# Taiwan Food and Drug Administration

# Assessment Report

**Trade Name：世冠飛適新型冠狀病毒疫苗/ Spikevax Injection**

**Active Ingredient：mRNA-1273.815 LNP(XBB.1.5 variant)**

**License Number： MOHW-BI 001262**

**Applicant：莫德納台灣股份有限公司**

**Approval Date：2024/06/26**

**Indication：**
**適用於 6 個月以上兒童、青少年及成人之主動免疫接種，以預防新型冠狀病毒疾病 (COVID-19，嚴重特殊傳染性肺炎)。**

For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

## Background Information

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| **Trade Name** | 世冠飛適新型冠狀病毒疫苗 / Spikevax Injection |
| **Active Ingredient(s)** | mRNA-1273.815 LNP(XBB.1.5 variant) |
| **Applicant** | 莫德納台灣股份有限公司 |
| **Dosage Form & Strengths** | 懸浮注射劑 2.1mg/mL |
| **Indication** | 適用於 6 個月以上兒童、青少年及成人之主動免疫接種，以預防新型冠狀病毒疾病 (COVID-19，嚴重特殊傳染性肺炎)。 |
| **Posology** | 詳如仿單 |
| **Pharmacological Category**<br>**ATC Code** | J07BN01 |

**Summary Report**

## 2.1 Chemistry, Manufacturing and Controls Evaluation

### 2.1.1 Drug Substance (DS)

The drug substance, mRNA-1273.815 LNP, comprises CX-038839 mRNA encapsulated within lipid nanoparticles (LNPs), which protect the mRNA from nucleolytic degradation in biological fluids. These LNPs, composed of SM-102, PEG2000-DMG, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and cholesterol, form a white to off-white dispersion.

Adequate information on the characterization of drug substance has been provided. Structural characterization studies for mRNA-1273.815 LNP-B were performed as part of analytical comparability which demonstrated comparability to the prototype mRNA-1273 LNP-B and previous developed variant mRNA-1273 LNP.

The drug substance specifications include tests for appearance, mRNA identity, total RNA content, purity, product-related impurities, %RNA encapsulation, mean particle size, polydispersity, lipid identification, lipid content, lipid impurities, in vitro translation, pH, osmolality, bacterial endotoxins, and bioburden. Batch analysis data from commercial-scale batches show that test results meet the specifications.

### 2.1.2 Drug Product (DP)

The mRNA-1273.815 drug product, also referred as Spikevax XBB.1.5, is indicated for active immunization against COIVD-19 caused by the SARS-CoV-2, particularly the XBB.1.5 variant strain. For the Taiwan market, the final mRNA-1273.815 drug product will be available in two presentations: a 5-doses multiple-dose vial (MDV; nominal 2.5 mL) and a single-dose pre-filled syringe (PFS; 0.5 mL) for intramuscular administration.

A detailed description of manufacturing process for both MDV and PFS presentations has been provided, including critical process parameters and in-process controls/tests for the critical steps involved. Process validation studies have demonstrated that the DP manufacturing process is well-controlled and capable of consistently producing a final product that meets the acceptance criteria.

The common specifications for both drug product presentations include tests for appearance, mRNA identity, total RNA content, purity, product-related impurities, %RNA encapsulation, in vitro translation, lipid identification, lipid content, lipid impurities, mean particle size, polydispersity, pH, osmolality, particulate matter, container content/deliverable volume, bacterial endotoxins, and sterility. Additionally,

break loose force and gliding force are also tested for the PFS drug product. The acceptance criteria for these specifications are well justified. All batches meet the specification requirements, and the data is consistent across manufacturing runs.

Real-time stability data for primary stability drug product batches (prototype and early variant strains) and supportive batches are provided. These stability data support the proposed shelf-life of 12 months when drug products are stored at the recommend condition of -15℃ to -50℃.

The overall data submitted is adequate and supports the conclusion that the manufacturing process of mRNA-1237.815 drug product is well-controlled and consistently produces mRNA-1273.815 of reproducible quality.

**2.2 Preclinical Pharmacology/Toxicology Evaluation**

The monovalent mRNA-1273.815 vaccine contains a single mRNA encoding full-length pre-fusion stabilized spike protein (S-2P) of the XBB.1.5/XBB.1.9.1 subvariant of Omicron. The design and manufacturing of mRNA-1273.815 are based on the same platform technology as the previously approved Moderna COVID-19 mRNA vaccines, and the non-clinical evaluation of mRNA-1273.815 was limited to mouse immunogenicity studies.

In BALB/c mice, XBB.1.5-containing vaccines (mRNA-1273.815 and mRNA-1273.231), either as a 2-dose primary series or a booster following a primary series of mRNA-1273, elicited robust S-2P-binding Ab (bAb) titers and numerically higher neutralization responses against XBB variants (e.g., XBB.1.5 and XBB.1.16) compared with BA.4/BA.5-containing vaccines, but low titers against the SARS-CoV-2 ancestral strains. Generally, vaccines tested elicited similar neutralizing Ab (nAb) titers against XBB.1.5 and against the other variants of XBB sublineages tested, including XBB.1.16, XBB.2.3.2, and EG.5.1. The vaccines containing variant-matched mRNA induced higher nAb titers against matched spike antigens than those vaccines containing variant-non-matched mRNA.

No challenge-protection studies were planned or performed to investigate the protective efficacy of XBB-containing vaccines against XBB variants infection. Nevertheless, as per the sponsor's prior justification, in a primary series study, the titers of XBB-neutralizing Ab elicited by mRNA-1273.815 were higher than the titers of BA.4/5-neutralizing Ab elicited by mRNA-1273.222. Moreover, the protective effect of mRNA-1273.222 against BA.4/BA.5 strains has been clinically proven. Therefore, by

the same logic, a vaccine containing XBB.1.5 (e.g., mRNA-1273.815) might protect humans against infection by XBB strains.

To support the NDA of mRNA-1273 variant vaccine(s), a battery of non-clinical safety/toxicity studies were included in the dossier, including one non-GLP biodistribution study and seven GLP rat repeated-dose toxicity studies with six SM-102-containing LNP mRNA-based vaccines, including but not limited to mRNA-1273, one GLP DART study, and a battery of GLP genotoxicity studies of SM-102 and PEG2000-DMG. All pivotal studies had been submitted previously and reviewed thoroughly to support the EUA of mRNA-1273 and the variant-containing vaccines in Taiwan. In line with WHO's perspectives on mRNA vaccines for infectious diseases, no biodistribution and/or safety/toxicity study done specifically for mRNA-1273.815 is deemed acceptable. In a GLP repeated-dose toxicity study of mRNA-1273 in rats, IM administration of mRNA-1273 at 40 mcg up to 3 doses once every 4 weeks was well tolerated. No effects other than the reversible typical responses to the immunization were identified.

In accordance with the WHO's guidelines on non-clinical evaluation of vaccines, secondary pharmacodynamics, safety pharmacology, genotoxicity, and carcinogenicity studies are generally not warranted for vaccines.

**2.4 Clinical Efficacy and Safety Evaluation**

**2.4.1 Efficacy Results**

The efficacy of Spikevax's primary vaccination and booster doses was based on clinical trials of mRNA-1273 (original strain). Trials included Study P301 Part A, P203 Part 1A, and Study P204 evaluating the primary vaccination for adults, adolescents and children. Studies evaluating the booster dose of mRNA-1273 in adults, adolescents and children included Study P201 Part B, P203 Part 1C and Study P204. Main data of those trials have been assessed during the EUA review. In the NDA application, P301 Part C for adults' booster was newly submitted.

- Study P301 Part A was designed as a blinded, randomized, placebo-controlled vaccine efficacy trial, presenting the efficacy of 2-dose mRNA-1273 administered to healthy and medically stable adults during the COVID-19 pandemic. The primary efficacy endpoint of Study P301 was symptomatic COVID-19 cases 14 days after the second injection. The primary efficacy analysis (25 Nov 2020) was performed on 196 COVID-19 cases, while vaccine efficacy based on the hazard ratio was 94.1% (95% CI: 89.3%, 96.8%; $p < 0.0001$). For the final efficacy analysis (04 May 2021), the vaccine

efficacy was 93.2% (95% CI: 91.0%, 94.8%; $p < 0.0001$).

Estimated efficacy against severe COVID-19 or death caused by COVID-19 was 97.6% (95% CI: 92.4%, 99.2%) and 100% (95% CI: not estimable, 100%), respectively. A follow-up period for the final blinded efficacy analysis provided a median of 148 days (approximately 5.3 months) from randomization to the open-label Part B participant decision visit. For the first booster dose, a non-concurrent, cross-study comparison between P301 Part C and Study P301 Part A was designed to infer the effectiveness.

Median duration between dose 2 and the booster in Study P301 Part C was over 6 months. Geometric mean ratio (GMR) of neutralizing antibodies (nAb) titers between Part C post-booster (Day 29) and Part A post dose 2 (Day 57) was 7.4 (95% CI: 6.9, 8.0), and was above the prespecified threshold for superiority (lower bound of 95% CI of > 1).The booster group, under a non-randomized setting, showed a lower COVID-19 incidence rate when compared to the non-booster group throughout both the Delta variant wave and the Omicron variant wave in P301 Part C.

- Study P203 Part 1A (adolescents) were designed to bridge the established efficacy of primary vaccination by comparing the non-inferiority of nAb titers between adolescents and younger adults in Study P301 Part A through cross-study comparisons. The coprimary endpoints for the non-inferiority were met for the GMR of adolescents (Study P203, n=340) to young adults (Study P301, n=295) nAb titers at Day 57 was 1.078 (95%CI: 0.940, 1.237, lower bound >0.667) and the difference of seroresponse rate (SRR) was -0.2 % (95%CI: -2.1%, 1.9%, lower bound>-10%). For the first booster dose of adolescents, the statistical design of Study P203 Part 1C (adolescents) employed a non-concurrent, cross-study comparison to demonstrate the non-inferiority of neutralizing antibody titers in each age group following the booster of mRNA-1273 compared to young adults in Study P301 Part A. The non-inferiority endpoints were statistically achieved for both GMR and SRR difference in this comparison.

- Study P204 Part 2 (children) were designed to bridge the established efficacy of primary vaccination by comparing the non-inferiority of nAb titers between children and younger adults in Study P301 Part A through cross-study comparisons. Under the same margin, the non-inferiority endpoints were met

for both GMR and SRR difference for the 6 to 11 years, 2 to 5 years, and 6 to 23 months age group as compared to the 18 to 25 years age group from P301.

Clinical effectiveness of the Spikevax containing an updated variant strain was based on the immunogenicity observed after administration of the updated vaccine, compared to the immunogenicity of the original strain vaccine. Previous EUA reviews have evaluated the immunogenicity of candidate vaccines with different variant antigens administered to adults as boosters in Study P205, which used a parallel, non-concurrent cohort design with Part G (mRNA-1273.214, omicron BA.1/original bivalent vaccine), Part H (mRNA-1273.222, omicron BA.4-.5/original bivalent vaccine), Part J (mRNA-1273.815, omicron XBB.1.5 monovalent vaccine), and Part F (mRNA-1273, the original vaccine). For children, the main data of Study P306 Part 1 has been assessed during the EUA review, and Study P306 Part 2 for evaluation of the booster dose was newly provided.

- In Study P205, participants previously received a 2 dose primary series of mRNA-1273 followed by a 50 µg booster dose of mRNA-1273 for at least 3 months were enrolled, eligible adults received another 50 µg dose of mRNA-1273 as the second booster in Part F, while a 50 µg dose of mRNA-1273.214 as the second booster was given in Part G. The coprimary immunogenicity endpoints were both met for the GMR of Part G to Part F, and the difference of SRR at Day 57.

  In Part H, eligible adults received another 50 µg dose of mRNA-1273.222 as the second booster. The GMR (Part H/Part F) at Day 29 met the pre-specified superiority criterion (lower bound of 95% CI of > 1). The SRR difference based on pre-booster baseline at Day 29 also met the pre-specified criterion (lower bound of 95% CI of > -5%).

  Part J enrolled adults who had received primary vaccination, the first booster, and one dose of mRNA-1273.222 as the second booster, with immunogenicity assessed using descriptive analysis. mRNA-1273.815 was given as a third booster dose for a median duration of 8.2 months to the second dose. Post-booster Day 29 results showed that neutralizing antibody against XBB.1.5 variant was elicited by administration of mRNA-1273.815.

- Study P306 was aimed to evaluate the mRNA-1273.214 vaccine as primary doses and as the first booster dose administered in children aged 6 months to

less than 6 years. Clinical effectiveness of primary vaccination would be inferred by the comparison of post-dose 2 immunogenicity of mRNA-1273.214 (Study 306 Part 1) and of mRNA-1273 (Study P204). By the previous EUA review record, the GMR against BA.1 in the PPIS Neg populations (Study P306 Part 1/Study P204) was 15.8 (95% CI: 11.4, 21.9). The difference of SRR against BA.1 was 9.6% (95% CI: 7.4, 16.2). Clinical effectiveness of the booster vaccine was inferred by the comparison of post-booster immune response of mRNA-1273.214 versus post-dose 2 immune response of mRNA-1273 in Study P204. The nAb results met the prespecified superiority and noninferiority criteria for both GMR (12.052; 95% CI: 10.526, 13.799) and SRR difference (12.9%; 95% CI: 8.2, 17.7) in PPIS-Neg set.

**2.4.2 Safety Results**

The safety profile of Spikevax was based on clinical trials of mRNA-1273 (original strain) and two variant-containing bivalent boosters. Trials included Study P301 Part C, P201 Part B, P203 Part C and Study P205 (Part F, G and H) and the safety sets covered adults and adolescents. Study P301 Part C presented data for 19609 adults, of whom 27.5% were individuals over 65 years old, with a median time of 316 days from dose 2 to the first booster and a median time of 161 days after the booster. Study P203 Part C presented data for 1405 adolescents with a median time of 315 days from dose 2 to the first booster and a median time of 204 days after the booster. For variant-containing vaccines used in adults, Study P205 was summarized based on the 508 adults who received mRNA-1273.222 (Part H), 437 adults who received mRNA-1273.214 (Part G), and 350 adults who received mRNA-1273 (Part F), as the second booster. Median time after variant booster ranged from 37 to 127 days. This safety database of individuals older than 12 years was considered sufficient to detect uncommon adverse events (AEs) and could possibly observe rare events.

In Study P301 A (n=15166), frequency of any solicited adverse reactions (ARs) and any of grade 3 reactions were higher after the second dose of mRNA-1273 than after the first dose of mRNA-1273. Pain was the most commonly reported local AR and local Grade 3 AR after both injections, and the frequency was also higher after the second injection. Frequency of solicited systemic ARs and any of Grade 3 reactions were also higher after the second dose than after the first dose. Fatigue and headache were the most commonly reported systemic AR and local Grade 3 AR after both injections, and the frequency was also higher after the second injection. The most common grade 4 systemic AR was fever, defined as a temperature above 40°C. Reactogenicity data for the first booster dose of mRNA-1273 are presented in Study

P201 Part B. In Study P205 Part F, G and H, the overall frequency of all, local, and systemic ARs of any of the second booster dose of variant vaccine was lower to or similar as the distribution after primary series of mRNA-1273 in Study P301 Part A. No Grade 4 ARs were reported in any of booster cohort.

In Study P301 Part A (n=15184), frequency of unsolicited treatment-emergent AE (TEAEs) observed or reported during 28-day follow-up period were 31.3% (versus placebo 28.6%), with 0.6% reported as serious cases. No notable difference of serious AE was observed between treatment groups. The most commonly reported unsolicited TEAEs in the mRNA-1273 group were fatigue (5.0%) and headache (4.9%). As of the data cutoff date of the submitted CSR, 2 and 8 fatal cases were recorded in Part A and Part B, respectively. None of the participants died due to COVID-19. None of deaths was considered related to the study vaccine.

Among the 19,609 participants who received the booster in Part C, 31.7% had unsolicited TEAEs with 0.5% reported as serious cases up to 28 days after the booster. Injection site pain (13.6%), fatigue (6.9%), and headache (4.9%) were reported most frequently. As of the data cutoff date of the submitted CSR, 27 participants (0.1%) had died due to any cause. Three cardiovascular deaths occurred during 28-day follow-up period, and were reported as unrelated to study vaccine due to preexisted comorbidities. Other three deaths were associated with COVID-19. The other deaths were reported as not related to study vaccine.

In all three Study P205 booster groups, unsolicited TEAEs were reported within 28 days after the booster from 19.2% to 22.7%. Distribution of frequency by Preferred Terms was similar to known profile of mRNA-1273. Serious cases were also reported in a similar percentage to that in Study P301. One of the SAEs was fatal, a subarachnoid hemorrhage diagnosed in a 70-year-old male with a history of cardiovascular disease. Four more deaths occurred after Day 28 which were considered by the investigator to be unrelated to study vaccine because the available causes of death could be attributed to preexisting comorbidities.

The reactogenicity profile of primary series in the adolescents (Stud P203) was consistent with that seen in adults (Study P301). The most common solicited local AR was pain, and the most common solicited systemic ARs were fatigue, headache, and myalgia. Unsolicited TEAEs up to 28 days after any injection occurred in the mRNA-1273 group was 23.4%. The most commonly reported unsolicited TEAEs in the mRNA-1273 group were injection site lymphadenopathy (5.1%), headache (3.7 %),

and fatigue (3.0%). Long-term safety was demonstrated through an over 300 days of median follow-up time after Dose 2. There were no deaths, related SAEs, or cases of MIS-C in the long-term follow-up. There were no new safety findings observed in the mRNA-1273 Booster Phase of Study P203. No participant reported events of myocarditis or pericarditis in the Booster Phase.

Study P204, not included in the module 2.7.4 summary, demonstrated the safety profile in children less than 12 years old through a median of about 6-month follow-up after dose 2. The reactogenicity profile of primary series in the children (Study P204) was consistent with that seen in adults (Study P301). Grade 4 fever were observed in a small number of children aged 6 to 23 months and 2 to 5 years. Commonly reported unsolicited TEAEs were generally reflective of respiratory illnesses which are typical in childhood, including upper respiratory tract infection and rhinorrhea, and irritability that specific in children less than 24 months old. There were no cases of MIS-C or fatal events. There were no cases of myocarditis or pericarditis in the long-term follow-up or evidence of new or delayed-onset safety concerns.

**2.5 Bridging Study Evaluation**

For the following reasons, the ethnic difference was considered to have no significant clinical impact. It is recommended to waive the bridging study.

1. The mechanism of action does not involve known genetic factors that may cause ethnic differences.
2. Spikevax could elicit a high immune response in Japanese. The safety profile and tolerance in Japanese were similar to known profile of that in the global trials, and were acceptable.
3. Based on existing real-world effectiveness data, there is no significant disparity in outcomes between East Asian populations and Western populations.
4. Through the emergency use authorization, Spikevax and Spikevax with variant components have been widely used by the Taiwanese population. Besides, apart from known potential risks of anaphylaxis and myocarditis/pericarditis, no other unexpected safety signals have been observed.

**2.6 Conclusion**

The overall benefit over risk of Spikevax is positive.

## 3. Post-Marketing Requirements

1. Provide the Complete Study Report for the following trial number after the

analysis of the trial is completed: P204, mRNA-1273-901, and mRNA-1273-P920.

2. In accordance with Article 8 of "Regulations for the Management of Drug Safety Surveillance", it is recommended to submit the updated version of the PBRER/PSUR along with the scheduled periodic safety reports. The PBRER/PSUR should include analysis and discussion of identified risks (e.g., anaphylaxis, myocarditis, pericarditis).
3. A quantitative analytical method is encouraged for potency testing in product release process.