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## LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE2	angiotensin-converting enzyme 2
BA.1	subvariant of Omicron
BA.4/BA.5	subvariants of Omicron (the spike protein of BA.5 is identical to that of BA.4)
COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
ETF	Emergency Task Force
FDA	Food and Drug Administration
JN.1	BA.2.86.1.1 subvariant of Omicron
KP.2	JN.1.11.1.2 subvariant of JN.1
LNP	lipid nanoparticle
LP.8.1	JN.1.11.1.1.1.3.8.1 subvariant of JN.1
mRNA	messenger RNA
S-2P	spike protein modified with 2 proline substitutions within the heptad repeat 1 domain
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TAG-CO-VAC	Technical Advisory Group on COVID-19 Vaccine Composition
US	United States
VOC	variant of concern
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization
XBB.1.5	subvariant of Omicron
XEC	a recombinant lineage of KS.1.1 (JN.1.13.1.1.1) and KP.3.3 (JN.1.11.1.3.3), which are subvariants of JN.1

## 2.6.1 INTRODUCTION

ModernaTX, Inc. (the Sponsor) used a scalable mRNA/LNP technology platform that allowed for a rapid response to the COVID-19 pandemic and was used to develop mRNA-1273, an LNP-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 contains a single mRNA that encodes the SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P). mRNA-1273 was proven highly effective against COVID-19 following SARS-CoV-2 infection and has been licensed or conditionally approved across multiple regions for the prevention of COVID-19 in individuals 6 months of age and older (SPIKEVAX™).

Starting in 2021, new SARS-CoV-2 variants led to breakthrough infections, necessitating updated vaccines. Health authorities recommend a framework to identify variants of concern and test updated COVID-19 vaccines, which is critical to preserve neutralization responses and protection against the infection/severe disease caused by SARS-CoV-2. The Sponsor has established a process to monitor emerging variants, classify them by immune-evading mutations, test matching vaccine candidates, and deploy them if requested by health authorities.

Variant-specific boosters were recommended by the WHO, EMA, and FDA in 2022. A bivalent booster combining mRNA-1273 with an Omicron BA.1 variant vaccine (mRNA-1273.214) or an Omicron BA.4/BA.5 variant vaccine (mRNA-1273.222) was approved. A monovalent Omicron XBB.1.5 booster (mRNA-1273.815) was subsequently approved in 2023 to address the rise in infections from the XBB family of Omicron subvariants. By August 2023, the WHO identified BA.2.86 as a variant under monitoring due to significant mutations. Its sublineage, JN.1, was classified as a variant of interest in December 2023, showing potential for immune escape even in recently vaccinated individuals ([WHO 2023](#)).

On 05 Jun 2024, the FDA VRBPAC recommended a monovalent JN.1-lineage vaccine composition for the 2024-2025 Formula of COVID-19 vaccines in the US. The epidemiology in the US indicated a rise in cases of the JN.1 subvariant, KP.2, leading the FDA to determine that the KP.2 strain should be the preferred JN.1 lineage for the COVID-19 vaccine formula (2024-2025 Formula). The FDA's request for a KP.2 variant vaccine aligned with the VRBPAC's unanimous vote on 05 Jun 2024. Additionally, the WHO Technical Advisory Group on COVID-19 Vaccine Composition and EMA Emergency Task Force recommended a monovalent JN.1-lineage vaccine for the 2024-2025 season ([EMA 2024](#)). In response, the Sponsor prepared both a JN.1 new variant vaccine (mRNA-1273.167) and a KP.2 new variant vaccine (mRNA-1273.712) for the 2024-2025 season.

The current variant landscape (early 2025) is dominated by multiple JN.1 descendants, such as XEC and LP.8.1, with LP.8.1 rapidly increasing and overtaking other variants. LP.8.1, which has acquired 9 spike protein mutations compared to JN.1, was classified as a variant under monitoring by the WHO on 24 Jan 2025 ([WHO 2025a](#)). Studies indicate that LP.8.1 has immune evasion capabilities versus currently approved JN.1 and KP.2 vaccines and high ACE2 binding, potentially supporting a growth advantage ([Liu et al 2025](#)). As of week 5 of 2025, LP.8.1 represented 13.9% of globally available sequences, a significant rise from 1.9% just 6 weeks earlier in epidemiological week 51 of 2024 ([WHO 2025b](#)). In the US, COVID-19 variant

surveillance estimated that LP.8.1 represented 48% to 62% of cases as of 29 Mar 2025, with a 95% prediction interval (CDC 2025).

The Sponsor's risk assessment indicates that a vaccine update to LP.8.1 will be most effective at neutralizing currently circulating strains, with cross-neutralization likely against older JN.1 strains that no longer circulate, as well as JN.1 strains yet to emerge. Preliminary investigations suggest that, given the rapid rise and immune evasion capabilities of LP.8.1, LP.8.1-containing vaccines should be investigated as a candidate vaccine for the 2025-2026 season.

Therefore, nonclinical studies conducted with an LP.8.1 vaccine (mRNA-1273.251) are herein summarized to support registration of an LP.8.1 new variant vaccine for prevention of COVID-19 caused by SARS-CoV-2 for the 2025-2026 season.

### 2.6.1.1 References

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