at 2-8 °C followed by up to 12 hours at up to 25°C was accepted. The product may not be refrozen after thawing.
After first opening, the drug product can be held for up for 6 hours at 2-25 °C. From the microbiological standpoint, the product should be used as soon as possible.

The manufacturing process for the active substance and finished product incorporates adequate control measures to prevent contamination and maintain control with regard to adventitious agent contamination.

4.3 Quality Conclusions

From the quality perspective the data presented in the application support the conclusion that the manufacture of is robust and sufficiently controlled to yield the product of consistent quality.

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5 Nonclinical Aspects

Pharmacodynamics
mRNA-1273 is an RNA-based vaccine against SARS-CoV-2 consisting of a chemically (N1-methylation of the base pseudouridine) and genetically modified (codon optimisation for translation in human cells) *in vitro* transcribed mRNA formulated as an mRNA-lipid complex in a Tris / acetate / sucrose solution. The modified mRNA encodes the pre-fusion stabilised coronavirus S-protein (introduction of two proline residues in the S-protein sequence, S-2P). The lipids used are SM-102, PEG2000-DMG, DSPC and cholesterol. The dose to be administered to humans is 0.2 mg / mL.

With respect to the pharmacodynamics of mRNA-1273, *in vitro* data in 293T cells and data from mice, hamster and non-human primates (NHPs) were provided by the applicant. In cells in culture, expression of the S-2P protein was detected on the surface of cells by flow cytometry. However, no detailed analysis of the expressed S-2P protein was performed *in vitro*. It was not studied whether membrane-bound S-2P protein could be proteolytically cleaved from the cell membrane to form a soluble protein outside of cells. The submitted data suggest that the modified mRNA is unstable and that the usage of N1-methyl-pseudouridine enhances its translatability in the target cells.

Prime-boost immunisation of mice (young and aged), hamster and NHPs with mRNA-1273 by the intramuscular route resulted in a dose-dependent robust induction of a humoral response characterised by S-protein binding IgG antibodies specific for the ACE2-receptor-binding domain and the S1-N-termimal domain. A prime-boost immunisation induced a stronger response than a prime alone. The prime-boost regimen induced neutralising antibodies in all three species. The boost was needed to induce a decent neutralising antibody titre. Human convalescent plasma contained the same or fewer S protein binding and neutralising antibodies than sera from vaccinated animals. A detailed dose-response analysis in mice showed that a dose of 5 μg mRNA-1273 was needed for maximum induction of the humoral response. In aged mice, it was shown that a boost was necessary for the induction of neutralising antibodies. Analysis of IgG2 and IgG1 revealed expression of both IgG subclasses in a balanced way in all three species, indicating a vaccine-mediated Th1 response.

The mRNA-1273 induced a T-cell response in **mice**. It was shown that a 1 μg mRNA-1273 dose induced a Th1 response with CD4+ and CD8+ cells expressing INFγ, IL-2 and TNF-α. In CD4+ cells, suboptimal doses induced Th2 responses as measured by the expression of IL-4, IL-5 and IL-13. In **NHPs**, a dose-dependent increase in Th1 responses was observed in CD4 cells, and Th2 responses were low. No substantial CD8 T-cell responses were detected after mRNA-1273 vaccination.

Challenge studies were performed in mice (young and aged), hamsters and NHPs. Before challenging, the animals were immunised (prime-boost, intramuscular) with mRNA-1273. For challenge studies in **mice**, a mouse-adapted SARS-CoV-2 MA virus was used whose S protein was genetically changed (two amino acid changes at positions Q498Y / P499T) to interact with the mouse ACE2 protein. An intranasal challenge with SARS-CoV-2 MA induced a respiratory disease characterised by weight loss, lung haemorrhage and viral replication in the respiratory tract. Untreated, mice started to recover after 4 days. The mRNA-1273 vaccine protected mice in a dose-dependent manner, showing protection from doses equal to and higher than 1 μg. Histological data showed vaccine-mediated reduced inflammation and reduced pneumocyte hyperplasia and reduced SARS-CoV-2 MA virus in the lung. In vaccinated animals, PCR analyses showed reduced viral load in the lung and nasal turbinates. Suboptimal vaccine doses below 1 μg did not result in enhanced respiratory disease (ERD). In order to evaluate vaccine-mediated **protection** of SARS-CoV-2

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infection **in older animals**, aged mice (1 year old) were studied. In aged mice a prime-boost vaccine regimen was needed to induce neutralising antibodies. In comparison to mRNA-1273, an inactivated SARS-CoV (DIV) was not able to induce a humoral immune response. Whereas mRNA-1273 induced low levels of inflammatory cytokines, the inactivated SARS-CoV induced substantial levels of inflammatory cytokines, including IL-1, IL-6, MIP-1 and G-CSF. The challenge of older mice with the adapted SARS-CoV-2 MA virus caused more severe disease. A 1 mg intramuscular dose of the mRNA-1273 protected the animals. A suboptimal dose of 0.1 μg resulted only in partial protection, but did not induce signs of ERD. The mRNA-1273 vaccine also protected **hamsters** after intranasal challenging with wild-type SARS-CoV-2 (USA-WA1/2020, 10^5 PFU). Vaccine-protected animals did not lose weight, and viral load was reduced from day 2 after challenge. Furthermore, the lung histology showed reduced inflammation. In **NHPs**, 100 μg mRNA-1273 vaccine was needed to reduce the viral load in both BAL and NS samples. The vaccine could not completely inhibit the virus replication in NHPs in the lower or upper respiratory tract.

At the point of approval, **no long-term efficacy data** were evaluated in animals after vaccination with mRNA-1273. A long-term study in NHPs is ongoing, and data should be available by the end of 2021.

No studies with respect to **safety pharmacology** were conducted, which can be accepted based on the absence of safety signals from GLP toxicity studies.

Pharmacokinetics

Standard pharmacokinetic studies with respect to absorption, metabolism and excretion (ADME studies) were not performed with mRNA-1273. Detailed ADME studies are not usually required for vaccines by international agreement, and the lack of these data is acceptable due to the nature of the mRNA-LNP product.

The limited submitted information in rats suggests that mRNA-LNP particles are primarily taken up by professional phagocytes such as dendritic cells and macrophages. The **modified mRNAs are expected to be degraded within hours in cells, and antigen expression peaks two days post-injection, with signs of clearance four days post-injection**.

No ADME studies were performed with the isolated lipid components. Data for very similar lipids were described in rats by the applicant, suggesting that the **lipids are primarily excreted in urine and faeces** and cleared from the body one week after injection. SM-102 half-lives were determined to be in the range of hours in serum and selected organs such as liver and spleen.

No biodistribution was determined in animals with the COVID-19 mRNA-1273 vaccine. Instead, biodistribution data for the CMV vaccine mRNA-1647 obtained in rats were submitted. This can be accepted, as the mRNA-1647 is formulated with the same lipids as the mRNA-1273, and the biodistribution is primarily determined by the lipid components of the mRNA-LNP particle. The mRNA-1647 contains six different modified mRNAs, and each mRNA molecule was measured in selected organs / tissues by a multiplex branched DNA (bDNA) assay.

Concentrations for all six mRNA-1647 constructs were detectable in plasma and tissues in a 1:1:1:1:1:1 ratio. Following a single IM dose, the maximum concentration (T_{max}) observed **in plasma** was 2 hours for all constructs and was followed by a rapid elimination phase with a half-life ($\mathbf{T_{1/2}}$) of **3 - 4 hours**.

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The **highest mRNA-1647 concentrations** were **observed at the injection site, followed by the proximal and distal lymph nodes and spleen**, consistent with distribution via the lymphatic system. In muscle, lymph nodes and spleen, the maximum observed concentration (C_{max}) was between 2 and 24 hours post-dose. The **$T_{1/2}$** was calculated as **15 hours for muscle, 30-35 hours for lymph nodes and 63 hours for spleen**.

Levels of mRNA above the lower limit of quantitation (LLOQ) were determined in most tissues analysed, including eyes, brain, liver, lungs, heart, GI tract, bone marrow and gonads. Overall, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist beyond 1 to 3 days in tissues.

Toxicology

Standard **GLP-compliant toxicity studies** were not performed with mRNA-1273. Instead, six GLP-compliant toxicity studies were performed with several modified mRNA vaccine products formulated with the four lipid components into mRNA-LNP particles, comparable with mRNA-1273. These vaccines were evaluated in Sprague Dawley rats after **three or four intramuscular weekly doses** (hind limb) and **recovery periods of two weeks**. The lack of a toxicity study with mRNA-1273 can be accepted based on the fact that the safety profiles of all evaluated mRNA-LNP vaccines were comparable, indicating that the observed effects were mainly due to the lipid components of the vaccine product. All studies were performed over a time frame of six weeks at most, which is in accordance with international guidelines and can be accepted based on the kinetics of these types of vaccines.

All animals developed the expected antibody responses. Generally, the vaccines showed a favourable safety profile, with reversing or reversible effects that can be attributed to the provoked immune reaction. The findings were dose-dependent and included injection site reactions, effects on lymph nodes and spleen, effects on cytokine levels and elevated body temperatures, haematology changes, effects on liver cells (and reduced body weight changes and food intake. **Injection site** findings included **swelling**, **oedema** and **erythema**, associated with a mixed inflammation consisting of neutrophils, macrophages and lymphocytes. As a secondary effect of the hind limb injection, some sciatic nerve inflammatory changes were also observed. Draining lymph nodes in the injection area were enlarged, associated with a perinodal mixed cell inflammation. In the **spleen**, minimal to mild decreased cellularity of the periarteriolar lymphoid sheath was observed at ≥ 10 µg/dose and was often associated with an increase in macrophages. **Haematology, coagulation and clinical chemistry changes** observed at ≥ 10 µg/dose included increases in neutrophil, eosinophil and large unstained cell counts (LUC), and decreases in lymphocyte, reticulocyte and platelet counts; **increases in APTT and fibrinogen; increases in globulin and decreases in albumin**. At high doses, increases in **IL-1β, IL-6, IP-10, MCP-1**, and **MIP-1α** were occasionally observed.

Generally, the mRNA-LNP vaccines show a favourable safety profile, and they were studied with adequate safety margins (up to more than 370-fold the human dose).

GLP-compliant **genotoxicity** studies were performed with **SM-102** and **PEG-2000-DMG**. The genotoxicity evaluations included *in vitro* analyses (bacterial reverse mutation tests, mammalian cell micronucleus tests) and, for SM-102 only, in vivo analyses (bone marrow micronucleus tests). For *in vivo* evaluations with SM-102, two studies were performed. In one study involving the use of a luciferase mRNA-LNP, no significant increase in the incidence of micronuclei was noted. In the second study, involving the use of mRNA-1706, a statistically significant increase in the incidence of

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micronucleated immature erythrocytes was found. In the absence of any *in vitro* clastogenicity, it can be concluded that inflammatory responses induced by the mRNA-LNPs contributed to this finding.

A GLP-compliant **developmental and reproductive toxicity** (DART) study was performed in female Sprague Dawley rats with mRNA-1273. A human clinical dose of the mRNA-LNP vaccine was administered twice before mating and twice during gestation. The only noteworthy findings were the development of wavy ribs and increased nodules on ribs, but these were not considered adverse as there was no effect on pup growth or viability. The wavy ribs and rib nodules resolve postnatally without medical intervention.

Final Risk Assessment

In preclinical studies, the mRNA-1273 vaccine showed a very good humoral and cellular immune stimulation towards a Th1 response. A prime-boost vaccine regimen resulted in a stronger response, and a boost was needed especially in aged animals. Protection from SARS-CoV-2-mediated disease was shown in all species tested. Based on the pharmacokinetics, it can be assumed that most of the mRNA-1273 stays locally at the injection site. However, a limited amount of the vaccine is distributed systemically. This systemic distribution might be favourable for the immune response. On the other hand, it also poses an extended risk with respect to the development of unpredictable adverse events. The safety profile is acceptable, and the findings can be explained by the expected immune response towards the vaccine. It can be concluded that, in the light of the current pandemics, the benefit of the vaccine outweighs the risk. The mRNA-1273 vaccine can be approved from the preclinical perspective.

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6 Clinical and Clinical Pharmacology Aspects

There are three clinical studies, and all are still ongoing:

- Phase 1 dose-escalation reactogenicity, safety and immunogenicity study (20-0003)
- Phase 2a, randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in adults aged 18 years and older (mRNA-1273-P201)
- Phase 3 (mRNA-1273-P301) efficacy, safety and immunogenicity study in adults aged 18 and over

6.1 Clinical Pharmacology

Mechanism of Action

COVID-19 Vaccine Moderna contains a nucleoside-modified mRNA encapsulated in lipid nanoparticles. The lipids in the mRNA-lipid complex protect the mRNA until it is delivered to the host cells where it enters the cytosol. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is non-replicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional Spike protein that is inserted into the cellular membrane of the expressing cell(s). The expressed, membrane-bound spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to the spike (S) protein of SARS-CoV-2 in the vaccinated individual. The immune response to the viral spike protein then prevents attachment and entry of SARS-CoV-2 into the host cells, thus preventing COVID-19 disease.

Immunogenicity

Phase 1 Study Immunogenicity Data

A phase 1, dose-ranging safety and immunogenicity study (20-0003) was carried out and was still ongoing at the time the vaccine was granted temporary authorisation by Swissmedic. Four doses were being tested: 25 µg, 50 µg 100 µg and 250 µg, administered to 120 healthy adults (males and non-pregnant females, aged 18-55, 56-70, and ≥ 71 years old). The immunogenicity follow-up was 119 days post first vaccination (57 days for the 50 µg dose as the 50 µg dose was added later).

The 100 µg dose of mRNA-1273, administered as two injections 28 days apart, resulted in the induction of neutralising antibodies (nAbs) in all participants by 1 week **after the second injection**. After a single injection of 100 µg of Spikevax, binding antibodies (bAbs) against spike glycoprotein were detectable in all participants in all three age strata, with further increases observed following the second injection. The serum bAb titres were higher after the two injections of the 100 µg dose than after the two injections of the 25 µg dose (age group 18 to 55 years of age). Also, two injections of 100 µg induced nAb responses that were similar to those measured in recipients of the 250 µg dose. Since two injections of 100 µg led to a lower incidence of reactogenicity than two injections of 250 µg, the 100 µg dose was preferred.

The 50 µg dose induced humoral immune responses that were comparable with those induced by the 100 µg dose (data for the 50 µg dose only available up to day 57), and a similar response was

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observed across all age cohorts. However, higher responses were observed after the second injection in older adults receiving the 100 µg dose compared to the 50 µg dose.

For cellular immunity (an exploratory endpoint), Th1-directed CD4+ T-cells were induced across all age groups. There was a limited Th2-directed response, which is desirable as it indicates a lesser risk of antibody-enhanced disease.

The humoral response (binding and neutralising antibodies) and cellular response were also tested against a panel of convalescent sera. The post-vaccine humoral response increased with dose and was comparable with or above that observed in convalescent sera for both the 50 and 100 µg doses.

Specifically, binding IgG antibodies against the spike protein (stabilised spike antigen, S-2P) were observed to have higher median values at day 43 and beyond in the Spikevax group than in the convalescent sera control group. Neutralising activity was observed for the 100 µg mRNA-1273 dose as of day 36; the neutralising activity was higher than that in the convalescent sera control group, and the median titres remained in the same range as the median titre in the convalescent sera control group at Day 119 across the age strata.

The study is ongoing, and analyses on days 209 and 394 are planned.

Phase 2a Study (P201) Immunogenicity Data

Based on the initial data from the above phase 1 study, two dose levels (50 µg and 100 µg) were chosen for evaluation in the phase 2a study. Safety, reactogenicity and immunogenicity (levels of specific binding antibody (bAb) and neutralising antibody (nAb)) were studied in two age cohorts:
Cohort 1 with 300 participants (≥ 18 to < 55 years old) and
Cohort 2 with 300 participants (≥ 55 years old).

The participants received either mRNA-1273 (the Spikevax vaccine) or saline placebo control (0.5 mL) as an intramuscular (IM) injection on Day 1 and Day 29. Within each age cohort, 100 participants received mRNA-1273 50 µg, 100 participants received mRNA-1273 100 µg, and 100 participants received saline placebo.

Generally, comparable neutralising and binding antibody responses were measured in the serum of participants who received either 50 µg or 100 µg doses of Spikevax administered 28 days apart. Even though the neutralising antibody titres after the first injection, though still very low, were somewhat higher after the 100 µg dose (day 29), the titres rose substantially for both doses after the second injection. For the binding antibodies, responses at Day 29 were slightly higher in participants who received 100 µg of mRNA-1273 than in those who received 50 µg of mRNA-1273.

At the time of the **primary analysis of safety and immunogenicity data,** participants had completed Day 57 study procedures. These data were evaluated for the initial temporary authorisation of Spikevax. Follow-ups are planned up to day 394 (Month 13). Results will be submitted at different time points and are part of the requirements for a change from a temporary to a definitive authorisation.

Phase 3 Study (P301) Immunogenicity Data

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Immunogenicity data for Study mRNA-1273-P301 were not yet available at the time of the temporary authorisation by Swissmedic.

6.2 Dose Finding and Dose Recommendation

Results of Study 20-0003 showed a consistent dose response across age groups by several measures of humoral immunogenicity for both binding and neutralising antibodies. The advancement of the 100 µg dose (administered as two injections, 28 days apart) to the Phase 2a and 3 studies was based on several observations:

- Two injections of 100 µg stimulated serum bAb titres greater than two injections of 25 µg in the 18 to 55 age group;
- Also in the 18 to 55 age group, two injections of 100 µg induced nAb responses similar to those measured in recipients of the 250 µg dose;
- Two injections of 100 µg led to a lower incidence of reactogenicity than two injections of 250 µg;
- Even though the 50 µg dose did not show pronounced differences compared to the 100 µg dose, the 100 µg dose was chosen because of comparable and acceptable reactogenicity and slightly higher immunogenicity.
- The 250 µg dose was only tested in the 18-55 age group and was not pursued further due to high reactogenicity.

The need for a second dose was based on the following observations:

- Peak titres of binding and neutralising antibodies across age groups and clinical trials were generally seen 7-14 days after the second dose (on days 36-43 post first dose). Decreases in titres became apparent soon thereafter and were reported until day 57 in the phase 2 study and day 119 in the phase 1 study. However, in the majority of participants, the antibody levels were generally sustained within the upper range or above those observed in human convalescent comparator sera. Neutralising antibody responses were generally comparable between age cohorts or superior in the younger participants.
- In both the phase 1 and phase 2a studies and across all age strata tested, the humoral immune response in terms of induction of antibodies binding the S protein and virus neutralising antibodies showed that two mRNA1273 doses given 4 weeks apart resulted in substantially higher titres compared to responses after only one dose. While binding antibody levels generally started to rise after the first vaccination (day 15), this was not always seen for neutralising antibody responses, which were induced mostly after the second vaccination.

Reactogenicity was also considered in the dose-finding process. After the first vaccination, solicited systemic adverse events were reported by 5 participants (33%) in the 25 µg group, 10 (67%) in the 100 µg group, and 8 (53%) in the 250 µg group.

Solicited systemic adverse events were more common after the second vaccination and occurred in 7 of 13 participants (54%) in the 25 µg group, all 15 in the 100 µg group, and all 14 in the 250 µg group, with 3 of those participants (21%) reporting one or more severe events.

None of the participants had fever after the first vaccination. After the second vaccination, no participants in the 25 µg group, 6 (40%) in the 100 µg group, and 8 (57%) in the 250 µg group

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reported fever; one of the events (maximum temperature, 39.6°C) in the 250 µg group was graded as severe. Thus reactogenicity was highest with the 250 µg dose.

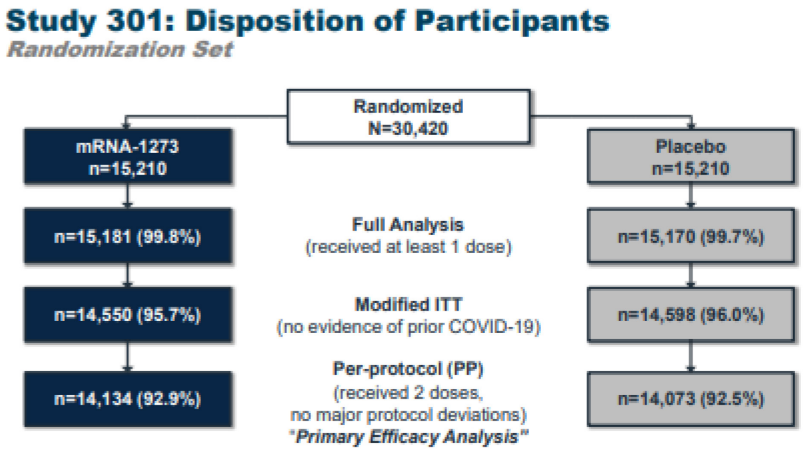
Evaluation of safety clinical laboratory values of grade 2 or higher and unsolicited adverse events revealed no patterns of concern.

6.3 Efficacy

Phase 3 Study
The ongoing phase 3 pivotal study of mRNA-1273 is a randomised (1:1 Spikevax versus normal saline control), stratified (by age and health risk), observer-blind and placebo-controlled trial in approximately 30,400 participants.

The trial enrolled participants 18 years of age and older. There were 99 clinical trial sites, all in the USA. Two 100 µg doses were administered four weeks apart.

Around 40% of participants had risk factors for severe COVID-19 and/or were over 65, and 75% of participants were under 65 years of age. 48% of study participants were female, 52% male.



PRIMARY OBJECTIVES
• To demonstrate the efficacy of mRNA-1273 to prevent COVID-19 in persons without prior SARS-CoV-2 infection (per protocol set, primary efficacy analysis).
• To evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart.

The **primary efficacy endpoint** required a PCR confirmed SARS-CoV-2 infection more than two weeks after the second dose of vaccine, along with pre-defined symptoms of COVID-19. The pre-defined symptoms included:

• The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR

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• The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
• The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalised) positive for SARS-CoV-2 by RT-PCR.

An event-based, **first interim analysis of the primary efficacy endpoint** was conducted using a **data cut-off of November 7, 2020.** A total of 27,817 participants randomised 1:1 to vaccine or placebo with a median of 7 weeks of follow-up post-dose 2 were included in the per-protocol efficacy analysis. In the vaccinated group, as compared to the placebo group, there was a **relative reduction in the incidence of COVID-19** in the period starting 14 days post-dose 2:

Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5.0% (95% CI: 86.5%, 97.8%) with 5 COVID-19 cases occurring in the vaccine group and 90 COVID-19 cases occurring in the placebo group.

Efficacy data from the **final scheduled analysis of the primary efficacy endpoint (data cut-off of November 21, 2020, with a median follow-up of >2 months post-dose 2)** confirmed a vaccine efficacy (VE) of 94.1% (95% CI: 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group. This was consistent with results obtained from the interim analysis.

The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to <65 years of age and 86.4% (95% CI: 61.4%, 95.5%) for participants ≥65 years of age.

See table below.

Primary Efficacy Analysis: Confirmed COVID-19 (symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom), **regardless of severity starting 14 days after the 2nd dose – Per-Protocol Set**

Age Group (Years)	COVID-19 Vaccine Moderna (Spikevax)			Placebo			% Efficacy (95% CI)*
	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	
Overall (≥18)	13,934	11	3.328	13,883	185	56.510	94.1 (89.3, 96.8)
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)
≥65 to <75	2,953	4	5.586	2,864	22	31.744	82.4% (48.9, 93.9)

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≥75	630	0	0	688	7	41.968	100% (NE, 100)

At the time of initial temporary authorisation by Swissmedic, the power of the study did not allow a conclusion to be drawn on vaccine efficacy for persons over 75 years of age.

As the study is ongoing, data on the *duration of protection* will be available later, taking into account the fact that, after 6 months of median follow-up, the placebo group participants were to be offered the vaccine. This was a necessary protocol amendment due to the fact that Spikevax became available in the US under an Emergency Use Authorisation in December of 2020. However, all study participants will still be followed for 24 months post-vaccination.

KEY SECONDARY OBJECTIVES
• To evaluate the efficacy of mRNA-1273 to prevent **severe COVID-19**.
• To evaluate vaccine efficacy (VE) against a **secondary definition of COVID-19**.

The secondary efficacy analyses shown below were done at the time of the data cut-off for the primary efficacy analysis.

Prevention of Severe COVID-19 (Per Protocol Set)
To be considered as **severe COVID-19**, the following criteria had to be met: a confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, plus any of the following:
• Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR
• Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
• Significant acute renal, hepatic or neurologic dysfunction, OR
• Admission to an intensive care unit or death.
Secondary efficacy analyses suggested a benefit of the vaccine in preventing protocol-defined severe COVID-19. There were 30 (0.2% of all per protocol placebo participants) severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group. Confidence intervals for the VE against severe COVID-19 cases could not be estimated, however, due to insufficient power of the study.

Vaccine Efficacy (VE) Against a Secondary Case Definition of COVID-19 (Per Protocol Set)
The secondary case definition of COVID-19 was according to the CDC case definition and required only ONE clinical symptom from an expanded list as well as a nasopharyngeal or nasal swab / saliva sample positive for SARS-CoV-2 virus.

There were 11 cases in the vaccine group and 221 in the placebo group. VE for this secondary case definition was 95.1% (95% CI: 91.1 to 97.3%).

Further secondary analyses also suggested a benefit of the vaccine in preventing COVID-19 starting 14 days after the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for some of these outcomes did not allow firm conclusions to be drawn.

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Following the Emergency Use Authorisation granted by the FDA on 18 December 2020, Amendment 6 of the phase 3 study added that all participants in the placebo arm who opt to cross over from placebo to active vaccination would have the opportunity to receive the vaccine. In any case, Moderna intends to continue the ongoing pivotal phase 3 study P301 with all participants followed up until 24 months after the second dose.

6.4 Safety

The safety of mRNA-1273 is largely based on data from the pivotal phase 3 study using data snapshots dated 11 Nov 2020 and 25 Nov 2020. The safety analysis set included 30,350 study participants: 15,184 received mRNA-1273 and 15,165 received placebo. The safety analysis set included all randomised participants of the phase 3 study who received one or more vaccine or control doses.

After the first **safety interim analysis of the phase 3 study,** which took place on **November 11, 2020** (median follow-up of 7 weeks following the second dose), the Sponsor submitted additional follow-up data **with a cut-off date of November 25, 2020**. This represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Deaths, other serious adverse events and unsolicited adverse events of interest were examined and showed no significant differences between the placebo and the vaccine groups.

Reactogenicity was assessed in the ongoing phase 3 clinical trial by observation of the solicited local and systemic ARs that occurred during the 7 days following each injection (i.e., on the day of injection and on 6 subsequent days).

Unsolicited AEs, observed or reported, were assessed during the 28 days following each injection (i.e., on the day of injection and 27 subsequent days).
AEs leading to discontinuation from dosing and/or study participation will be assessed through Day 759 or withdrawal from the study, as will the MAAEs and SAEs.

Post-marketing surveillance is ongoing since temporary marketing authorisation was granted. It is based on national and international data from spontaneous reporting (pharmacovigilance) and from post-authorisation studies, see the RMP summary on Swissmedic's website, RMP summaries (swissmedic.ch).

Reactogenicity
Solicited local ARs were reported by a majority of participants in the mRNA-1273 group and were reported at a higher incidence in the mRNA-1273 group (92.4%) than in the placebo group (29.3%) after any injection. Solicited systemic ARs were reported by the majority of participants in the mRNA-1273 group and were more prevalent in the mRNA-1273 group (84.1%) than in the placebo group (53.5%) after any IP injection. In the mRNA-1273 group, the incidence and severity of solicited systemic ARs appeared to increase after the second injection.

For differences in reactogenicity in the placebo versus the vaccine groups after dose 1 and after dose 2, please see the table titled "*mRNA-1273 P301 Solicited Local and Systemic Adverse Reactions Within 7 Days After Dosing (Safety Analysis Set**)" in the prescribing information attached to this document.

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Commonly identified solicited adverse reactions were injection site pain, fatigue, headache, myalgia, arthralgia, erythema/redness at the injection site, axillary swelling and tenderness, nausea/vomiting, fever. The frequency and severity of these reactions increased in the mRNA-1273 group after the second dose.

Adverse Reactions
As above, see also the "*Tabulated list of adverse reactions*" identified at the time of temporary authorisation in the attached copy of the original prescribing information.

The incidence of unsolicited TEAEs (vaccine: 23.9%; placebo: 21.6%), severe TEAEs (1.5%; 1.3%), and MAAEs (9.0%; 9.7%) during the 28 days after any injection were generally similar in participants who received mRNA-1273 and those who received placebo. The incidence was also comparable in adults 18 to < 65 years of age compared with participants 65 years of age and older who received mRNA-1273 (21.5% versus 23.1%, respectively). There was no difference in the incidence of unsolicited TEAEs based on SARS-CoV-2 serology at baseline.

A slightly higher incidence of all hypersensitivity events in the vaccine group versus the placebo group (1.5% vs. 1.1%, respectively), which was driven mainly by injection site rash (n=37 (0.2%) vs. n=1 (<0.1%)), injection site urticaria (n=15 (<0.1%) vs. n=0) and rash (n=45 (0.3%) vs. n= 34 (0.2%)).

An SMQ of angioedema revealed a balanced incidence of 0.3% in each study arm.

Autoimmune diseases: The frequency of autoimmune-related adverse events is comparable, for both arms of trial P301, with 28 (0.2%) of subjects in the placebo arm and 32 (0.2%) of subjects in the vaccine arm reporting such events.
Facial palsy (three cases in the verum arm, one in the placebo arm) has been observed.

A total of 8 deaths occurred in Study mRNA-1273-P301, with 4 deaths occurring in the mRNA-1273 group and 4 deaths occurring in the placebo group. None were attributed to COVID-19 nor considered related to study product. The causes of death were consistent with those that are expected in the population enrolled in the study.

Post-marketing Data
Very rare hypersensitivity/anaphylactic events were identified internationally post-marketing and led to the instruction to monitor vaccine recipients for at least fifteen minutes following dosing.

Within a few months after temporary authorisation, cases of myocarditis were identified through pharmacovigilance surveillance with a frequency that was higher in vaccine recipients after the second dose than what would be expected as background incidence.
See https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/marktueberwachung/health-professional-communication--hpc-/dhpc-mrna-impfstoffe-gegen-covid-19.html and the published updated prescribing information.

Other very rare adverse events were identified later through the international and Swiss pharmacovigilance systems. See current prescribing information Arzneimittelinformation (swissmedicinfo.ch) and Swissmedic homepage Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – update (swissmedic.ch).

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6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Benefit

At the time of the pre-defined primary endpoint analysis, the median follow-up of the phase 3 study was two months. There were 196 cases of COVID-19 during the 2-month median follow-up, of which 185 occurred in the placebo group and 11 in the vaccine group. Spikevax thus showed a vaccine efficacy of 94.1% (with 95% CI of 89.3% to 96.8%). The lower limit of 89.3% for the 95% CI for the primary endpoint exceeded the pre-specified 30% margin established by the WHO and FDA, and thus the endpoint was met.

Reduced severe COVID-19 disease (0 vs 30 cases in mRNA-1273 vs placebo groups, respectively), and immunogenicity lasting for at least 119 days at last analysis were further data showing a beneficial effect of the vaccine.

Uncertainties and Risks

- The median follow-up of 2 months is too short to obtain sufficient long-term efficacy and safety data. In particular, duration of protection is as yet unknown, as are vaccine efficacy in certain age groups or the protection against hospitalisation and deaths (the latter has been shown using epidemiological data since the temporary authorisation was granted).
- There are currently no established immune correlates of protection.
- Persistence of immunogenicity is unknown.
- Whether the 50 microgram dose may be effective in younger age groups and cause less reactogenicity has not been tested.
- As seasonal influenza vaccines and other vaccines were not given concurrently with the COVID-19 vaccine, there are no data on the possibility of simultaneous vaccinations with other types of vaccines.
- Potential interactions between vaccine and medicines have not been studied.
- The need for a second dose in previously infected persons has not been tested.
- No data, or very limited data, are available on pregnant and lactating women, immunocompromised persons, and paediatric subjects.
- Protection against developing variants is unknown.
- There are no data yet on asymptomatic infections in vaccine recipients and potential spread to contacts.
- There are no long-term data on rare, unexpected risks that may appear with time or as more people get vaccinated.
- The reactogenicity (especially systemic) may be severe in a small percentage of vaccine recipients, even more so after the second dose.
- Some cases of anaphylaxis have been observed, which led to the recommendation to monitor vaccine recipients for a certain time period following injection.
- Not known at the time of temporary authorisation, cases of myocarditis were identified in very rare cases after vaccination, which led to publication of a DHPC and changes to the prescribing information.

Benefit / Risk Assessment

Spikevax was the second COVID-19 vaccine to receive a temporary marketing authorisation in Switzerland.

Given the pandemic situation as described above under “Medical Context”, the high vaccine efficacy, and the lack, so far, of any prohibitive safety signals, the benefit-risk assessment is overwhelmingly

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positive. The phase 1, 2 and 3 trials are ongoing and will continue to provide immunogenicity, safety and efficacy data. These ongoing studies as well as other studies planned by the company (see also RMP Summary) will provide answers with time and will be necessary for the conversion from a temporary to a full authorisation.

Based on the totality of the scientific evidence available so far, the known and potential benefits of Moderna COVID-19 Vaccine outweigh the known and potential risks of the vaccine for the prevention of COVID-19 in individuals 18 years of age and older. Follow-up of the phase 3 trial, post-marketing and “real world” studies as well as international safety surveillance are very important and will be considered before a change from temporary to full authorisation can be made.

In view of the rolling submission procedure and temporary authorisation in accordance with Art. 9a TPA, the Swiss prescribing information will be updated as needed.

See www.swissmedicinfo.ch for the latest version.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Spikevax (COVID-19 mRNA Vaccine (nucleoside modified)) was the version approved at the time of the initial temporary authorisation of Spikevax. The information for healthcare professionals has been updated since the initial authorisation.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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Placeholder for text approval stamp

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions. The following product information will be regularly updated as soon as new data and safety reports are available.
COVID-19 Vaccine Moderna authorization is temporary - see section “Properties/Effects”.

COVID-19 Vaccine Moderna

COVID-19 mRNA Vaccine (nucleoside modified)

Composition

Active substances

One dose (0.5 mL) contains 0.10 mg 5’-capped messenger RNA (mRNA), encoding the pre-fusion stabilized Spike (S) glycoprotein of 2019 novel Coronavirus (SARS-CoV-2) (embedded in lipid nanoparticles).

Excipients

Lipid SM-102, Cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene (PEG2000-DMG), Trometamol, Trometamol hydrochloride, Acetic acid, Sodium acetate, Sucrose, Water for injection.

Each 0.5 mL dose contains 0.033 mg sodium.

Pharmaceutical form and active substance quantity per unit

White to off-white Dispersion for injection, 0.20 mg/mL.
Each vial contains 5 ml of dispersion.

Indications/Uses

COVID-19 Vaccine Moderna is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in individuals 18 years of age and older.
The use of this vaccine should be in accordance with official recommendations.

Dosage/Administration

COVID-19 Vaccine Moderna should be administered by a trained healthcare worker.

COVID-19 Vaccine Moderna vials are for multiple use. A maximum of 10 doses of 0.5 mL volume can be withdrawn from each multiple-dose vial.

Usual dosage

COVID-19 Vaccine Moderna is a two-dose regimen. The second dose should be administered one month after the first dose. (see Warnings and Precautions)
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.
A patient card to which the name of the vaccine, the batch number, the date of the second dose and information on reporting of adverse events should be handed out to the patient.
There are no data available on the interchangeability of COVID-19 Vaccine Moderna with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of COVID-19 Vaccine Moderna should receive the second dose of COVID-19 Vaccine Moderna to complete the vaccination course.

Elderly patients

In an ongoing Phase 3 clinical study, the safety and efficacy of COVID-19 Vaccine Moderna was assessed in individuals 18 years of age and older, including 3,768 subjects 65 years of age and older. No dosage adjustment is required in elderly individuals ≥65 years of age.

Children and adolescents

The safety and efficacy of COVID-19 Vaccine Moderna in individuals less than 18 years of age have not yet been established. No data are available.
COVID-19 Vaccine Moderna is not indicated in children and adolescents < 18 years of age.

Mode of administration

COVID-19 Vaccine Moderna should be administered by the intramuscular route. The preferred site is the deltoid muscle of the upper arm.
Do not administer this vaccine intravenously or subcutaneously or intradermally.
The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.
No dilution is required.
For precautions to be taken before administering the vaccine, see section “Warnings and precautions”.
For instructions regarding thawing, handling and disposal of the vaccine, see section “Other information”.

Contraindications

COVID-19 Vaccine Moderna is contraindicated in individuals with known severe allergic reactions (eg, anaphylaxis) to any component of the vaccine or to a previous dose of COVID-19 Vaccine Moderna.

Warnings and precautions

Hypersensitivity and anaphylaxis

Anaphylaxis has been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following administration of the COVID-19 Vaccine Moderna. Close observation for at least 15 minutes is essential following vaccination. The second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 Vaccine Moderna.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine Moderna may be lower in immunosuppressed individuals.

Persons at Risk of Bleeding

As with other intramuscular injections, COVID-19 Vaccine Moderna should be given with caution in individuals with bleeding disorders, such as haemophilia, or individuals currently on anticoagulant therapy, to avoid the risk of haematoma following the injection.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in persons with severe febrile illness or acute infection.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of Vaccine Effectiveness

Individuals may not be fully protected until 14 days after their second dose. As with all vaccines, vaccination with COVID-19 Vaccine Moderna may not protect all vaccine recipients.

Excipients with known effect

Sodium

This vaccine contains less than 1 mmol sodium (23 mg) per 0.5 mL dose and is considered 'sodium-free'.

Interactions

No interaction studies have been performed

Other Vaccines

There are no data to assess the concomitant administration of Moderna COVID-19 Vaccine with other vaccines.

Pregnancy, lactation

Pregnancy

No adequate and well-controlled studies of Moderna COVID-19 Vaccine use in pregnant women have been conducted. Available data on COVID-19 Vaccine Moderna administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see Preclinical data).

Lactation

It is not known whether COVID-19 Vaccine Moderna is excreted in human milk. Data are not available to assess the effects of Moderna COVID-19 Vaccine on the breastfed infant or on milk production/excretion. Therefore, use of Moderna COVID-19 Vaccine is not recommended in breastfeeding mothers.

Fertility

No data are available on fertility in humans with use of Moderna COVID-19 Vaccine .

Effects on ability to drive and use machines

No studies on the effects of the Moderna COVID-19 Vaccine on the ability to drive and use machines have been performed. Some of the effects mentioned under section "Undesirable Effects" may affect the ability to drive or use machines.

Undesirable effects

Summary of the safety profile

The safety of COVID-19 Vaccine Moderna was evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of COVID-19 Vaccine Moderna

(n=15,185) or placebo (n=15,166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older.

The most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

Tabulated list of adverse 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)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Tabulated List of Adverse Reactions

MedDRA System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Nervous system disorders	Very common	Headache
	Rare	Acute peripheral facial paralysis**
Gastrointestinal disorders	Very common	Nausea/vomiting
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills Pyrexia Injection site swelling
	Common	Injection site erythema, Injection site urticaria, Injection site rash
	Uncommon	Injection site pruritus
	Rare	Facial swelling***

*Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site.
**Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the COVID-19 Vaccine Moderna group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.
***There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination

Overall, there was a slightly higher rate of some solicited adverse reactions in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Local and systemic adverse reactions, as well as Grade 3 solicited adverse reactions were more frequently reported after Dose 2 than after Dose 1. Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination.

List of adverse reactions

Table 2: mRNA-1273 P301 Solicited Local and Systemic Adverse Reactions Within 7 Days After Dosing (Safety Analysis Set*)

Local Injection Site Reaction	**Vaccine Group Dose 1; n (%)** N=15164	**Placebo Group Dose 1; n (%)** N=15151	**Vaccine Group Dose 2; n (%)** N=14673	**Placebo Group Dose 2; n (%)** N=14562
Pain				
Any	12690 (83.7)	2658 (17.5)	12943 (88.2)	2477 (17.0)
Grade 3 or 4[a]	416 (2.7)	55 (0.4)	604 (4.1)	40 (0.3)
Erythema				
Any	430 (2.8)	67 (0.4)	1257 (8.6)	56 (0.4)
Grade 3 or 4[b]	42 (0.3)	13 (<0.1)	287 (2.0)	15 (0.1)
Swelling/Induration				
Any	932 (6.1)	52 (0.3)	1789 (12.2)	49 (0.3)
Grade 3 or 4[b]	82 (0.5)	6 (<0.1)	254 (1.7)	11 (<0.1)
Axillary swelling/ Tenderness[c]				
Any	1553 (10.2)	722 (4.8)	2090 (14.2)	567 (3.9)
Grade 3 or 4	49 (0.3)	27 (0.2)	67 (0.5)	19 (0.1)
Systemic adverse reaction				
Fever				
Any	115 (0.8)	44 (0.3)	2278 (15.5)	43 (0.3)
Grade 3 or 4[d]	15 (<0.1)	8 (<0.1)	215 (1.5)	5 (<0.1)
Headache				
Any	4951 (32.7)	4027 (26.6)	8602 (58.6)	3410 (23.4)
Grade 3 or 4[e]	271 (1.8)	196 (1.3)	659 (4.5)	162 (1.1)
Fatigue				
Any	5635 (37.2)	4133 (27.3)	9582 (65.3)	3403 (23.4)
Grade 3 or 4[f]	151 (1.0)	105 (0.7)	1428 (9.7)	106 (0.7)
Myalgia				
Any	3441 (22.7)	2071 (13.7)	8508 (58.0)	1809 (12.4)
Grade 3 or 4[f]	90 (0.6)	47 (0.3)	1318 (9.0)	52 (0.4)
Arthralgia				
Any	2511 (16.6)	1783 (11.8)	6284 (42.8)	1569 (10.8)
Grade 3 or 4[f]	61 (0.4)	37 (0.2)	770 (5.2)	44 (0.3)
Nausea/Vomiting				
Any	1262 (8.3)	1074 (7.1)	2785 (19.0)	934 (6.4)
Grade 3 or 4[g]	10 (<0.1)	12 (<0.1)	21 (0.1)	11 (<0.1)
Chills				
Any	1253 (8.3)	878 (5.8)	6482 (44.2)	809 (5.6)
Grade 3 or 4[h]	24 (0.2)	14 (<0.1)	191 (1.3)	17 (0.1)

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N= number of exposed participants who submitted any data for the event, percentages are based on n/N
[a] Pain - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
[b] Erythema and Swelling/Induration - Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
[c] Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e., lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.
[d] Fever - Grade 3: ≥39.0 – ≤ 40.0°C; Grade 4: > 40.0°C
[e] Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
[f] Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
[g] Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
[h] Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

The reactogenicity and safety profile in 343 subjects receiving COVID-19 Vaccine Moderna, that were seropositive for SARS-CoV-2 at baseline, was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Properties/Effects

ATC code

J07BX03

Mechanism of action

COVID-19 Vaccine Moderna encodes for the pre-fusion stabilized Spike protein of SARS-CoV-2. After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into protein. The mRNA delivery system is based on the principle and observation that cells in vivo can take up mRNA, translate it, and express protein antigen(s) in the desired conformation. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional Spike protein that is inserted into the cellular membrane of the expressing cell(s). The Spike protein is membrane bound, mimicking the presentation of natural infection.

The expressed Spike protein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations. The specific mechanism of protection for the SARS-CoV-2 virus remains under investigation.

Pharmacodynamics

Not applicable.

Clinical efficacy

The randomised, placebo-controlled, observer-blind Phase 3 clinical study (NCT04470427) excluded individuals who were immunocompromised or had received immunosuppressants within 6 months, as well as participants who were pregnant, or with a known history of SARS-CoV-2 infection. Participants with stable HIV disease were not excluded. Any vaccine within 28 days prior to or after any dose of Covid-19 Moderna vaccine was not permitted, with the exception of the influenza vaccine, which could be administered 14 days before or 14 days after any dose of COVID-19 Vaccine Moderna. Participants were also required to observe a minimum interval of 3 months after receipt of blood/plasma products or immunoglobulins prior to the study in order to receive either placebo or COVID-19 Vaccine Moderna.
A total of 30,351 subjects were followed for a median of 92 days (range: 1-122) for the development of COVID-19 disease post dose 1.
The primary efficacy analysis population (referred to as the Per Protocol Set or PPS), included 28,207 subjects who received either COVID-19 Vaccine Moderna (n=14,134) or placebo (n=14,073) and had a negative baseline SARS-CoV-2 status. The PPS study population included 47.4% female, 52.6% male, 79.5% White, 9.7% African American, 4.6% Asian, and 6.2% other. 19.7% of participants identified as Hispanic or Latino. The median age of subjects was 53 years (range 18-94). A dosing window of –7 to +14 days for administration of the second dose (scheduled at day 29) was allowed for inclusion in the PPS. 98% of vaccine recipients received the second dose 25 days to 35 days after dose 1 (corresponding to -3 to +7 days around the interval of 28 days).
COVID-19 cases were confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT PCR) and by a Clinical Adjudication Committee. Vaccine efficacy overall and by key age groups are presented in Table 3.

Table 3: Primary Efficacy Analysis: confirmed COVID-19[#] regardless of severity starting 14 days after the 2nd dose – Per-Protocol Set

Age Group (Years)	COVID-19 Vaccine Moderna			Placebo			% Efficacy (95% CI)*
	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	
Overall (≥18)	14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)
≥65 to <75	2,953	4	5.586	2,864	22	31.744	82.4% (48.9, 93.9)
≥75	630	0	0	688	7	41.968	100% (NE, 100)

[#] COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose.
*VE and 95% CI from the stratified Cox proportional hazard model
** CI not adjusted for multiplicity. Multiplicity adjusted statistical analyses were carried out in an interim analysis based on less COVID-19 cases, not reported here.

Efficacy against severe COVID-19

Among all subjects in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 of 185 (16%) cases reported in the placebo group. Of the 30 participants with severe disease, 9 were hospitalised, 2 of which were admitted to an intensive care unit. The majority of the remaining severe cases fulfilled only the oxygen saturation (SpO2) criterion for severe disease (≤ 93% on room air).

Additional Efficacy Analyses

Table 5: Subgroup Analyses of Vaccine Efficacy - COVID-19 14 days after dose 2 per Adjudication Committee Assessments (primary efficacy analysis set) – Per-protocol Set

Subgroup	COVID-19 Vaccine Moderna			Placebo			%Efficacy (95% CI)**
	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	Subjects N	COVID-19 Cases n	Incidence Rate of COVID-19 per 1,000 Person-Years	
Overall High risk*	3,206	4	5.227	3,167	43	57.202	90.9 (74.7, 96.7)
High risk* 18 to <65	2,155	2	3.947	2,118	35	70.716	94.4 (76.9, 98.7)
Not High risk* 18 to <65	8,396	5	2.594	8,403	121	63.054	95.9 (90.0,98.3)
Females	6,768	7	4.364	6,611	98	62.870	93.1 (85.2,96.8)
Males	7,366	4	2.352	7,462	87	50.730	95.4 (87.4,98.3)

* Subjects at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease or HIV infection), regardless of age
** VE and 95% CI from the stratified Cox proportional hazard model

The vaccine efficacy of COVID-19 Vaccine Moderna to prevent COVID-19, regardless of prior SARS-CoV-2 infection (determined by baseline serology and nasopharyngeal swab sample testing) from 14 days after Dose 2 was 93.6% (95% confidence interval 88.5, 96.4%).

Befristete Zulassung

Aufgrund einer zum Zeitpunkt der Begutachtung des Zulassungsgesuches unvollständigen klinischen Datenlage, wird das Arzneimittel COVID-19 vaccine Moderna befristet zugelassen (Art. 9a Heilmittelgesetz). Die befristete Zulassung ist zwingend an die zeitgerechte Erfüllung von Auflagen gebunden. Nach deren Erfüllung kann die befristete Zulassung in eine ordentliche Zulassung überführt werden.

Pharmacokinetics

Absorption

Not Applicable.

Distribution

Not Applicable.

Metabolism

Not Applicable.

Elimination

Not Applicable.
Evaluation of pharmacokinetic properties is not required for vaccines.

Preclinical data

COVID-19 Vaccine Moderna has not been evaluated for carcinogenicity or male infertility in animals. Given the short-term administration of COVID-19 Vaccine Moderna, long-term animal studies to evaluate the carcinogenic potential of COVID-19 Vaccine Moderna are not required.

Animal Toxicology

Intramuscular administration of Moderna COVID-19 Vaccine (or other Moderna mRNA investigational vaccines) using the same formulation every 2 weeks up to 4 doses to rats at doses ranging from 9 to 150 mcg/dose resulted in transient injection site erythema and oedema, body temperature increases, and a generalized systemic inflammatory response. Transient and reversible changes in laboratory tests (including increases in eosinophils, activated partial thromboplastin time, and fibrinogen) were observed. Transient hepatocyte vacuolation and/or Kupffer cell hypertrophy, often observed without liver enzyme elevations, was observed and considered secondary to the systemic inflammatory response. In general, all changes resolved within 2 weeks.

Mutagenesis

SM-102, a proprietary lipid component of COVID-19 Vaccine Moderna, is not genotoxic in the bacterial mutagenicity and the human peripheral blood lymphocytes chromosome aberration assays. Two intravenous in vivo micronucleus assays were conducted with mRNA therapies using the same lipid nanoparticle (LNP) formulation as COVID-19 Vaccine Moderna. Equivocal results observed at high systemic concentrations were likely driven by micronuclei formation secondary to elevated body temperature induced by a LNP-driven systemic inflammatory response. The genotoxic risk to humans is considered to be low due to minimal systemic exposure following intramuscular administration, limited duration of exposure, and the negative in vitro results.

Reproductive Toxicity

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 micrograms) and other ingredients included in a single human dose of COVID-19 Vaccine Moderna was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in maternal animals from prior to mating to the end of the study on lactation day 21 as well as in foetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryo foetal or offspring development or postnatal development. No data are available of mRNA1273 vaccine placental transfer or excretion in milk.

Animal pharmacologic and efficacy data

Nonclinical pharmacology evaluations in young and aged wild-type mice (Balb/c, C57/BL6, and C4B6 strains), Golden Syrian hamsters, and non-human primate (rhesus macaques, NHP) animal models were conducted to test for immunogenicity of COVID-19 Vaccine Moderna and protection from SARS-CoV-2 challenge. These nonclinical studies demonstrated that COVID-19 Vaccine Moderna was tolerated, was immunogenic, protected animals vaccinated at dose levels as low as 1 mcg/dose in mice and hamsters and 30 mcg/dose in NHPs from viral replication in both the nose and lower respiratory tract after viral challenge, and did not lead to enhanced respiratory disease (ERD) at protective or sub-protective dose levels in these animal models. In addition, Th1-directed CD4 T-cell responses were measured in all animal species and a robust CD8 response was measured in mice.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Chemical and physical in-use stability has been demonstrated for 6 hours at 2°C to 25ºC after initial puncture. From a microbiological point of view, the product should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user

Special precautions for storage

Store in the freezer (between -25 to -15°C).
Do not store on dry ice or below -40ºC.
COVID-19 Vaccine Moderna can be stored refrigerated between 2° to 8°C for up to 30 days if not entered (needle-punctured).
The total storage time of an unopened vial after removal from refrigerated conditions should not exceed 12 hours at 8° to 25°C.
Do not refreeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

COVID-19 Vaccine Moderna vials are for multiple use. Ten (10) doses of 0.5 mL volume each can be withdrawn from each multiple-dose vial. An additional overfill is included in each vial to ensure that 10 doses of 0.5 mL can be delivered.

Thaw each vial before use:

- Thaw in refrigerated conditions between 2°C to 8°C for at least 2 hours and 30 minutes. Let each vial stand at room temperature for at least 15 minutes before administering.
- Alternatively, thaw at room temperature between 15°C to 25°C for at least 1 hour.
- Do not re-freeze vials after thawing.

Swirl the vial gently after thawing and between each withdrawal. Do not shake.

COVID-19 Vaccine Moderna is a white to off-white dispersion. It may contain white or translucent product-related particulates. Inspect COVID-19 Vaccine Moderna vials visually for foreign particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

Withdraw each 0.5 mL dose of vaccine from the vial using a new sterile needle and syringe for each injection to prevent transmission of infectious agents from one person to another. The dose in the syringe should be used promptly.

This product is preservative free. Once the vial has been entered (needle-punctured) to withdraw the initial dose, the product should be used immediately and be discarded after 6 hours. Do not refreeze.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

Authorisation number

68267 (Swissmedic)

Packs

Pack-size: 10 multiple-dose vials. Each vial contains 10 doses of 0.5 mL.
COVID-19 Vaccine Moderna is supplied in a 10 mL Type I (or Type I equivalent) glass vial with a 20 mm Fluro Tec-coated chlorobutyl elastomer stopper and a flip-off plastic cap with aluminium seal.

Marketing authorisation holder

Moderna Switzerland GmbH, Basel

Date of revision of the text

January 2021