mRNA-1273 vaccine (Moderna) against COVID-19
Background document

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Contents

General considerations on mRNA vaccines

The messenger ribonucleic acid (mRNA) vaccine platform has advantages as a pandemic-response strategy, given its efficiency in immunogen design and manufacturing. As mRNA is a non-infectious, non-integrating platform, there is no potential risk of infection or insertional mutagenesis. Additionally, mRNA is degraded by normal cellular processes. Efficient *in vivo* delivery can be achieved by formulating mRNA into carrier molecules, allowing rapid uptake and expression in the cytoplasm. mRNA is the minimal genetic vector; therefore, anti-vector immunity is avoided, and mRNA vaccines can be administered repeatedly. Lipid nanoparticle (LNP)-formulated mRNA vaccine technology allows the delivery of precise genetic information together with an adjuvant effect to antigen-presenting cells. It is molecularly well defined, free of materials of animal origin, and synthesized by an efficient, cell-free in vitro transcription process from DNA templates. The technology associated with this vaccine is also capable of bypassing time-consuming standardization processes, thus speeding up its commercial production. Two mRNA vaccines have received Emergency Use Authorization, the BNT162b2 vaccine by BioNTech and Pfizer, and the COVID-19 vaccine (mRNA-1273) by Moderna.

Characteristics of COVID-19 vaccine COVID-19 vaccine mRNA-1273 (Moderna)

Moderna's mRNA-1273 COVID-19 vaccine is a LNP-encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein, and was developed by Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID).

Vaccine composition and storage

The vaccine contains a synthetic mRNA- single-stranded, 5'-capped messenger RNA-encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose. The Moderna COVID-19 Vaccine is provided as a frozen suspension [stored between -25º to -15ºC (-13º to 5ºF)] multi-dose vial containing 10 doses.

The vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine must be thawed prior to administration. After thawing, a maximum of 10 doses (0.5 mL each) can be withdrawn from each vial. Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F) and discarded after 6 hours.

Vaccine dosing

The Moderna COVID-19 Vaccine, mRNA-1273 (100µg) is administered intramuscularly as a series of two doses (0.5 mL each), given 28 days apart.

Efficacy of the Moderna mRNA-1273 COVID-19 vaccine

Trial population

The Phase 3 pivotal registration trial of the vaccine was conducted at sites in 99 centres across the United States and involved in total about 30,000 participants aged 18 years or older with no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 (1). Participants were healthy or had stable pre-existing medical conditions. In total, 25% (7512/30351) were aged 65 years or over (mean age: 70.6 years; range: 40-95 years) and 16.7% (5065/30351) participants were under 65 years and at risk of severe Covid-19 illness (mean age: 49.0 years; range: 18-79 years). The vaccine was administered in 2 doses separated by 28 days. The median age at vaccination was 51 years. Participants were randomised equally between vaccine and placebo groups. Women who were pregnant or breast-feeding were excluded. 2.2% of participants had serological or virological evidence of a past SARS-CoV-2 infection at entry to the trial. Most were white (79%) and similar numbers of males and females were included. The median body mass index was 28.1. The primary analysis of the trial results was conducted when participants had been followed for a median of 64 days after the second vaccine dose and 61% had more than 56 days of follow-up.

Efficacy against Covid-19

The primary endpoint was specified as efficacy against symptomatic Covid-19 at least 14 days after the second dose among participants who were seronegative at trial entry. There were 196 cases who met this definition, with 11 cases in the vaccinated group and 185 in the placebo group with the estimate of vaccine efficacy (VE) being 94.1% (95% confidence interval (CI) 89.3% - 96.8%).

Analyses were also conducted including all cases from the time of the first dose. There was evidence of protection both between the first (14 days after receipt of dose 1) and receipt of the second doses (VE=84.8%, 95% CI 66.1% - 94.2% - 7 cases in vaccine group, 46 cases in placebo group) and between the second dose and 14 days after the second dose (VE=100%, 95% CI 78.6% - 100% - 0 cases in vaccine group, 19 cases in placebo group). More detailed analyses indicated that there was no evidence of efficacy until approx. 12 days after the first dose.

In the period 14 or more days after the second vaccine dose, no significant variations in the estimates of vaccine efficacy were apparent when the primary analyses were stratified according to sex, age, race and ethnic group, or into those at high risk of severe Covid-9. In particular, among those aged 65 years or older there were 4 cases in the vaccinated group and 29 cases in the placebo group (VE 86.4%, 95% CI 61.4% - 95.2%).

Efficacy against severe Covid-19

A total of 30 cases of severe Covid-19 occurred in trial participants 14 or more days after the second dose, all were in the placebo group (VE=100%, 95% CI 86.9% - 100%).

Summary

The vaccine was highly efficacious against laboratory-confirmed Covid-19 from 14 days after the second vaccine dose until the end of the follow-up period, which was, on average, about 2 months

after the second dose. Evidence of efficacy emerged from about 12 days after the first vaccine dose. No evidence of variations in efficacy were found in the various subgroups that were analysed and, importantly, in subgroups of participants likely to be at higher risk of severe Covid-19, including those over 65 years, the estimates of efficacy were very high. Efficacy against severe Covid-19 was also very high, with all 30 cases occurring 14 or more days after the second dose being in the placebo group.

Safety of the Moderna mRNA-1273 COVID-19 vaccine

In the Phase 3 trial, safety data was collected from 30,351 participants ≥18 years of age, randomized 1:1 to vaccine or placebo, who received at least one dose of the vaccine (n=15,185) or placebo (n=15,166). 87.9% of study participants had at least 28 days of follow-up after Dose 2, and the median follow-up time for all participants was 9 weeks (>2 months) after Dose 2 (1).

The safety data supported a favorable safety profile. Reactogenicity symptoms, defined as solicited local injection site or systemic reactions during the 7 days after vaccination, were frequent and mostly mild to moderate and short-lived after dosing for both adult age groups. Reactogenicity and adverse events (AEs) were generally milder and less frequent in participants in the older group (≥65 years of age) compared with the younger group (18 to <65 years of age) and tended to increase after the second dose.

The vaccine's AE profile did not suggest any specific safety concerns. Severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in older adults (≥65 years of age) as compared to younger adults. The incidence of serious adverse events (SAEs), deaths, and discontinuations due to AEs were low and comparable for both the vaccine and placebo groups. There were no specific safety concerns identified in subgroup analyses by age, sex, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection at enrollment.

Adverse Events

Adverse events, that occurred within 28 days following each vaccination, were reported by 23.9% (n=3,632) of participants who received the vaccine and 21.6% (n=3,277) of participants who received placebo. The most common adverse reactions in participants 18 years of age and older were pain at the injection site (92.0%), fatigue (70.0%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23.0%), axillary swelling/tenderness (19.8%), fever (15.5%), swelling at the injection site (14.7%), and erythema at the injection site (10.0%). The median durations for pain were 2-3 days. The highest rates of pain were in participants 18 to <64 years after dose 2, with 90.1% reporting any pain and 4.6% reporting Grade 3 pain. The median duration for fatigue in vaccine recipients was 2 days after any dose. The highest rates of fatigue were reported by participants 18 to 64 years after the second dose, with 67.6% reporting any fatigue, 10.6% reporting Grade 3, and 1 participant reporting Grade 4 (after Dose 1).

Delayed localized injection site reaction with onset after 7 days was more frequent in the vaccine group compared to the placebo group and mostly seen after the first dose.

Adverse Events of Special Interest (that would potentially require longer follow up)

Lymphadenopathy related events

Lymphadenopathy-related events were reported by 173 (1.1 %) of vaccine recipients and 95 (0.63 %) of placebo recipients. These events included lymphadenopathy (axillary swelling and tenderness of the vaccination arm), lymphadenitis, lymph node pain, vaccination-site lymphadenopathy, injection-site lymphadenopathy, and axillary mass. These were plausibly related to vaccination.

The median duration of lymphadenopathy following any dose was 1 to 2 days, and <1% reported Grade 3 axillary swelling/tenderness. Lymphadenopathy was more frequently observed in participants 18 to 64 years of age after dose 2, with 16.0% reporting any severity lymphadenopathy and 0.4% reporting Grade 3 lymphadenopathy.

Bell's Palsy

There were three reports of Bell's palsy in the vaccine group and one in the placebo group. In the vaccine recipients, the events occurred 22, 28, and 32 days after dose 2 vaccination. One event was a serious adverse event (reported as resolving), one case has resolved and one is ongoing. In the placebo recipients, the event occurred 17 days after dose 1. Causality assessment is confounded by predisposing factors in all the participants. The usual incidence of Bell`s palsy is 15-30/100,000/year. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population and an association between COVID-19 and Bell's palsy has been reported. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine. Surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations is a requirement and Bell`s palsy has been addressed in the risk management plan.

Hypersensitivity-related events

233 events (1.5%) occurred in the vaccine arm and 166 events (1.1%) in the placebo arm. The hypersensitivity related events included injection site rash, injection site urticaria and maculo-papular rash. There is a plausible relationship to vaccination of these events.

No anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine were reported during the trial.

Serious Adverse Events

The frequency of serious adverse events was low (1.0% in the vaccine arm and 1.0% in the placebo arm), without meaningful imbalances between study arms.

As of December 3, 2020, there were 13 deaths in total with 6 in the vaccine and 7 in the placebo group. No causal relationship was determined.

The SAE's thought to be related to the vaccine (as per the FDA) include intractable nausea and vomiting in a 65 year old 1 day post the second dose. Two subjects, who were 46 and 51 years old,

reported facial swelling one and two days post the second dose, respectively. Both subjects had prior dermal fillers.

Special populations

Pregnancies

Women were screened for pregnancy prior to each vaccination and were excluded or discontinued from vaccination if there was a positive test. As of December 2, 2020, 13 pregnancies (6 in the vaccine and 7 in the placebo group) have been reported.

The pregnancy outcomes in the placebo group include spontaneous abortion and an elective abortion. The other outcomes are not known to date and the pregnant women are being followed.

A combined developmental and perinatal/postnatal reproductive toxicity study of the vaccine in rats concluded that the vaccine at a dose of 100 µg, given prior to mating and during gestation periods, did not have any adverse effects (including on female reproduction, fetal/embryonal development, or postnatal developmental).

Summary

The safety data supported a favorable safety profile. Reactogenicity was mostly mild to moderate, less frequent and severe in adults ≥65 years than in younger adults and generally more frequent after the second dose in age groups. There were no safety concerns identified in subgroup analyses by age, sex, race, ethnicity, comorbidities and health risks for severe COVID-19, and prior SARS-CoV-2 infection

Delayed localized injection site reaction with onset after 7 days was more frequent in the vaccine group compared to the placebo group and mostly seen after the first dose.

Lymphadenopathy events were more frequent in the vaccine group compared with placebo and are plausibility related. Hypersensitivity-related events were more frequent in the vaccine group compared with placebo. No anaphylactic or severe hypersensitivity reactions with temporal relation to vaccination were reported during the trial. Three cases of Bell's palsy were reported in vaccine recipients, and one in placebo recipients. Although there is no clear basis upon which to conclude a causal relationship at this time, further surveillance for Bell's palsy is required as part of the risk

References

1. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020.

World Health Organization

Annexes

Note:

The annexes contain the grading of recommendations, assessment, development and evaluations – *GRADE tables* (Annex 1 to 6) and the SAGE evidence-to-recommendation framework tables – *ETR tables* (Annex 7-9). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 11 January 2021).