Effectiveness and Safety of Variant-Updated COVID-19 Vaccines

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BACKGROUND

- SARS-CoV-2 continues to evolve antigenically, with ongoing emergence of new subvariants containing spike protein mutations associated with altered neutralisation sensitivity[1]
- Periodic updates of COVID-19 vaccine formulations are implemented to maintain alignment with circulating SARS-CoV-2 strains[2]
- mRNA-1273 and mRNA-1283 are lipid nanoparticle–encapsulated mRNA vaccines targeting the SARS-CoV-2 spike protein. mRNA-1273 encodes the full-length prefusion stabilised spike protein, while mRNA-1283 encodes the receptor binding domain (RBD) and N-terminal domain (NTD) of the spike protein[3-5]
- Updated 2025-2026 formulations of mRNA-1273.251 and mRNA-1283.251, which contain the SARS-CoV-2 LP.8.1 variant sequence, were evaluated in Phase 3b/4 open-label studies in individuals aged ≥65 years and ≥12 to <65 years with underlying conditions associated with increased risk for severe COVID-19. Each study included an initial descriptive component (Part A) and a subsequent hypothesis-driven component (Part B) designed to further characterise the immunogenicity and safety of the updated formulations
- Here, we present interim immunogenicity and safety results from the descriptive components (Part A) of these Phase 3b/4 studies evaluating mRNA-1273.251 and mRNA-1283.251; hypothesis-driven evaluations (Part B) are ongoing

OBJECTIVES

- To describe interim immunogenicity and safety following administration of updated mRNA-1273.251 and mRNA-1283.251 containing the LP.8.1 variant sequence in individuals at increased risk for severe COVID-19 (descriptive components)
- To characterise cross-variant neutralising antibody (nAb) responses following administration of mRNA-1273.251 and mRNA-1283.251 against contemporaneously circulating SARS-CoV-2 variants

METHODS

- Two independent Phase 3b/4 open-label studies (NCT06585241; NCT07089706) evaluated updated LP.8.1-containing mRNA-1273.251 and mRNA-1283.251 formulations
- Studies were conducted in individuals aged ≥65 years and ≥12 to <65 years who had ≥1 underlying condition associated with increased risk for severe COVID-19
- Participants received a single dose of mRNA-1273.251 50 µg or mRNA-1283.251 10 µg
- Immunogenicity assessments included
  - nAb responses at baseline and Day 29 against the vaccine-matched LP.8.1 variant
  - Exploratory analysis of Day 29 cross-neutralising antibody responses against currently circulating variants (XFG, NB.1.8.1, and BA.3.2.2) in a randomly selected subset of participants using a fit-for-purpose assay approach
- Safety assessments included unsolicited adverse events (AEs; Days 1-29), serious AEs, AEs of special interest, and AEs leading to study withdrawal (through end of study)

RESULTS

Participants

- Baseline demographics and clinical characteristics across study parts are presented in **Table 1**

Table 1. Baseline Demographics of Study Participants (Safety Set)

	mRNA-1273.251 Part A (N = 103)	mRNA-1283.251 Part A (N = 172)
Age, years		
Mean (SD)	61.5 (14.3)	56.3 (15.1)
Median (min, max)	64.0 (16.0, 94.0)	59.0 (15.0, 86.0)
Age group, n (%)		
≥12 to <65 years	54 (52.4)	110 (64.0)
≥65 years	49 (47.6)	62 (36.0)
Sex, n (%)		
Female	55 (53.4)	106 (61.6)
Male	48 (46.6)	66 (38.4)
Race group, n (%)		
Asian	3 (2.9)	2 (1.2)
Black	57 (55.3)	64 (37.2)
Missing	0	2 (1.2)
Other	1 (1.0)	12 (7.0)
White	42 (40.8)	92 (53.5)
Ethnicity, n (%)		
Hispanic or Latino	2 (1.9)	5 (2.9)
Not Hispanic or Latino	96 (93.2)	165 (95.9)
Baseline body mass index, n (%)		
<30 kg/m^2	48 (46.6)	76 (44.2)
≥30 kg/m^2	55 (53.4)	96 (55.8)
Time since last prior COVID-19 vaccine, days		
n	80	81
Mean (SD)	938.4 (452.7)	1045.1 (460.0)
Median (min, max)	913.0 (242.0, 1665.0)	1027.0 (199.0, 2031.0)

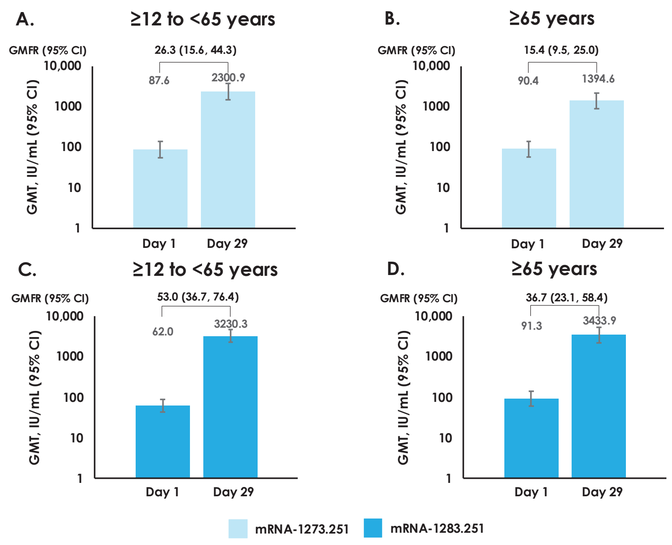
Safety

- mRNA-1273.251 and mRNA-1283.251 were well-tolerated through Day 29
- No serious AEs, AEs of special interest, deaths, or AEs leading to study discontinuation were reported
- Reported AEs were infrequent and considered unrelated to study vaccination

Immunogenicity

- mRNA-1273.251 and mRNA-1283.251 elicited robust increases in nAb titres against the vaccine-matched LP.8.1 variant at Day 29 across age groups (**Figure 1**)
- For mRNA-1273.251, geometric mean fold rise (GMFR) from baseline was 26.3 (95% CI: 15.6, 44.3) in participants aged ≥12 to <65 years and 15.4 (95% CI: 9.5, 25.0) in participants aged ≥65 years
- For mRNA-1283.251, GMFR from baseline was 53.0 (95% CI: 36.7, 76.4) in participants aged ≥12 to <65 years and 36.7 (95% CI: 23.1, 58.4) in participants aged ≥65 years

Figure 1. Day 29 nAb Titres (ID_{50}) Against LP.8.1 Following mRNA-1273.251 and mRNA-1283.251 (Part A, PPIS)



GMFR, geometric mean fold rise; GMT, geometric mean titre; ID_{50}, 50% inhibitory dose; nAb, neutralising antibody; PPIS, per-protocol immunogenicity set; RT-PCR, reverse transcription polymerase chain reaction.

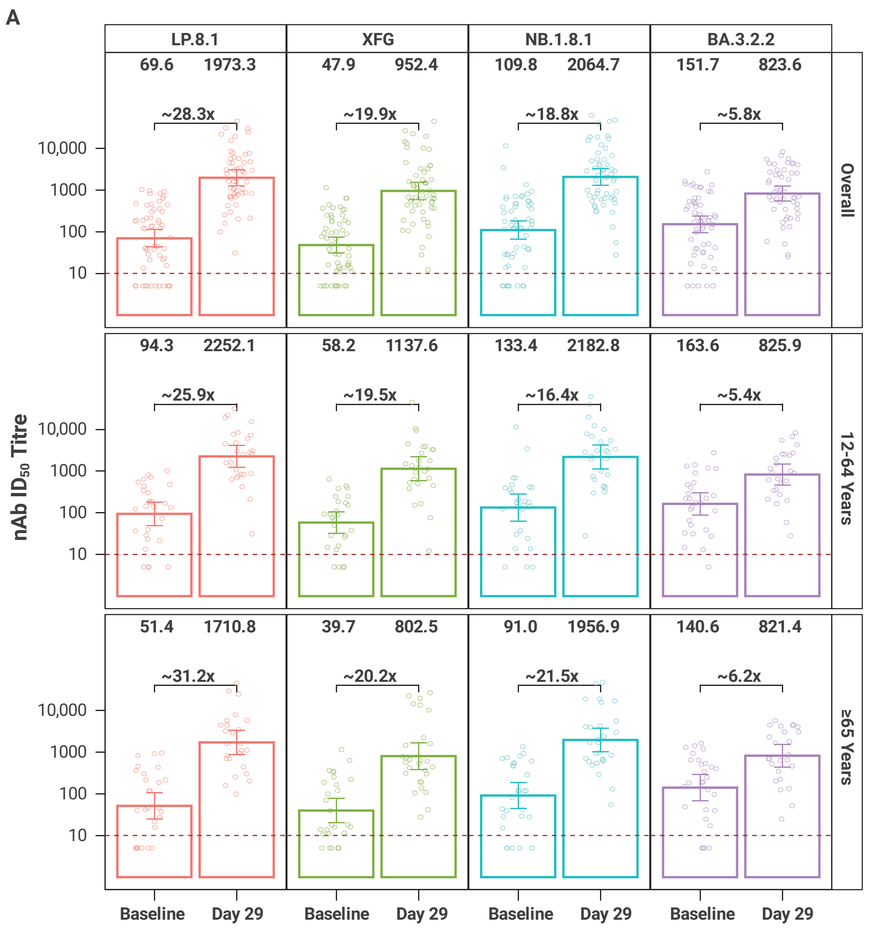
The PPIS for the prespecified analysis comprised all enrolled participants who received either mRNA-1273.251 or mRNA-1283.251, had negative RT-PCR tests on Days 1 and 29, and had no major protocol deviations that could affect the integrity of key study data.

Neutralising antibody titres against LP.8.1 at Days 1 and 29 are presented for the following age groups: Panel A shows participants aged ≥12 and <65 years who received mRNA-1273.251; Panel B shows participants aged ≥65 years who received mRNA-1273.251. Panel C shows participants aged ≥12 and <65 years who received mRNA-1283.251. Panel D shows participants aged ≥65 years who received mRNA-1283.251. Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 × LLOQ. Antibody values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ.

Day 29 Cross-Neutralisation of Emerging Variants

- Both mRNA-1273.251 and mRNA-1283.251 elicited substantial Day 29 increases in nAb titres against LP.8.1 and currently circulating variants (XFG, NB.1.8.1, and BA.3.2.2) (**Figure 2**)

Figure 2. nAb Responses Elicited by (A) mRNA-1273.251 and (B) mRNA-1283.251 Against Vaccine-Matched (LP.8.1) and Emerging Variants (XFG, NB.1.8.1, and BA.3.2.2), Fit-for-Purpose Analysis



ID_{50}, 50% inhibitory dose; LLOQ, lower limit of quantification; LOD, limit of detection; nAb, neutralising antibody; ULOQ, upper limit of quantification.

Dashed lines represent LOD. n ranges from 25-56 participants.

A fit-for-purpose approach was applied to enable rapid assay development and sample testing for newly emerging variants. Accordingly, LOD was applied for analyses across all 4 variants, although the LP.8.1 assay was fully validated and its LLOQ and ULOQ were established through a formal validation process. Antibody values below the LOD were imputed as 0.5 × LOD. Values above the ULOQ were not capped.

CONCLUSIONS

- Updated LP.8.1-containing mRNA-1273.251 and mRNA-1283.251 elicited robust nAb responses against the vaccine-matched variant across age groups
- Both mRNA-1273.251 and mRNA-1283.251 were well-tolerated through Day 29, with no reported serious AEs, AEs of special interest, or AEs leading to study discontinuation
- Exploratory analyses demonstrated that both mRNA-1273.251 and mRNA-1283.251 elicited cross-neutralising antibody responses against currently circulating variants, including XFG, NB.1.8.1, and BA.3.2.2, but these were lower than the LP.8.1 responses
- These findings support the use of updated variant-containing mRNA vaccines to maintain nAb responses against evolving SARS-CoV-2 variants

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Disclosures

SC, ALF, EFM, JL, AC, VU, WX, XC, JF, BG, AN, RW, DKE, and RD are employees of Moderna, Inc., and may hold stock/stock options in the company. KJ is an employee of CenExel and holds stock in the company. DCM reports laboratory funding from Moderna, Inc. RS has nothing to declare.

ADDITIONAL INFORMATION

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