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A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine

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ABSTRACT

Background: Vaccines are urgently needed to prevent the global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We assessed the safety and immunogenicity of vaccine candidate mRNA-1273, encoding the prefusion-stabilized spike protein of SARS-CoV-2.

Methods: This phase 2, randomized, observer-blind, placebo-controlled trial was conducted at 8 sites in the USA, in healthy adults aged ≥18 years with no known history or risk of SARS-CoV-2 infection, and had not previously received an investigational CoV vaccine or treatment. Participants were stratified into two age cohorts (≥18-<55 and ≥55) and were randomly assigned (1:1:1) to either 50 or 100 μg of mRNA-1273, or placebo administered as two intramuscular injections 28 days apart. The primary outcomes were safety, reactogenicity, and immunogenicity assessed by anti-SARS-CoV-2-spike binding antibody level (bAb). Secondary outcome was immunogenicity assessed by SARS-CoV-2 neutralizing antibody (nAb) response.

Results: Between 29 May and 8 July 2020, 600 participants were randomized, 300 per age cohort. The most common solicited adverse reactions were pain at injection site, headache, and fatigue following each vaccination in both age cohorts. One serious adverse event deemed unrelated by the site investigator occurred 33 days post-vaccination one. mRNA-1273 induced bAb and nAb by 28 days post-vaccination one that were higher at the 100 μg dose relative to the 50 μg dose; this difference was less apparent post-vaccination two. Binding antibodies and nAb increased substantially by 14 days following the second vaccination (day 43) to levels exceeding those of convalescent sera and remained elevated through day 57.

Conclusions: Vaccination with mRNA-1273 resulted in significant immune responses to SARS-CoV-2 in participants 18 years and older, with an acceptable safety profile, confirming the safety and immunogenicity of 50 and 100 μg mRNA-1273 given as a 2 dose-regimen.

ClinicalTrials.gov; NCT04405076.

1. Introduction

Coronaviruses (CoVs) belong to the *Coronaviridae* family of viruses that can cause mild to severe illness, such as Middle East Respiratory Syndrome (MERS CoV) and Severe Acute Respiratory Syndrome (SARS-CoV) [1]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in Dec 2019, has caused a worldwide pandemic of coronavirus disease 2019 (COVID-19), leading to widespread morbidity and mortality [2–4].

The urgent need for safe and effective interventions to mitigate the global spread of SARS-CoV-2 has prompted international efforts to develop antivirals and vaccines. Numerous vaccine

Abbreviations: AE, adverse event; ARs, adverse reaction; bAb, serum binding antibody; CoV, coronaviruses; COVID-19, coronavirus disease 2019; CRO, clinical research organization; eDiary, electronic diary; ELISA, enzyme-linked immunosorbent assay; LLOQ, lower limit of quantification; MAAE, medically-attended adverse event; MN, microneutralization; mRNA, messenger ribonucleic acid; nAb, serum neutralizing antibody; RT-PCR, reverse transcription polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULOQ, upper limit of quantification.

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candidates based on traditional and new platforms are currently being evaluated including nucleic acid (DNA and RNA), viral vector (replicating and non-replicating), virus-like particles, peptide-based, recombinant protein, live attenuated and inactivated virus modalities. The focus of most of the candidates has been on the SARS-CoV-2 spike protein as antigen [5–7].

COVID-19 vaccines are in various stages of clinical development, with several candidates in pivotal phase 3 clinical trials, including mRNA-based vaccines [8,9]. The use of mRNA technology is a promising pandemic response-strategy which combines a readily adaptable means of designing immunogens with rapid manufacturing and scale-up, thereby enabling shorter vaccine development timelines compared with other approaches [10,11]. mRNA-based vaccines encoding viral antigens have been shown to be immunogenic against infectious pathogens with an acceptable safety profile in several clinical studies, including early phase trials of COVID-19 vaccines [12–20]. Additionally, preliminary findings from the interim analyses of two phase 3 trials of mRNA vaccines, BNT162b2 and mRNA-1273, demonstrated efficacy in prevention of COVID-19 and no significant safety concerns to date [21,22].

mRNA-1273 is a lipid-nanoparticle (LNP) encapsulated mRNA vaccine encoding a pre-fusion stabilized form of the SARS-CoV-2 spike protein (S-2P). In preclinical studies, mRNA-1273 induced potent neutralizing antibody responses to SARS-CoV-2 that were protective against infection in the lungs and noses of mice without evidence of immunopathology [23]. Vaccination of rhesus macaques with a 2-dose regimen of mRNA-1273 induced robust SARS-CoV-2 neutralizing activity and rapid protection in the upper and lower airways, in the absence of associated immunopathologic changes in the lung [24].

In a phase 1 clinical trial (ClinicalTrials.gov, NCT04283461), mRNA-1273, administered as two injections 28 days apart, was investigated at doses of 25, 50, 100 and 250 μg in participants 18–55 years of age, and at 25, 50, and 100 μg in older cohorts (56–70 and >71 years) [16,19]. Anti-SARS-CoV-2-spike binding and neutralizing antibody levels induced by mRNA-1273 vaccine were similar to or higher than those in convalescent plasma from recovered COVID-19 patients. Vaccine recipients also developed Th-1 directed T-cell responses with minimal Th-2 responses. There were no significant safety concerns, and adverse reactions were mainly mild or moderate in the younger and older age groups at the 25 and 100 μg doses. The 100 μg dose induced higher antibody titers than the 25 μg dose, whereas the 250 μg dose did not lead to significant increases, which supported evaluation of the 100 μg dose in phase 2 and phase 3 vaccine trials [16,19,25].

The aim of this randomized, placebo-controlled, dose-confirmation study was to further evaluate the safety and immunogenicity of mRNA-1273 given as two vaccinations in 600 healthy adults, 18 years of age and older. Dose levels of 50 and 100 μg mRNA-1273 were chosen for evaluation based on available safety and immunogenicity data [15,16,19], in two cohorts of participants ≥18–<55 and ≥55 years old, in an effort to further elucidate the dose–response relationship of 50 and 100 μg mRNA-1273, based on the safety and immunogenicity in a larger cohort of healthy adults.

2. Methods

2.1. Study design and participants

This randomized, placebo-controlled dose-confirmation trial enrolled participants at 8 sites in the US. The study was conducted in accordance with the International Council on Harmonization of Good Clinical Practice guidelines and the protocol was approved by regulatory and institutional committees (supplementary material). All participants provided informed consent.

Eligible participants were adults ≥18 years, considered by the investigator to be in good health, who could comply with study procedures and had a body mass index of 18 kg/m^2–30 kg/m^2. Excluded from the study were those with a known history of SARS-CoV-2 infection, exposure to someone with SARS-CoV-2 infection or COVID-19 disease, and acutely ill or febrile (≥38.0°C/100.4°F) 24 h prior to or at screening. Also excluded were those who had received prior administration of an investigational CoV vaccine, current prophylactic treatment with investigational agents against COVID-19, and healthcare or emergency response workers. Pregnant or breastfeeding females, and sexually active males and females unwilling to use adequate contraception for at least 3 months after the second study vaccination were also excluded. See additional eligibility criteria in the supplementary protocol.

2.2. Randomization and blinding

Dose levels of 50 and 100 μg mRNA-1273 were evaluated in two age cohorts, comprised of healthy adult participants aged ≥18–<55 (cohort 1) and ≥55 (cohort 2). Within each age cohort, approximately 300 participants were randomly assigned in a 1:1:1 ratio to receive 50 and 100 μg of mRNA-1273 or placebo. The randomization was performed in a blinded manner using a centralized Interactive Response Technology. Vaccine dose preparation and administration were performed by unblinded pharmacy personnel who did not participate in any other aspects of the study. All study staff, participants, clinical research organization (CRO) and sponsor personnel will remain blinded to dosing assignment until study-end (day 394), except those involved with the day 57 primary analysis. To enable the primary analysis, limited members of the sponsor team and CRO were unblinded.

The mRNA-1273 vaccine candidate is comprised of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 encapsulated in a lipid nanoparticle as described previously with modification required for large-scale manufacturing [16,24].

2.3. Procedures

The study was initiated by parallel enrollment of all 300 participants in the younger cohort and a sentinel group of 50 participants in the older cohort (Fig. S1). Acceptable safety of the sentinel group and all available data from cohort 1 was confirmed by an independent safety monitoring committee before vaccination of the remaining participants in cohort 2 (N = 250).

The mRNA-1273 vaccine and placebo were administered as a deltoid intramuscular injection using a 2-dose regimen with the first dose given on day 1 and the second on day 29. Vaccine was provided at a concentration of 0.5 mg/mL using normal saline to dilute the doses prior to administration. Each injection was administered in a volume of 0.5 mL containing 50 or 100 μg of mRNA-1273, or saline placebo. Both the first and second doses were administered in the same (preferably nondominant) arm. Participants were monitored for a minimum of 60 min post-injection. Assessments included vital sign measurements and monitoring for local or systemic reactions.

Participants were instructed on performing and recording self-assessments via an electronic diary (eDiary). Safety and reactogenicity assessments included monitoring and daily recording of solicited local and systemic adverse reactions (ARs) using the eDiary during 7 days after each injection, unsolicited adverse events (AEs) observed or reported during the 28 days following each injection, AEs leading to discontinuation from dosing and/or study participation or withdrawal from the study, medically-attended

adverse events (MAAEs), and serious adverse events (SAEs) from days 1 through 394, and results of safety laboratory tests, vital sign measurements, physical examination findings, and assessments for SARS-CoV-2 infection from day 1 through study completion. After the day 57 visit, participants received monthly prompts via the eDiary to capture occurrence of AEs, MAAEs, SAEs and any COVID-19 symptoms. Solicited local ARs included pain, erythema, and swelling/induration at the injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm. Solicited systemic ARs were headache, fatigue, myalgia, arthralgia, nausea/vomiting, rash, fever, and chills. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) was used in this study with modification for rash, solicited ARs, and vital signs (Table S1).

2.4. Detection of SARS-CoV-2 infection and immunogenicity assessments

For the detection of SARS-CoV-2 genomic RNA, nasopharyngeal (NP) swab samples were collected at days 1, 29, and 57 and RNA was measured using a real-time reverse transcription polymerase chain reaction (RT-PCR) assay (Viracor Eurofins Clinical Diagnostics, supplementary methods) [26]. SARS-CoV-2 RNA was detected using a predetermined baseline cycle threshold value of 38. Participants experiencing pre-specified SARS-CoV-2 disease criteria during the study were asked to contact the study site for a prompt, thorough clinical assessment.

Immunogenicity was assessed in blood samples collected on days 1 and 29 (before administration of vaccine) and days 43, and 57. The assay methods are detailed in the supplementary methods. Briefly, serum binding antibody (bAb) levels against SARS-CoV-2 were measured by enzyme-linked immunosorbent assay (ELISA) specific to the S-2P protein developed in collaboration with PPD laboratories (Richmond, Virginia, USA). The anti-spike antibody concentration (μg/ml) was determined by interpolation from an 11-point dilution of an anti-SARS-CoV-2 spike monoclonal antibody (clone CR3022, Rockland, Inc, Limerick, PA). Serum neutralizing antibody (nAb) titers against SARS-CoV-2 were measured using a live virus microneutralization (MN) assay based on an *in situ* ELISA readout. The assay was qualified for evaluation of human serum and conducted in accordance with Battelle laboratory protocols and qualified critical reagents (Columbus, Ohio, USA). The final reportable value for each sample was the MN_{50} titer. Human sera from COVID-19 convalescent patients collected at least 15 days post-infection confirmed by RT-PCR (BioIVT, Westbury, NY, USA and Aalto Bio Reagents Ltd, Dublin, Ireland) served as a reference for the ELISA and MN assays.

2.5. Outcomes

The primary objectives were to evaluate the safety, reactogenicity, and immunogenicity assessed by the level of SARS-CoV-2 spike glycoprotein-specific binding antibody (bAb) of 2 dose levels of mRNA-1273 vaccine, each administered as two vaccinations, 28 days apart. The secondary objective was to evaluate the immunogenicity of 2 dose levels of mRNA-1273 vaccine, each administered as two vaccinations 28 days apart, assessed by nAb titer. The primary safety endpoints were solicited ARs through 7 days after each injection, unsolicited AEs through 28 days after each injection, MAAEs and SAEs throughout the entire study period, safety laboratory abnormalities at days 29 and 57 (cohort 2 only), and vital sign measurements and physical examination findings. The primary immunogenicity endpoint was the level of bAb measured by ELISA on days 1, 29, 43, 57, 209, and 394. The secondary objective endpoints were titer of SARS-CoV-2-specific nAb on days 1, 29, 43, 57, 209, and 394, and seroconversion on days 29, 43, 57, 209, and 394 as measured by an increase of SARS-CoV-2-specific nAb titer from below the lower limit of quantification (LLOQ) to ≥LLOQ, or a 4-times higher titer in participants with pre-existing nAb titers.

2.6. Statistical analysis

There was no formal hypothesis-testing in this study. No formal power calculation was done. The number of proposed participants was considered sufficient to provide a descriptive summary of the safety and immunogenicity of two different dose levels of mRNA-1273.

Data presented are from the primary analysis of safety and immunogenicity when all participants had completed day 57 study procedures but prior to the final analysis of all endpoints to be performed after all participants have completed 13-month study procedures. Descriptive results of safety and immunogenicity analyses are presented. Analyses were performed by treatment group overall (2 cohorts combined) and for each cohort individually. Safety analyses were based on the safety set consisting of all randomly assigned participants who received any study vaccination, except solicited ARs which were based on the solicited safety set comprising all participants who were randomly assigned, received any study injection and contributed any solicited AR data. Safety analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals, as appropriate, for local reactions, systemic events and any unsolicited adverse events, MAAEs and SAEs according to preferred terms in the Medical Dictionary for Regulatory Activities (Version 23.0) by group. Summary statistics were provided for abnormal laboratory values and grading shifts.

Immunogenicity analyses were performed in the per-protocol dataset comprised of all randomly assigned participants who had baseline data available and at least one post-injection assessment for the analysis endpoint, complied with two injection schedule and timings of immunogenicity blood sampling with post-injection results available for at least one assay component, and did not have SARS-CoV-2 infection at baseline nor major protocol deviations that could impact the immunogenicity analysis. For the immunogenicity endpoints, geometric mean (GM) of specific bAb levels and GM titers (GMT) for nAb with the corresponding 95% CI at each timepoint are reported. Descriptive summary statistics including median, minimum, and maximum are also provided. Antibody values reported as below the LLOQ were replaced by 0.5 × LLOQ. Values that were greater than the upper limit of quantification (ULOQ) were converted to the ULOQ. The number and percentage of participants with seroconversion in SARS-CoV-2-specific nAb titers from baseline are reported with a 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint.

All analyses were conducted using SAS Version 9.4 or higher (SAS Institute).

3. Results

Between 22 May 2020 and 08 July 2020, 1090 participants were screened and 600 eligible participants were randomized (Fig. 1). Of these, 300 participants were included in each age cohort (≥18–< 55 years and ≥55 years), and randomly assigned to receive 50 or 100 μg of mRNA-1273 vaccine or placebo administered as two injections. Thirteen participants did not receive a second vaccination, including one who experienced an AE related to SARS-CoV-2 infection, five lost to follow-up, one who withdrew consent, two AEs, one of which was considered serious and the other a solicited AR, and four due to other reasons.

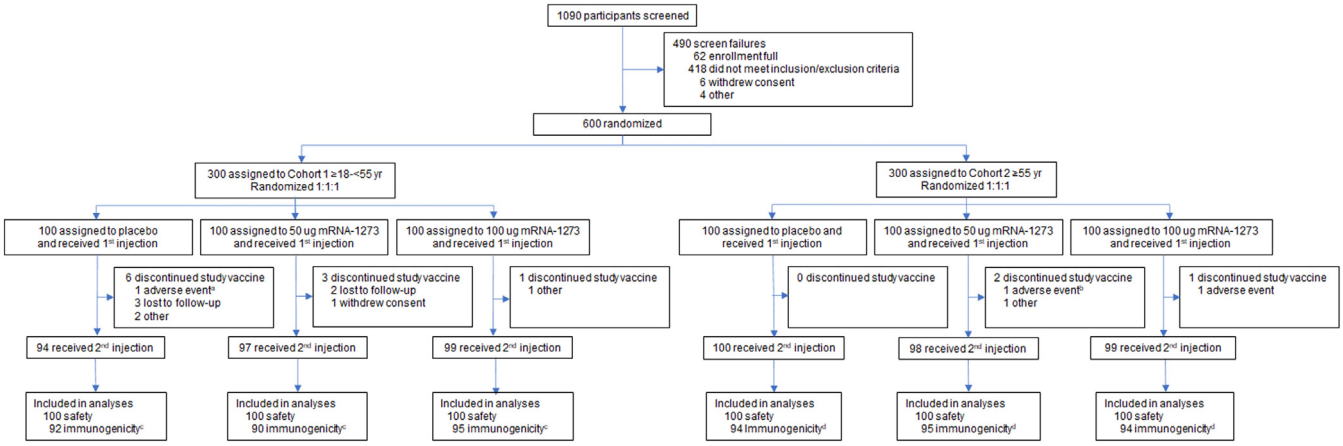

Fig. 1. Trial profile. Percentages are based on the number of randomized participants in the study. [a]Confirmed adverse event of SARS-CoV-2 infection. [b]Considered a serious adverse event due to community-acquired pneumonia that led to study vaccine discontinuation that occurred on day 33 and resolved on day 58, outside the primary endpoint evaluation of unsolicited AEs through 28 days after each injection. [c]n = 92, 90, and 95 for both bAb and nAb in placebo, 50 μg and 100 μg mRNA-1273 groups, respectively. [d]n = 94, 95, and 94 for bAb and 89, 89, and 91 for nAb in placebo, 50 μg and 100 μg mRNA-1273 groups, respectively. The "other" reasons for study vaccine discontinuations included 3 false positive COVID-19 infection results reported from central labs and 1 participant that reported a positive COVID-19 infection result from an external lab at day 15.

The baseline characteristics were generally balanced across study vaccine groups in each cohort (Table 1). Mean ages were 37.4 (range 18–54) and 64.3 (range 55–87) years, 59% and 71% were females, and the majority of participants were white (92% and 97%) in the younger and older cohorts, respectively.

Solicited local and systemic ARs through day 7 were mainly mild or moderate in severity in both cohorts after the first and second vaccinations (Fig. 2 and Table S2). The incidences of ARs occurred at higher frequencies in participants who received mRNA-1273 than placebo. The most commonly reported local AR after vaccination one was pain at the injection site in younger participants in the 50 μg (73%) and 100 μg (86%) mRNA-1273 and placebo (14%) groups, and for 50 μg (58%) and 100 μg (81%) mRNA-1273, and placebo (7%) in older participants. After vaccination two, injection site pain was also the most frequent local AR with higher incidences in the 50 μg (80%) and 100 μg (90%) mRNA-1273 groups than placebo (10%) in younger recipients, and at 50 μg (79%) and 100 μg (81%) mRNA-1273 versus placebo (6%) in older recipients.

The most frequent solicited systemic ARs after the first vaccination were headache in the 50 μg (29%) and 100 μg (25%) mRNA-1273, and placebo (18%) groups in younger adults, and for 50 μg (29%) and 100 μg (18%) mRNA-1273, and placebo (18%) in older adults. Fatigue was also commonly reported in the 50 μg (24%) and 100 μg (30%) mRNA-1273 and placebo (17%) groups in younger participants and for 50 μg (24%) and 100 μg (20%) mRNA-1273, and placebo (19%) in older participants. Systemic ARs occurred more frequently after the second vaccination in the mRNA groups in both cohorts and most commonly were headache for 50 μg (51%) and 100 μg (56%) mRNA-1273 and placebo (15%) in the younger cohort and 50 μg (48%) and 100 μg (50%) mRNA-1273 and placebo (19%) in the older cohort. Fatigue was also frequently reported in the 50 μg (45%) and 100 μg (66%) mRNA-1273 and placebo (20%) groups in younger adults, and for 50 μg (61%) and 100 μg (64%) mRNA-1273 and placebo (22%) in older adults. Additionally, incidences of myalgia, arthralgia, nausea/vomiting, and chills increased after the second vaccination in the mRNA-1273 groups of both cohorts.

The majority of solicited AR were mild and moderate in severity. The incidence of grade 3 reactions increased after the second vaccination, particularly for systemic reactions. The greatest overall incidence of grade 3 reactions was reported for fatigue (9.1%) and myalgia (7.6%) after the second dose of 100 μg of mRNA-1273. Mean durations for solicited ARs were similar across the placebo and mRNA-1273 groups and ranged from 2.4 to 3.1 days in young adults and 2.1–3.7 days in older adults after vaccination one (Table S3). The mean duration of any solicited ARs were also generally comparable across the mRNA-1273 and placebo groups after vaccination two, ranging from 3 to 4 days in younger and 1.9–3.4 days in older adults.

There were no significant differences in the rates of unsolicited AEs reported through 28 days after each vaccination, across the mRNA-1273 and placebo groups in the younger (77 [26%]) and older (87 [29%]) cohorts (Table 2 and Table S4). The majority of AEs were generally mild and moderate in severity, and no deaths or serious AEs were reported. There were 11 (4%) severe events in the younger and 5 (2%) in the older cohorts. The incidences of MAAEs were similar in younger (29 [10%]) and older (27 [9%]) participants across placebo and mRNA-1273 groups regardless of treatment attribution.

Unsolicited AEs related to study vaccine were reported in 31 (10%) younger and 25 (8%) older participants and occurred at a higher incidence at 100 μg mRNA-1273 (18%) than placebo (6%) in younger adults (Table 2). No deaths or unsolicited AEs that led to discontinuation from study vaccine or the study occurred within 28 days. One SAE of community-acquired pneumonia occurred on day 33 at 50 μg mRNA-1273 in the older cohort, resolved on day 58 and led to study vaccine discontinuation. This event was considered not related to investigational vaccine by the investigator. No study pause rules were met. The overall incidence of study vaccine-related severe AEs was low in both younger (7 [2%]) and older (1 [<1%]) adults across the placebo and both mRNA-1273 groups. Severe events occurring in >1% of participants included fatigue for placebo (2%), fatigue (1%), arthralgia (2%), and axillary pain (1%) for 50 μg mRNA-1273, and headache (1%) for 100 μg mRNA-1273 in younger individuals, and fatigue (1%) for 50 μg mRNA-1273 in those older (Table S4). Study vaccine-related MAAEs were higher in younger (5 [3%]) than older (2 [1%]) participants with all of the events in the younger cohort occurring in the mRNA-1273 groups.

Three participants were symptomatic and had positive NP swabs for SARS-CoV-2, two of whom had received placebo and one who received 50 μg of mRNA-1273. Four participants were found to have positive NP swabs for SARS-CoV-2 yet remained

Table 1
Demographics.

Characteristic n (%)	Cohort 1 (≥18 - <55 yr)					Cohort 2 (≥55 yr)				
		mRNA-1273					mRNA-1273			
	Placebo N=100	50 μg N=100	100 μg N=100	Total N=200	Overall N=300	Placebo N=100	50 μg N=100	100 μg N=100	Total N=200	Overall N=300
Age years, mean (range)	37.3 (18-53)	36.6 (18-54)	38.3 (18-54)	37.5 (18-54)	37.4 (18-54)	64.3 (55-84)	64.6 (55-87)	63.9 (55-87)	64.3 (58-87)	64.3 (55-87)
Female	60 (60)	64 (64)	53 (53)	117 (59)	177 (59)	69 (69)	73 (73)	71 (71)	144 (72)	213 (71)
Race										
White	94 (94)	93 (93)	90 (90)	183 (92)	277 (92)	99 (99)	95 (95)	98 (98)	193 (97)	292 (97)
Black or African American	3 (3)	3 (3)	7 (7)	10 (5)	13 (4)	0	2 (2)	1 (1)	3 (2)	3 (1)
Asian	2 (2)	0	2 (2)	2 (1)	4 (1)	1 (1)	2 (2)	0	2 (1)	3 (1)
American Indian/Alaska Native	0	2 (2)	0	2 (1)	2 (1)	0	0	1 (1)	1 (<1)	1 (<1)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	1 (1)	0	1 (1<)	1 (<1)
Multiracial/Other	1 (1)	2 (2)	1(1)	3 (2)	4 (1)	0	0	0	0	0
BMI kg/m2, Mean (SD)	25.3 (3)	25.6 (3)	24.8 (3)	25.2 (3)	25.2 (3)	25.4 (3)	25.6 (3)	25.2 (3)	25.4 (3)	25.4 (3)

BMI=body mass index; Percentages are based on the number of randomized participants.

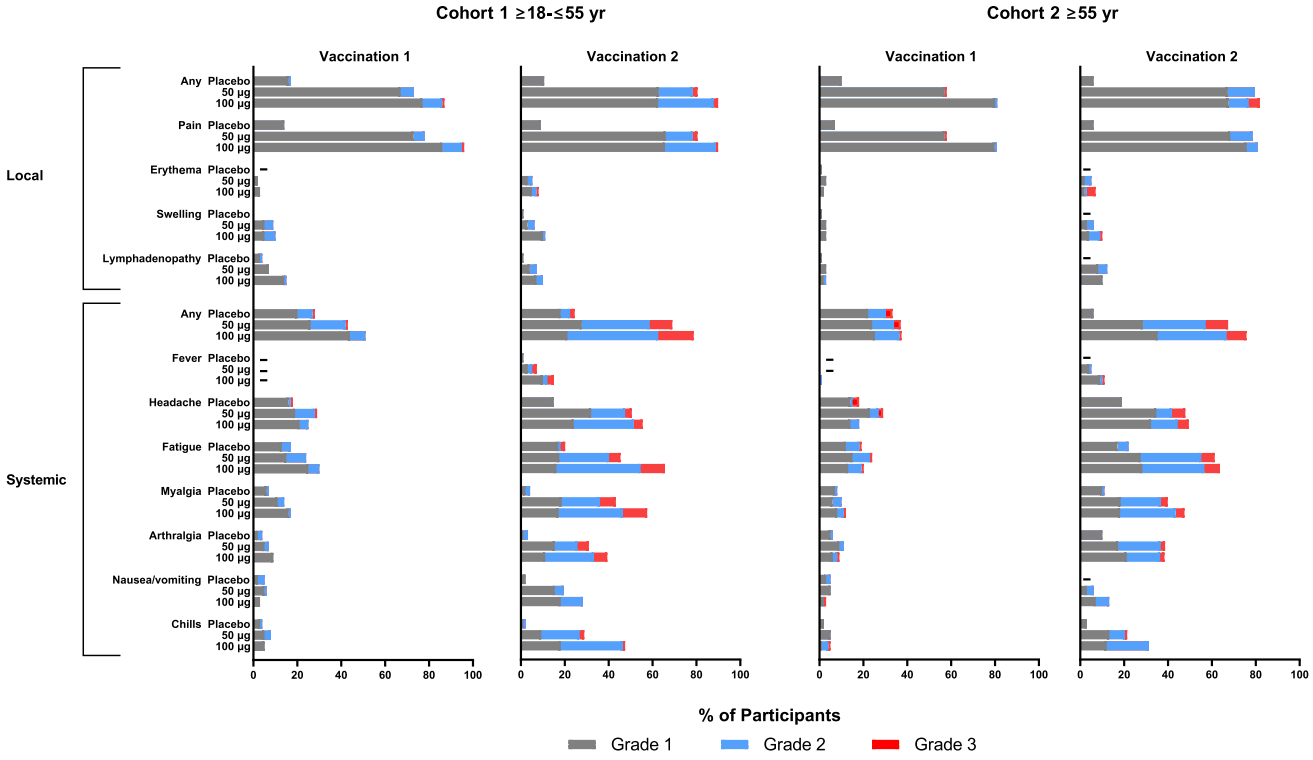

Fig. 2. Solicited local and systemic adverse reactions within 7 days post-vaccinations one and two in each cohort. Percentages of participants with solicited local and systemic adverse reactions by dose, grade and vaccination in cohorts 1 and 2. Percentages are based on the solicited safety set comprising all participants who were randomly assigned, received any study vaccine and submitted any solicited adverse reaction data. In the eDiary, rash was not reported by grade. Lymphadenopathy included any localized axillary swelling or tenderness ipsilateral to the vaccination arm. Dashes indicate no reported data for the adverse reactions. CI = Confidence intervals.

asymptomatic, three of whom had received placebo and one who received 50 μg of mRNA-1273. All were referred to the health department for isolation/contact tracing, and notification of the participant's primary providers. Despite numerous participants in the 100 μg group reporting exposures to SARS-CoV-2 and a smaller number developing symptoms consistent with COVID-19, none had positive NP swabs at scheduled or unscheduled time points. No clinically significant laboratory abnormalities were reported (Table S5).

None of the placebo or mRNA-1273 participants had detectable anti-SARS-CoV-2-spike bAb at baseline. Both doses of mRNA-1273 induced increases in the levels of anti-SARS-CoV-2-spike bAb from baseline by day 29, 28 days after the first vaccination (Fig. 3A). Anti-SARS-CoV-2-spike bAb levels increased substantially by 14 days (day 43) after the second vaccination to GM mean (95% CI) peak levels of 189 (173–207) and 239 (221–259) μg/ml at 50 and 100 μg mRNA-1273 respectively in younger participants, and 153 (135–175) and 162 (142–185) μg/ml in older participants. These levels vastly exceeded those in convalescent COVID-19 sera (48 [38–60] μg/ml). Antibody levels remained elevated through day 57, 28 days after vaccination, in the younger (146 [132–161] and 181 [164–200)] μg/ml) and older (107 [93–123)] and 121

Table 2
Incidence of unsolicited adverse events after any vaccination.

Adverse Event n (%)	Cohort 1 (≥18 – <55 yr)				Cohort 2 (≥55 yr)			
		mRNA-1273				mRNA-1273		
	Placebo N=100	50 μg N=100	100 μg N=100	Total N=200	Placebo N=100	50 μg N=100	100 μg N=100	Total N=200
Any regardless of attribution[a]	24 (24)	27 (27)	26 (26)	53 (27)	27 (27)	30 (30)	30 (30)	60 (30)
Serious	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0
Medically-attended	10 (10)	11 (11)	8 (8)	19 (10)	7 (7)	11 (11)	9 (9)	20 (10)
Led to discontinuation from study vaccine	0	0	0	0	0	0	0	0
Led to discontinuation from study	0	0	0	0	0	0	0	0
Severe	2 (2)	5 (5)	4 (4)	9 (5)	2 (2)	2 (2)	1 (1)	3 (2)
Any attributed to study vaccine[b]	6 (6)	7 (7)	18 (18)	25 (13)	7 (7)	9 (9)	9 (9)	18 (9)
Serious	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0
Medically-attended	0	1 (1)	4 (4)	5 (3)	1 (1)	0	1 (1)	1 (<1)
Led to discontinuation from study vaccine	0	0	0	0	0	0	0	0
Led to discontinuation from study	0	0	0	0	0	0	0	0
Severe	2 (2)	3 (3)	2 (2)	5 (3)	0	1 (1)	0	1 (<1)

n is the number of participants reporting an adverse event (AE). Unsolicited AEs are any events not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. AEs are summarized up to 28 days post-vaccination in the safety set consisting of all randomly assigned participants who received any study vaccination (except solicited ARs which were based on the solicited safety set). [a]AE regardless of attribution to study vaccine. [b]Attributed to study vaccine by investigator as having a reasonable possibility of a causal relationship.

[105–139)] μg/ml) cohorts at the 50 and 100 μg mRNA-1273 doses, respectively.

Neutralizing antibody titers were undetectable at baseline in all study participants. After the first vaccination at both mRNA-1273 doses, nAb GMTs increased from baseline by day 29, 28 days post-vaccination one (Fig. 3B and Table 3). Fourteen days following the second vaccination (day 43), nAbs were significantly enhanced to maximum GMTs (95% CI) of 1733 (1611–1865) μg/ml at 50 μg mRNA-1273 and 1909 (1849–1971) μg/ml at 100 μg mRNA-1273 in younger adults, and 1827 (1722–1938) μg/ml at 50 μg mRNA-1273 and 1686 [1521–1869]) μg/ml at 100 μg mRNA-1273 in older adults. These GMTs were 5–6 fold higher those of the convalescent COVID-19 control sera (321 [235–438] μg/ml). Little numeric change in nAb GMTs was observed at 28 days post-vaccination two (day 57) with titers remaining high for both mRNA-1273 dose levels and in both age groups.

SARS-CoV-2-specific nAb responses met criteria for seroconversion in 70% and 83% of younger recipients at the 50 and 100 μg mRNA-1273 doses respectively, and 61% and 70% in older participants by day 29, 28 days after the first vaccination (Table 3). By day 43, 14 days after the second vaccination, seroconversion rates of 100% were observed for all participants tested in both cohorts. Seroconversion rates of 100% were also observed at day 57 in younger and older participants at both mRNA-1273 doses.

A post-hoc exploratory analysis of immunogenicity in subgroups of participants aged ≥55-<65, ≥65-74 and ≥75 years was performed (Tables S6 and S7). Increases in levels of anti-SARS-CoV-2-spike bAb and nAb at days 29 and post-second vaccination at both the 50 and 100 μg doses were generally comparable across the age subgroups and with those observed in the younger (18–55 years) study participants. Seroconversion rates were also comparable across the age groups and with those in the younger participants. It should be noted that the small size of the ≥75 year-old subgroup (n = 22) precludes definitive conclusions to be made.

4. Discussion

In this randomized, controlled phase 2 trial, the SARS-CoV-2 vaccine candidate mRNA-1273, administered as a two-dose vaccination regimen at 50 and 100 μg, exhibited robust immune responses and an acceptable safety profile in healthy adults aged 18 years and older. Local and systemic adverse reactions were mostly mild-to-moderate in severity, were ≤4 days of median duration and were less commonly reported in older compared with younger adults. Anti-SARS-CoV-2 spike binding and neutralizing antibodies were induced by both doses of mRNA-1273 within 28 days after the first vaccination, and rose substantially to peak titers by 14 days after the second vaccination, exceeding levels of convalescent sera from COVID-19 patients. The antibodies remained elevated through the last timepoint assessed at 57 days. Neutralizing responses met criteria for seroconversion within 28 days after the first vaccination in the majority of participants, with rates of 100% observed at 14 and 28 days after the second vaccination. While no formal statistical testing was done, binding and neutralizing antibody responses were generally comparable in participants who received the 100 μg mRNA-1273 and the 50 μg dose at all time points and across both age groups. Overall, the results of this randomized, placebo-controlled trial extend previous immunogenicity and safety results for mRNA-1273 in the phase 1 study in an expanded cohort including participants older than 55 years of age [16,19].

The safety and reactogenicity profile of the mRNA-1273 vaccine through 28 days after the last dose was consistent with data previously published for other mRNA vaccines, including those of recent COVID-19 studies [12–20]. Solicited local and systemic symptoms were reported more frequently after mRNA-1273 than placebo and were reported at higher frequencies after the second dose. The occurrence of some solicited AR, fever and chills for example, were higher in participants who received 100 μg compared with 50 μg of mRNA-1273; however, the reactogenicity was generally not dose-dependent. The reported rates in participants ≥55 years of age tended to be lower than in participants 18–55 years of age, although formal statistical comparisons were not performed. Unsolicited AEs, including severe AEs, regardless of relationship to study vaccination, occurred at similar frequencies across the mRNA groups and placebo groups in both age cohorts. Treatment-related AEs occurred at higher rates in the mRNA group compared with placebo in younger participants, attributed to a greater frequency of injection site reactions (e.g., pain, erythema, induration) reported as unsolicited events per criteria described in the protocol. The safety profile of mRNA-1273 seen in the two age cohorts in this study was also consistent with the results observed in the phase 1 trial of mRNA-1273 [19].

Neutralizing antibody levels have been shown to correlate with protection against viral diseases; however, immune correlates to SARS-CoV-2 in humans are less well-understood [16,19,24].

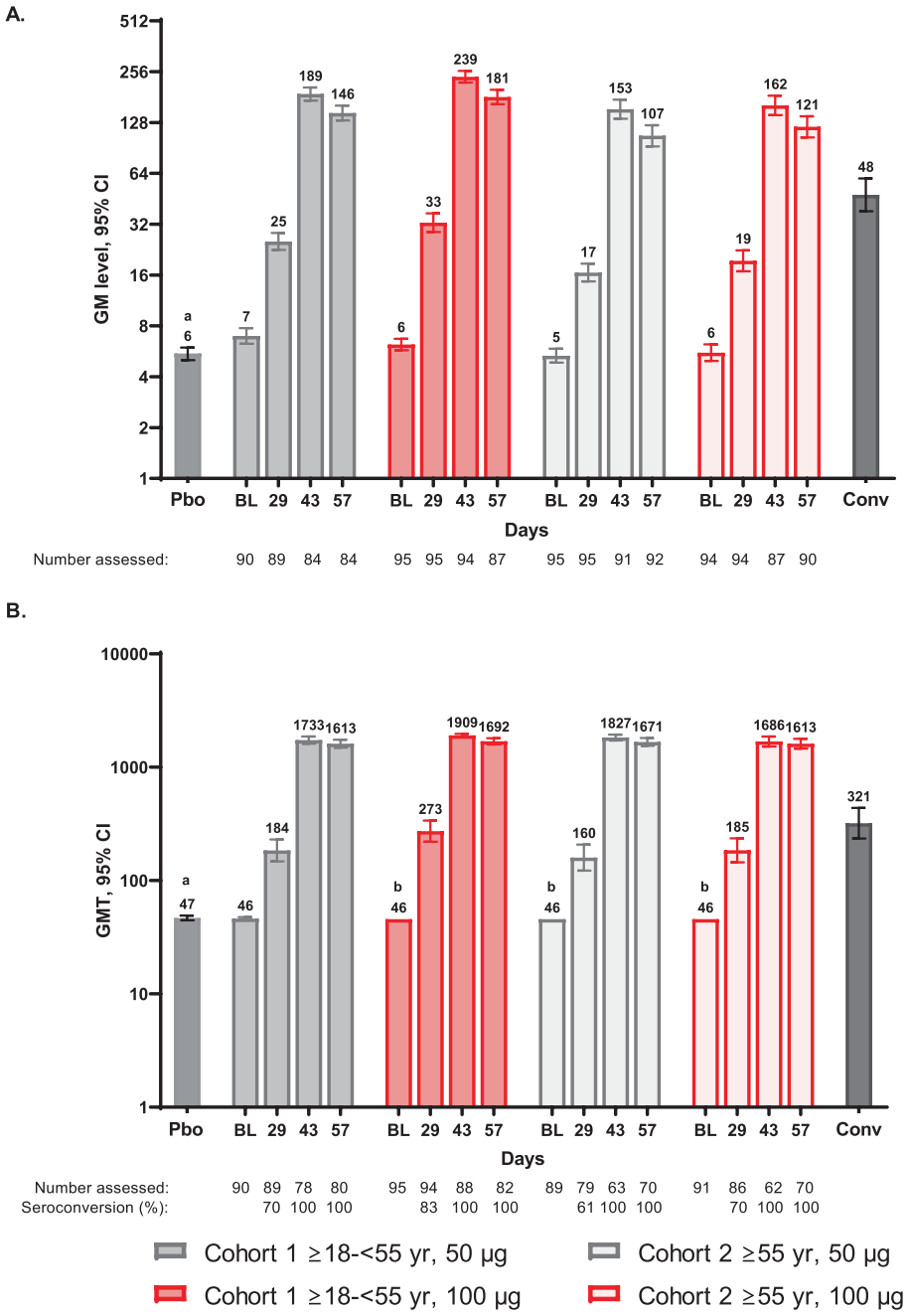

Fig. 3. SARS-CoV-2-spike binding and neutralizing antibody responses. Percentage of participants in the per-protocol set having SARS-CoV-2-specific bAb (A) and nAb (B) at the corresponding visit days. Antibody values below the LLOQ were replaced by 0.5 × LLOQ. Values greater than the ULOQ were converted to the ULOQ. For visit day 29, visit window (−3/+7 days) was used to define per-protocol. If the visit (day 29) was disrupted and could not be completed at day 29 (−3/+7 days) as a result of the COVID-19 pandemic, the window was extended to day 29 + 21 days. The 95% CI were calculated based on the t-distribution of the log-transformed values for GMT and GM levels, then back transformed to the original scale for presentation. The bAb values reported are ELISA concentrations µg/ml and nAb values are MN_{50} titers (LLOQ = 91.1 and ULOQ = 2031.9). Seroconversion rate at the participant level was defined as a change of nAb titer from below the LLOQ to ≥LLOQ, or a 4-times or higher ratio in participants with pre-existing nAb. Human convalescent sera collected from COVID-19 symptomatic patients at least 15 days post-infection confirmed by RT-PCR, and tested by MN (n = 32) and by ELISA (n = 119) served as reference control titers. [a]Responses in participants who received placebo averaged across days, study vaccine group and cohorts. [b]95% CIs were not estimable. Number of participants in the per-protocol set with SARS-CoV-2-specific nAb levels at the corresponding visit. bAb = binding antibody, BL = baseline, Conv = convalescent sera, ELISA = Enzyme-Linked Immunosorbent Assay, GM = geometric mean, LLOQ = lower limit of quantification, MN = microneutralization, nAb = neutralizing antibody, Pbo = placebo, ULOQ = upper limit of quantification.

Antibody-mediated immune responses are likely to be effective against SARS-COV-2, based on evidence from studies in non-human primate challenge models and the reported results for both COVID-19 convalescent sera and monoclonal antibody therapies in early clinical trials [24,27–30]. In that regard, it is encouraging that vaccination with mRNA-1273 elicited similar neutralizing activity in younger and older adults, a finding consistent with those demonstrated in the phase 1 studies of mRNA-1273 [16,19,31]. Moreover, robust and comparable bAb concentrations and nAb titers were observed at both mRNA-1273 dose levels and were substantially enhanced following the second vaccination to levels higher than those in human convalescent serum from COVID-19 patients. Overall, these data indicate dose-dependent immune responses to the first and second vaccinations with both doses of

Table 3
Neutralizing antibody geometric mean titers and seroconversion rates.

	Cohort 1 (≥18 – <55 yr)				Cohort 2 (≥55 yr)			
		mRNA-1273				mRNA-1273		
	Placebo N=92	50 μg N=90	100 μg N=95	Total N=185	Placebo N=89	50 μg N=89	100 μg N=91	Total N=180
Baseline (n)[a]	92	90	95	185	89	89	91	180
GMT	45.6	46.2	45.6	45.9	45.6	45.6	45.6	45.6
(95% CI)[b]	(NE-NE)	(44.9-47.6)	(NE-NE)	(45.2-47.0)	(NE-NE)	(NE-NE)	(NE-NE)	(NE-NE)
Day 29 (n)[c]	90	89	94	183	88	79	86	165
GMT	47.3	184	273	225	47.3	160	185	172
(95% CI)[b]	(43.9-51.0)	(147-230)	(220-338)	(193-263)	(43.8-51.1)	(122-208)	(145-236)	(144-206)
Seroconversion								
n (%)	1 (1)	62 (70)	78 (83)	140 (77)	1 (1)	48 (61)	60 (70)	108 (66)
(95% CI)[d]	(0-6.0)	(59.0-79.0)	(73.8-89.9)	(69.7-82.4)	(0-6.2)	(49.1-71.6)	(58.9-79.2)	(57.7-72.7)
Day 43 (n)[c]	87	78	88	166	88	63	62	125
GMT	45.6	1733	1909	1824	47.3	1827	1686	1755
(95% CI)[b]	(NE-NE)	(1611-1865)	(1849-1971)	(1755-1896)	(43.9-51.1)	(1722-1938)	(1521-1869)	(1656-1862)
Seroconversion								
n (%)	0	78 (100)	88 (100)	166 (100)	1 (1)	63 (100)	62 (100)	125 (100)
(95% CI)[d]	(0-4.2)	(95.4-100)	(96.0-100)	(97.8-100)	(0-6.2)	(94.3-100)	(94.2-100)	(97.1-100)
Day 57 (n)[c]	84	80	82	162	87	70	70	140
GMT	48.5	1613	1692	1652	47.1	1671	1613	1642
(95% CI)[b]	(44.4-53.0)	(1488-1747)	(1586-1805)	(1570-1739)	(44.0-50.5)	(1545-1807)	(1460-1782)	(1542-1748)
Seroconversion								
n (%)	2 (2)	80 (100)	82 (100)	162 (100)	1 (1)	70 (100)	70 (100)	140 (100)
(95% CI)[d]	(0-8.3)	(95.5-100)	(95.6-100)	(97.7-100)	(0-6.2)	(94.9-100)	(94.9-100)	(97.4-100)

CI = confidence intervals, GMT = geometric mean titer, nAb = neutralizing antibody, NE = not estimable. Antibody values below the lower limit of quantification (LLOQ) were replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) were converted to the ULOQ. LLOQ = 91.1 and ULOQ = 2032. For visit day 29, visit window (−3/+7 days) was used to define per-protocol. If the visit (day 29) was disrupted and could not be completed at day 29 (−3/+7 days) as a result of the COVID-19 pandemic, the window was extended to day 29 + 21 days. Seroconversion at participant level defined as a change of nAb titer from below the lower limit of quantification (LLOQ) to equal to or above LLOQ, or a 4-times or higher ratio in participants with pre-existing nAb titers. [a]Non-missing baseline data. [b]95% CI based on the t-distribution of the log-transformed values for GMT back transformed to the original scale for presentation. [c]Based on per-protocol set for SARS-CoV-2-specific nAb. [d]Calculated using the Clopper-Pearson method.

mRNA-1273 and confirm that a robust immune response is generated at both 50 and 100 μg dose levels.

Vaccines developed based on mRNA technology can be rapidly engineered and scaled-up, offering accelerated timelines to determine efficacy compared to more traditional approaches [10,11]. In particular, the mRNA platform provides an important rapid-response strategy in times of epidemics and pandemics, as well as for emerging pathogens, and other unmet medical needs. To date, an mRNA medicine has not been approved for human use, although multiple mRNA vaccines have shown encouraging immunogenicity and safety results in early-stage clinical trials against other viruses such as influenza, Zika, rabies, respiratory syncytial, and cytomegalovirus [12–20]. The success of larger-scale mRNA trials will further enhance the development of mRNA vaccines. In line with this, recent preliminary results from two large phase 3 trials demonstrated the efficacy of mRNA vaccines for COVID-19 with no significant safety concerns [21,22].

While this was the first randomized, placebo-controlled trial to evaluate the mRNA-1273 vaccine, there are some limitations. The study population was not designed at the time to be representative of those at risk for SARS-CoV-2 infection or COVID-19. Importantly, the safety and effectiveness of this vaccine is being assessed in larger and more diverse populations in the 30,000 participant-phase 3 Coronavirus Efficacy and Safety Study (COVE) study. Additionally, the present study was not designed for statistical comparison of superiority or equivalence between doses of mRNA-1273; thus, conclusions are necessarily qualitative. Although antibody responses were generated by mRNA-1273 that, on average, exceeded those of convalescent sera, at the present time a serologic correlate of protection against SARS-CoV-2 remains to be determined. Additional data informing the duration of immunogenicity and the longer-term safety of mRNA-1273, will be provided in the 13-month follow-up to the end-of-study in this trial, as well as from the expanded testing in the ongoing COVE trial.

In conclusion, the results of this phase 2 trial provide additional evidence supporting the immunogenicity and safety of a 2-dose regimen of the SARS-CoV-2 vaccine mRNA-1273 at 50 and 100 μg doses. The 13-month end-of study assessment of this trial and the ongoing phase 3 COVE trial may provide additional longer-term data on the safety and effectiveness of mRNA-1273 vaccine.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Roderick McPhee, Wenmei Huang, Hamilton Bennett, Rolando Pajon, and Brett Leav are employees of Moderna, Inc., and may hold stock/stock options in the company. Biliana Nestorova is a contract employee of Moderna, Inc. Laurence Chu has no conflict of interest.

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Author disclosures

R.M., W.H., H.B., R.P., and B.L. are employees of Moderna, Inc., and may hold stock/stock options in the company. BN is a contract employee of Moderna, Inc.

Contributors

LC was the lead investigator. WH analyzed the data, RP was responsible for the immunogenicity assays, RM, BN and HB contributed to study supervision, and LC, RM, WH, RP, BN and BL interpreted the data. The article was drafted by JET with input from LC, RM, WH, RP, BN, and BL. All authors contributed to the review and editing of the manuscript and approved the final version for submission.

Data sharing statement

Moderna is committed to sharing data supporting the findings of eligible studies. The results of this study are preliminary and the study is ongoing. Access to patient-level data and supporting clinical documents with qualified external researchers may be available upon request once the trial is complete.

Role of the funding source

Employees of the study sponsor, Moderna, Inc., contributed to the study design, data collection, analysis and interpretation, and writing of the report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.02.007.

References

[1] Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019;17:181–92.
[2] WHO. WHO Coronavirus Disease (COVID-19) Dashboard. November 9, 2020. https://covid19.who.int/?gclid=CjwKCAjwps75BRAcEiwAEiACMVdInLBoj_EeG7jJA_kaMRM93bsTUDSzJE8Qb7Z2C2Em4mlzqLkEKxoCH54QAvD_BwE.
[3] Viruses. CSGotICoTo. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536–44.
[4] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
[5] Thanh Le T, Andreadakis Z, Kumar A, Gomez Roman R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov 2020;19:305–6.
[6] Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. N Engl J Med 2020;382:1969–73.
[7] Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. Lancet 2020;396:1595–606.
[8] Society RAP. COVID Vaccine tracker; 2020.
[9] Doshi P. Will covid-19 vaccines save lives? Current trials aren't designed to tell us. BMJ 2020;371. m4037.
[10] Jackson NAC, Kester KE, Casimiro D, Gurunathan S, DeRosa F. The promise of mRNA vaccines: a biotech and industrial perspective. NPJ Vaccines 2020;5:11.
[11] Kowalski PS, Rudra A, Miao L, Anderson DG. Delivering the Messenger: Advances in Technologies for Therapeutic mRNA Delivery. Mol Ther 2019;27:710–28.
[12] Feldman RA, Fuhr R, Smolenov I, Mick Ribeiro A, Panther L, Watson M, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. Vaccine 2019;37:3326–34.
[13] Alberer M, Gnad-Vogt U, Hong HS, Mehr KT, Backert L, Finak G, et al. Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet 2017;390:1511–20.
[14] Richner JM, Himansu S, Dowd KA, Butler SL, Salazar V, Fox JM, et al. Modified mRNA Vaccines Protect against Zika Virus Infection. Cell 2017;169:176.
[15] Moderna Announces Additional Positive Phase 1 Data from Cytomegalovirus (CMV) Vaccine (mRNA-1647) and First Participant Dosed in Phase 2 Stud. 2020.
[16] Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med 2020;383:1920–31.
[17] Walsh EE, Frenck R, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. RNA-Based COVID-19 Vaccine BNT162b2 Selected for a Pivotal Efficacy Study. medRxiv 2020.
[18] Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020;586:589–93.
[19] Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med 2020;383:2427–38.
[20] Aliprantis AO, Shaw CA, Griffin P, Farinola N, Railkar RA, Cao X, et al. A phase 1, randomized, placebo-controlled study to evaluate the safety and immunogenicity of an mRNA-based RSV prefusion F protein vaccine in healthy younger and older adults. Hum Vaccin Immunother 2020:1–14.
[21] 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.
[22] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020.
[23] Corbett KS, Edwards D, Leist SR, Abiona OM, Boyoglu-Barnum S, Gillespie RA, et al. SARS-CoV-2 mRNA Vaccine Development Enabled by Prototype Pathogen Preparedness. bioRxiv 2020.
[24] Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. N Engl J Med 2020;383:1544–55.
[25] Widge AT, Rouphael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med 2020.
[26] ACCELERATED EMERGENCY USE AUTHORIZATION (EUA) SUMMARY SARS-CoV-2 RT-PCR TEST (Viracor Eurofins Clinical Diagnostics). 2020.
[27] Lilly announces proof of concept data for neutralizing antibody LY-CoV555 in the COVID-19 outpatient setting. https://investor.lilly.com/node/43721/pdf2020.
[28] Regeneron's Regn-Cov2 Antibody Cocktail Reduced Viral Levels and Improved Symptoms in Non-Hospitalized Covid-19 Patients. https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and2020.
[29] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA 2020;324:460–70.
[30] Libster R, Perez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med 2021.
[31] Ciabattini A, Garagnani P, Santoro F, Rappuoli R, Franceschi C, Medaglini D. Shelter from the cytokine storm: pitfalls and prospects in the development of SARS-CoV-2 vaccines for an elderly population. Semin Immunopathol 2020;42:619–34.