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mRNA-1273 Discussion with The Dutch National Institute for Public Health and the Environment (RIVM)

Discussion document

November 5, 2020

Introductions

RIVM Representatives

Dr. 5.1.2e, Medical Microbiologist and Bacteriological and Parasitological Diagnostics Department Head

Dr. 5.1.2e, Senior Scientific Advisor

Moderna representatives

5.1.2e, Head, Regulatory Affairs

5.1.2e, Chief Medical Officer

Agenda

Introductions

Non-Clinical Development

Clinical Development

Manufacturing Plans

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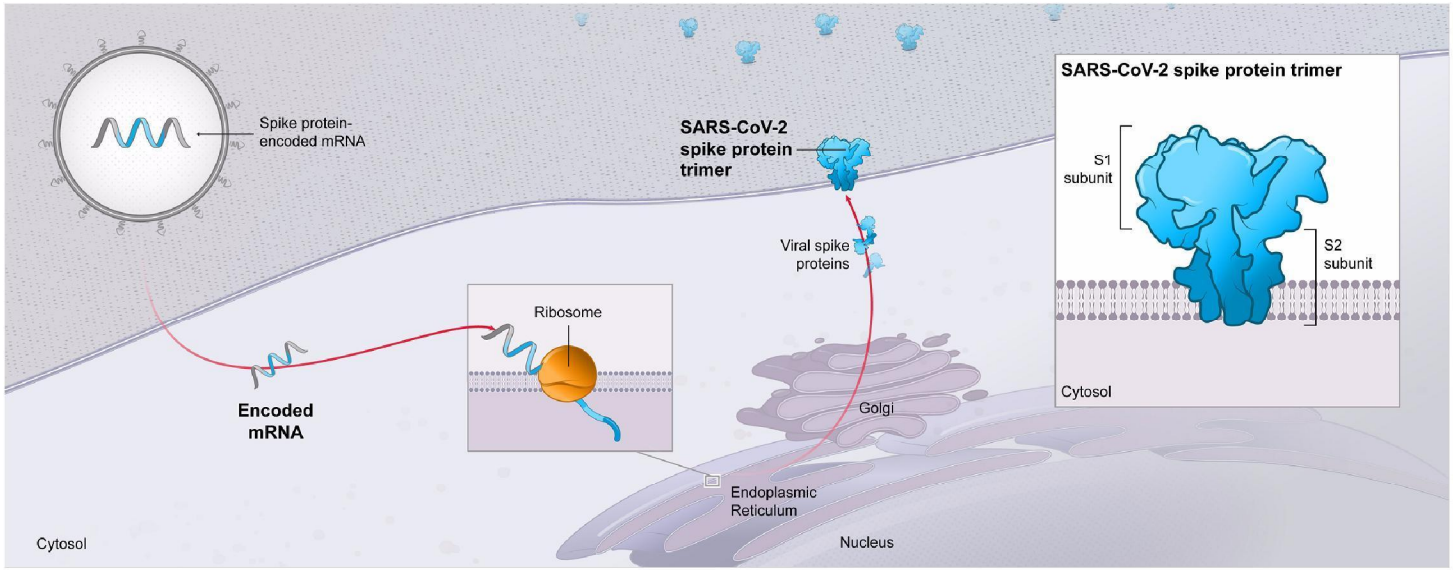
mRNA-1273: Nonclinical overview

mRNA-1273 encodes for the full-length Spike Protein in the Pre-fusion Conformation (S-2P)

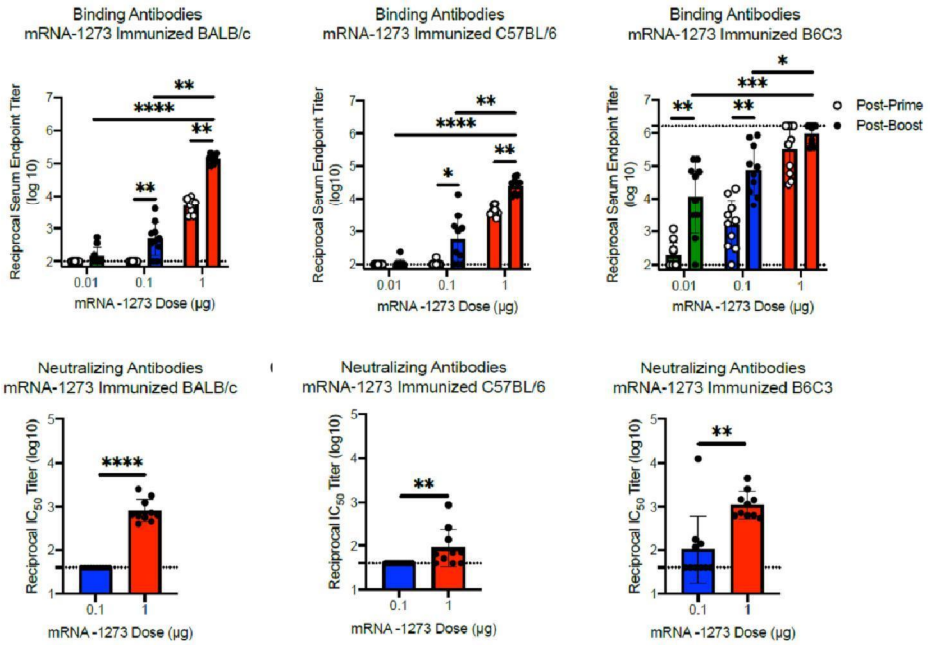


Includes unpublished / confidential data

Overview of results generated to date

Results type	Summary of results
1 Immunogenicity	• Observed dose-dependent increases in binding and neutralizing antibody titers and CD8 T-cell responses following immunization with mRNA-1273 in mice, hamster, and NHPs – Prime-only dosing generated robust neutralizing antibody responses, however, boost led to a significant increase – Antibody titers observed in hamsters and NHPs were higher than what is seen in human convalescent sera • Binding and neutralizing antibody titers were highly correlated across a broad range of doses
2 Protection	• Vaccination at 100 µg was fully protective both the lungs and nose of NHPs • Protection was observed in mice at 1 µg with a 0 and 3 week dosing schedule and down to 0.1 µg with 0 and 4 week dosing • Prime only regimen induced protection at a both a dose of 1 and 10 µg
3 Disease enhancement	• Previous work with mRNA platform technology in hMPV helps de-risk likelihood of observing disease enhancement • Vaccination with mRNA-1273 generated a balanced ratio of IgG1 to IgG2a, indicating a Th2-biased response is not induced • Robust Th1-directed T-cell responses were observed post-vaccination in mice and NHPs, providing further evidence that a Th2-biased response is not occurring • Robust neutralizing antibody response in and efficacy following vaccination with mRNA-1273 strengthens the argument that disease enhancement is unlikely • Lung histopathology analysis of mice and NHPs challenged post-vaccination did not show evidence of enhanced disease

1 mRNA-1273 elicits high binding and neutralizing antibody titers in multiple mouse strains

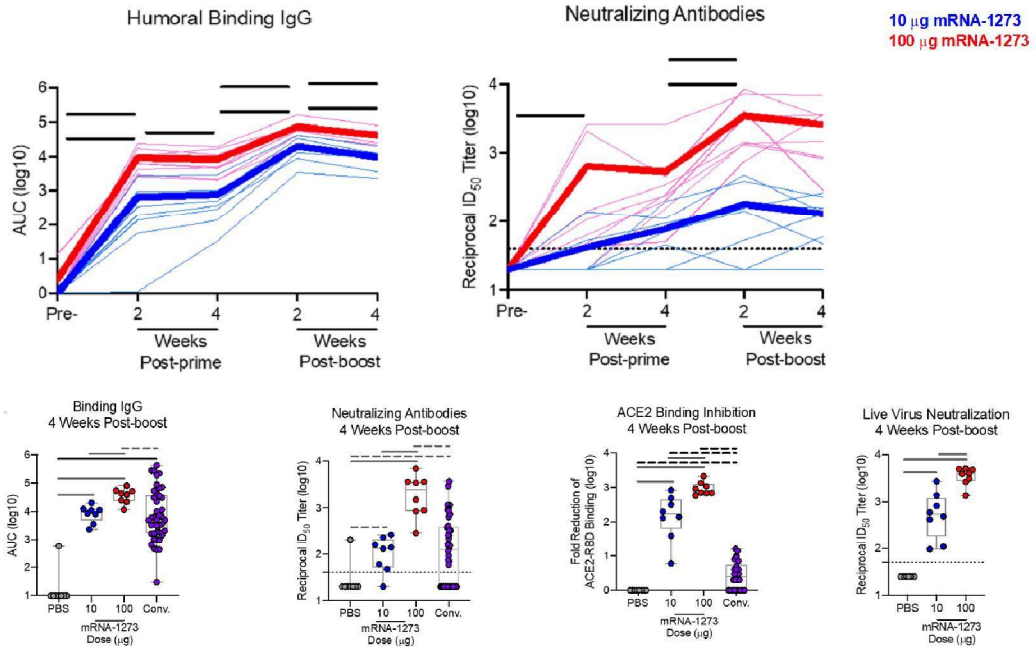


Source: Nature

Key takeaways

- Vaccination induced significant binding and neutralizing antibody responses in all three mouse strains evaluated
  - Neutralizing antibody responses at a dose of 0.1 µg were only detected in B6C3 mice
- Boost led to significantly higher binding antibody responses at both doses of 0.1 and 1 µg

1 mRNA-1273 generates a robust immune response in NHPs

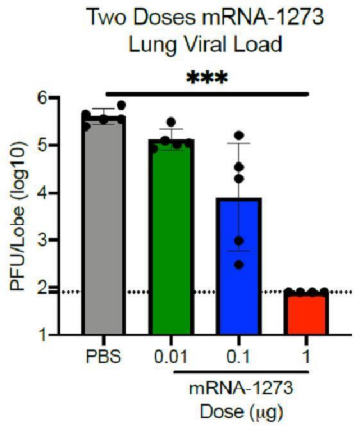


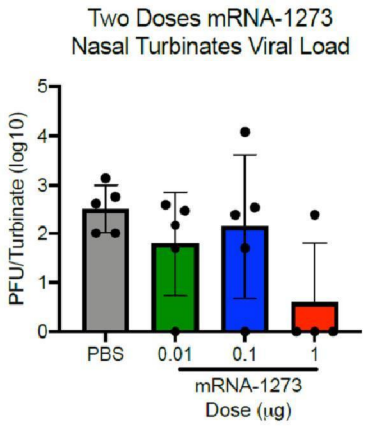
Source: NEJM

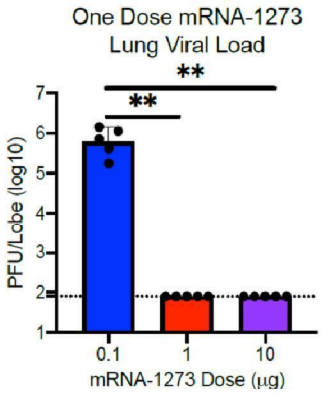
Key takeaways

- **mRNA-1273 elicits robust binding and neutralizing antibody responses in NHPs,** in particular at 100 µg dose
- Relative to convalescent sera, **binding and neutralizing antibody titers for the 100 µg group were 5- and 15-fold higher, respectively**
  - The same convalescent sera samples were evaluated in this study and alongside the phase 1 clinical trial samples

2 Prime-boost and prime only vaccination of mRNA-1273 was able to protect mice from challenge with SARS-CoV-2





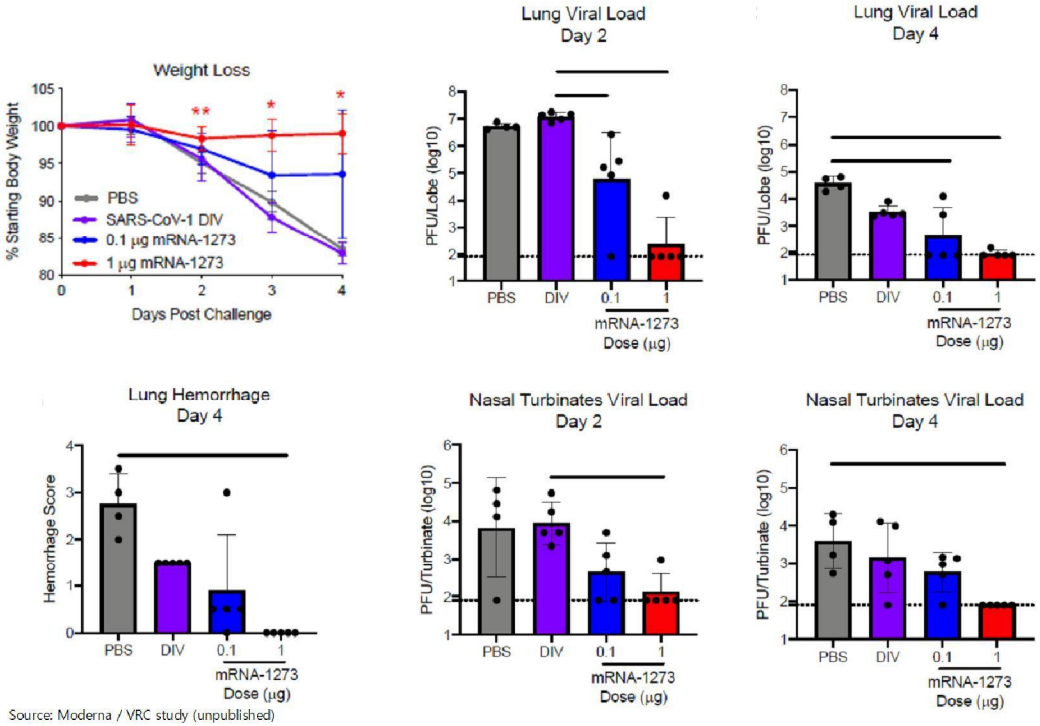


Key takeaways

- Prime-boost vaccination at 0 and 3 weeks is fully protective in the lungs at a dose of 1 µg dose
  - Decreased viral titers were observed at 0.1 µg dose, indicating some protection even in the absence of detectable levels of neutralizing antibodies
- A single dose of mRNA-1273 was fully protective at doses of 1 and 10 µg

Source: Nature

❷ Aged mice are protected by mRNA-1273 and show no sign of disease enhancement



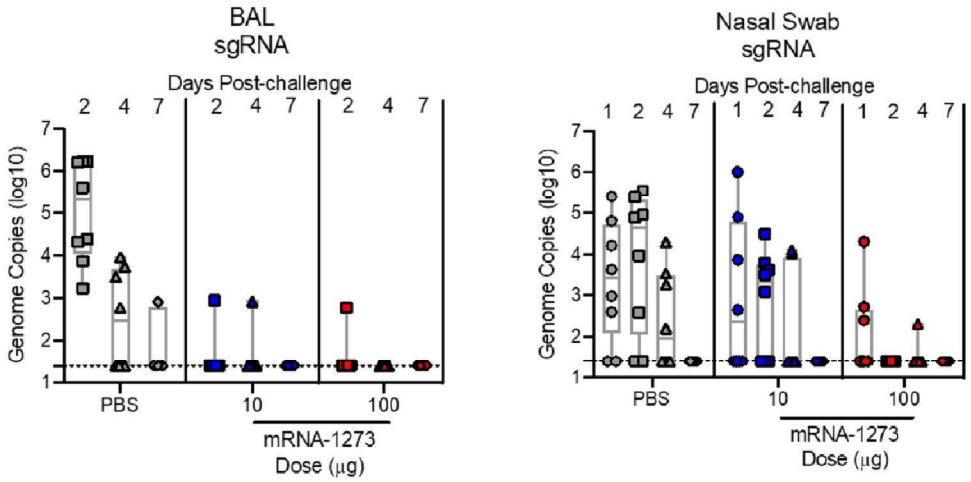
Source: Moderna / VRC study (unpublished)

Unpublished, confidential data

Key takeaways

- mRNA-1273 protects aged BALB/c mice from SARS-CoV-2 disease in a dose-dependent manner, with breakthrough at the 0.1 µg dose
- Sub-protective doses of mRNA-1273 do not lead to enhanced weight loss, viral load, or lung hemorrhage, suggesting disease enhancement is unlikely
- SARS-CoV DIV does not protect aged BALB/c mice from SARS-CoV-2 disease and does not lead to enhanced weight loss, viral load, or lung hemorrhage

❷ mRNA-1273 is fully protective in the lung and nose in NHPs



Note: *Subgenomic RNA (sgRNA) PCR measures replicating virus, while PCR can be used to assess both replicating and non-replicating virus*

Key takeaways

- Vaccination with 100 µg of mRNA-1273 is **fully protective in the lung and the nose**
- 10 µg of mRNA-1273 is fully **protective in the lung** and partially protective in the nose

Source: NEJM

Includes unpublished / confidential data

Summary slide

- Moderna's platform mRNA/LNP technology allowed for **rapid response** to the pandemic
- Our platform engages our immune system
  - Engaging non-specific response elements (**innate response**) to activate the immune system
  - Drives **adaptive response** that include robust T-cell and B-cell memory
- Non-clinical and clinical evaluations to date demonstrate that mRNA-1273 is mRNA-1273 is
  - **Safe and well tolerated**
  - **Immunogenic**
  - Drives a robust SARS-CoV-2 specific **antibody** and **T-cell** response
- Nonclinical animal challenge studies demonstrate that mRNA-1273:
  - **Fully protects animals** from challenge at dose levels as low as 1 µg/dose in mice and hamsters and 30 µg/dose in NHPs
  - **Does not lead to enhanced respiratory disease** (ERD) at protective or sub-protective dose levels
- Clinical:
  - mRNA-1273 is currently being evaluated in a Phase 3, 30,000 subject trial in the US

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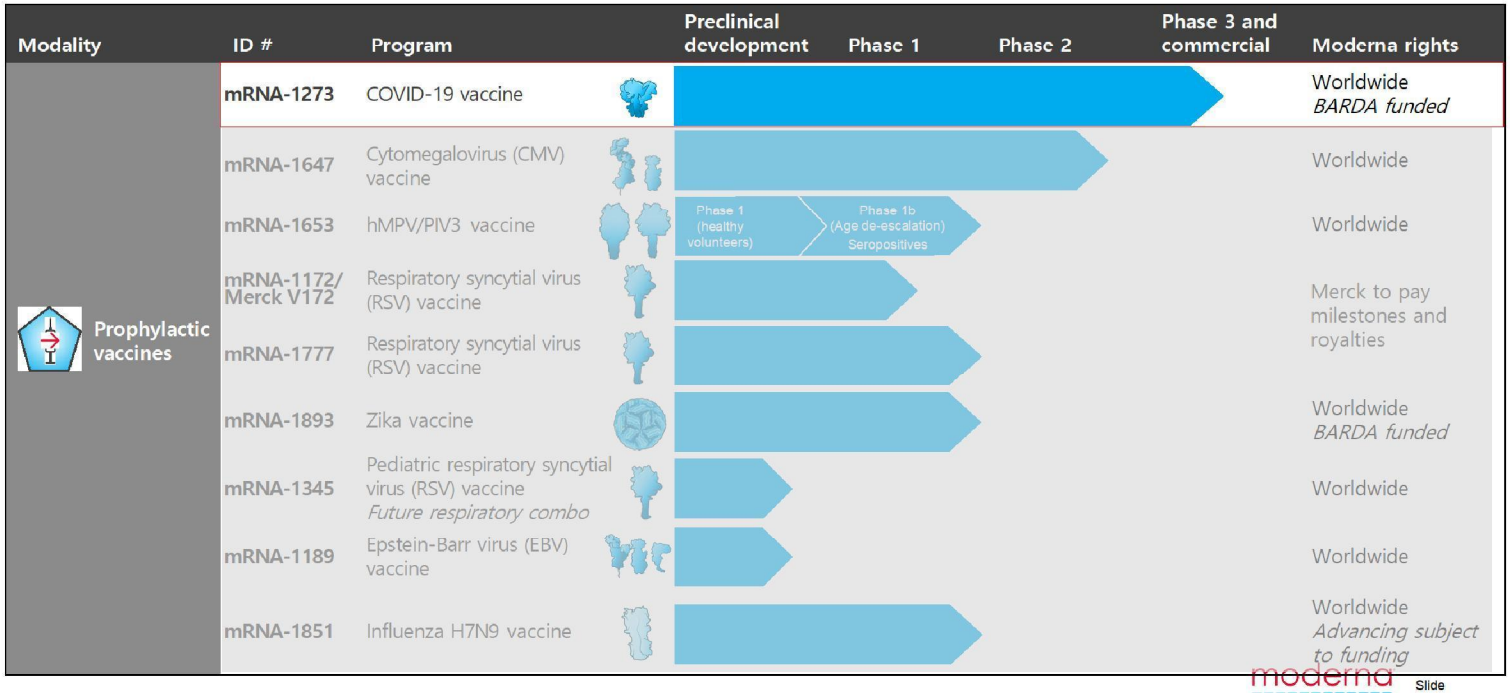
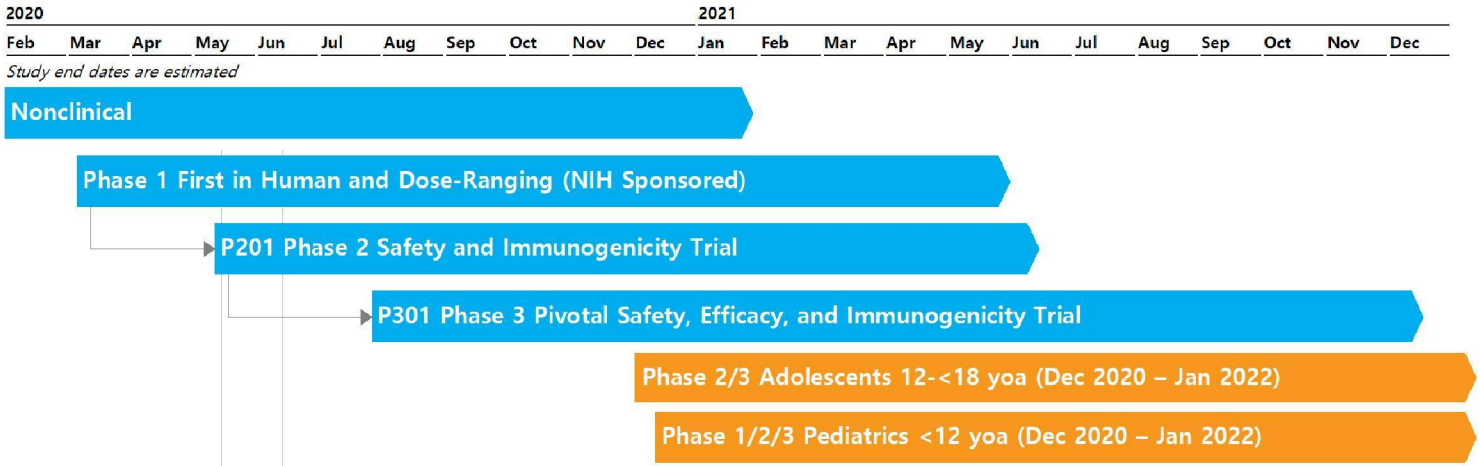
mRNA-1273 Clinical Development Program

Moderna's Prophylactic Vaccines in Clinical Development



27 Oct 2020

mRNA-1273 Clinical Development Plan



Dose Selection for P301
Safety and immunogenicity P101
Response relative to convalescent sera

Data Package Required Prior to Start
P301 Safety & immunogenicity from P101 (post-dose 2 data for 100ug cohorts)
P201 safety report from SMC
Animal model data demonstrating nAbs, protection from challenge, Th-1-biased CD4+ T-cells and protection from ERD

Other populations for further evaluation *(timing TBD)*
Pregnant women
Immunocompromised populations

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mRNA-1273 NIH-Sponsored, Phase 1, Safety and Dose-Ranging Study (N=120)

Phase 1 trial overview (NCT04283461)

Protocol Title: **Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults**

Study Groups

Cohorts[1]	Age groups	Dosage (D1, D29)	Sample size	Enrollment status
1-3	18 to 55	25, 100, 250 mcg	45	Fully enrolled (45/45)
4, 5	56 to 70	25, 100 mcg	20	Fully enrolled (20/20)
7, 8	≥71	25, 100 mcg	20	Fully enrolled (20/20)
10-13	18-55, 56-70, ≥71	50 mcg	35	Fully enrolled (35/35)

Population: Healthy males and females at or above 18 years of age
"All-comers" with regard to SARS-CoV-2 serostatus (baseline serology will be collected)

Study Endpoints: Safety (solicited AR x 7 days post each injection; unsolicited AE 28 days post-vaccination; SAE and MAAE)
Immunogenicity (e.g., ELISA, pseudoneutralization, live virus neutralization and intracellular cytokine staining assay)

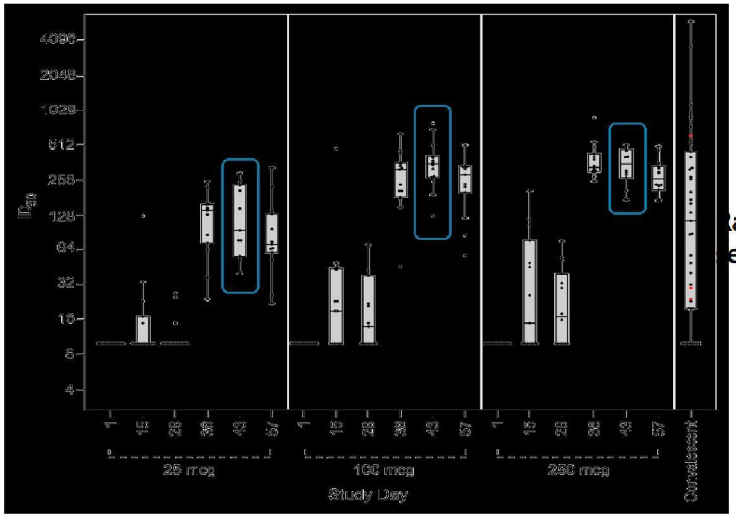
Study duration: Approximately 13 months for each participant corresponding to a 12-month follow up after the last vaccine administration

1. Cohorts 6 and 9 (250 mcg cohorts) will not be enrolled on this study

Jackson L, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2- preliminary report. N Engl J Med. 14 Jul 2020; DOI: 10.1056/NEJMoa2022483

Dose selection of 100 mcg was based on comparable nAb titers to 250 mcg with improved safety profile

Pseudovirus neutralization assay titers (ID_{50}): age 18 – 55 Years



ange of convalescent era

Key Takeaways

- Day 14 post-dose 2, nAbs were observed in all participants
- The lowest responses were in the 25 mcg dose group
- Responses in the 100 mcg and 250 mcg groups were similar to the upper half of the range of convalescent sera

Jackson L, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2- preliminary report. N Engl J Med. 14 Jul 2020; DOI: 10.1056/NEJMoa2022483

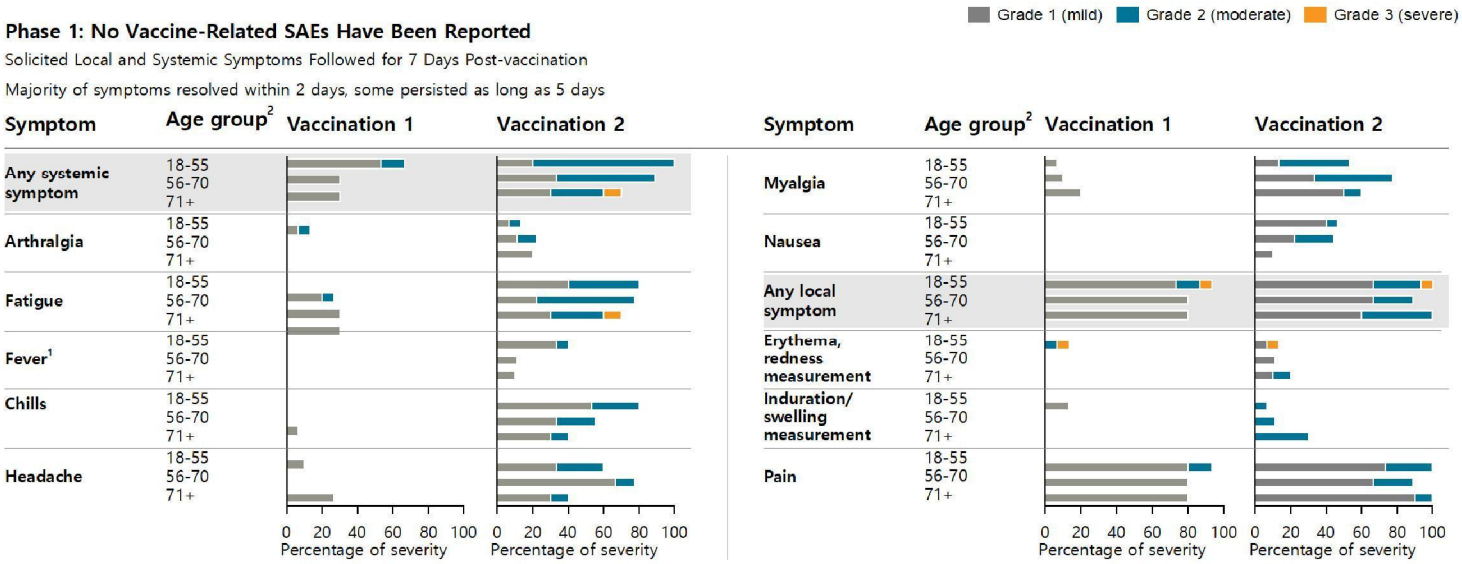
Interim unpublished data

100 mcg mRNA-1273 Well-Tolerated Across Age Groups

Phase 1: No Vaccine-Related SAEs Have Been Reported

Solicited Local and Systemic Symptoms Followed for 7 Days Post-vaccination

Majority of symptoms resolved within 2 days, some persisted as long as 5 days

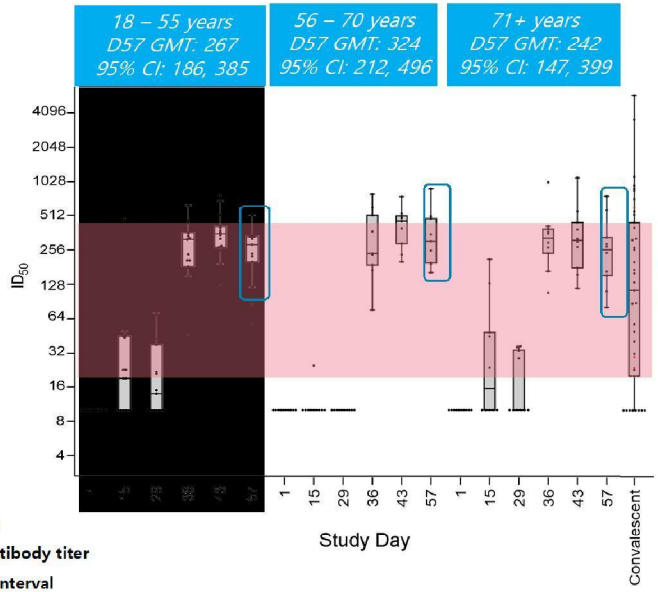


1. Fever percentages reflect the number of subjects with at least one measurement available in the data system as the denominator. This denominator may differ from other systemic symptoms, which are solicited in-clinic at the post-dose assessment
2. 18-55: N=15; 56-70: N=10; 71+: N=10; N = All subjects receiving Dose 1 with any solicited event data recorded in the database

Jackson L, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2- preliminary report. N Engl J Med. 14 Jul 2020; DOI: 10.1056/NEJMoa2022483

SARS-CoV-2 nAb Comparable Across Age Strata and to Convalescent Sera out to Day 57 PD2

Pseudovirus neutralization assay titers (ID50)- 100 µg at Day 1 and Day 29



Range of convalescent sera

D57: one month post-do

GMT: geometric mean antibody titer

95% CI: 95% confidence interval

PD2= Post-dose 2

Vaccination administered at Day 1 and Day 29

Jackson L, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2- preliminary report. N Engl J Med. 14 Jul 2020; DOI: 10.1056/NEJMoa2022483

Interim unpublished data

Key Takeaways

- PD2 pseudovirus neutralization responses were detected in all participants
- PsV titers were comparable across age groups
- PsV median titer for 56-70 and 71+ YOA above convalescent sera median titer at Day 57 PD2

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Phase 2 Dose Confirmatory Study to Evaluate Safety and Immunogenicity of mRNA-1273 (N=600)

Phase 2 trial overview (NCT04405076)

Protocol Title

A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

Study Groups

Cohorts	Age groups	Dosage IM (D1, D29) 1:1:1	Sample size	Enrollment status
Cohort 1	18 to <55	50mcg, 100mcg, placebo	300	Fully enrolled (300/300)
Cohort 2 Sentinel	≥55	50mcg, 100mcg, placebo	50	Fully enrolled (50/50)
Cohort 2 Full	≥55	50mcg, 100mcg, placebo	250	Fully enrolled (250/250)

Participant Population

Healthy males and females at or above 18 years of age

"All-comers" with regard to SARS-CoV-2 serostatus (baseline serology will be collected)

Study Endpoints

Safety (solicited AR x 7 days post each injection; unsolicited AE to day 57; SAE and MAAE throughout the study); assessment of any cases of Covid-19; potential assessment for asymptomatic infection

Immunogenicity (ELISA, nAb)

Study Duration

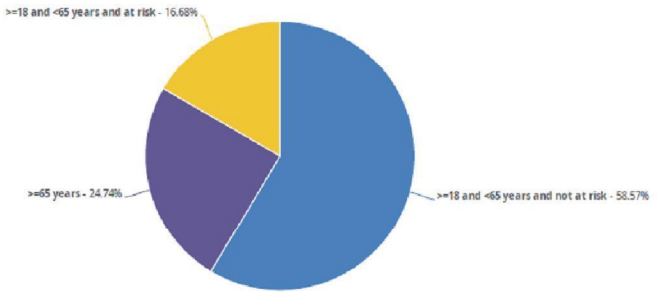
Approximately 13 months for each participant corresponding to a 12-month follow up after the last vaccine administration

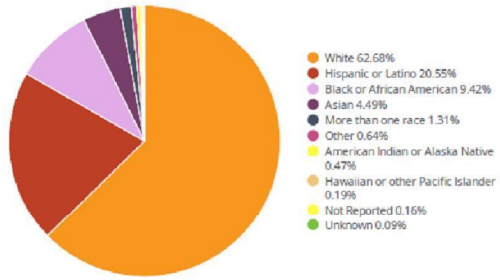
Pivotal Phase 3 Efficacy, Safety and Immunogenicity Study (N=30,000)

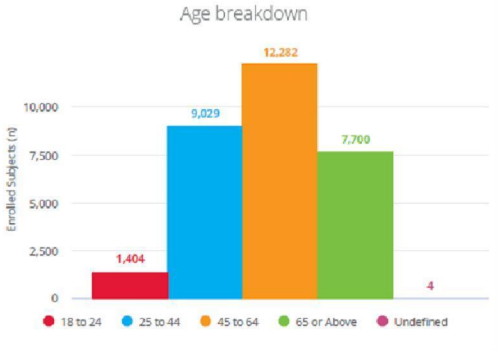
Phase 3 trial overview (NCT04470427)

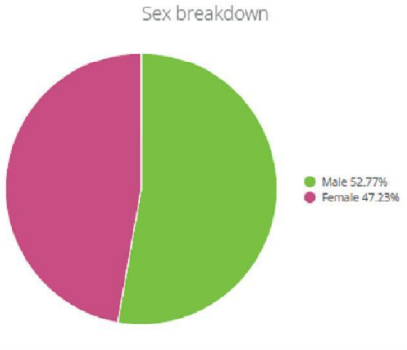
Protocol Title	A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older			
Study Groups	**Strata**	**Dosage IM (D1, D29) 1:1**	**Sample Size**	**Enrollment status**
	≥ 65 years	100mcg, placebo	25-40%	Started July 27
	< 65 years at increased risk for complication of COVID-19 ("at risk")	100mcg, placebo		Started July 27
	< 65 years and not at risk	100mcg, placebo	60-75%	Started July 27
Participant Population	Approximately 30,000 participants (case driven) whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection "All-comers" with regard to SARS-CoV-2 serostatus (baseline serology will be collected)			
Study Objectives	To demonstrate the efficacy of mRNA 1273 to prevent COVID 19 To evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart			
Study Duration	Approximately 25 months for each participant corresponding to a 24-month follow up after the last vaccine administration			

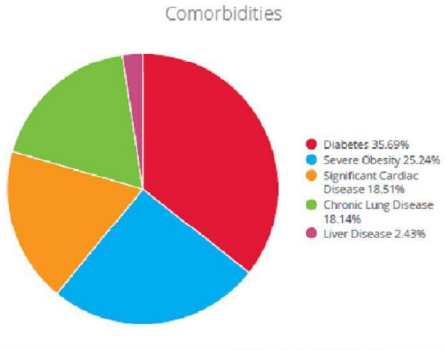
Overall Study Demographics at Study Completion











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Summary

- mRNA-1273 encodes the pre-fusion-stabilized Spike protein (S-2P) in a Lipid Nanoparticle
- Pre-clinical data have demonstrated induction of neutralizing Abs and protection against viral challenge in mice and Non-Human Primates
- Interim data from Phase 1 study indicate that a 100 mcg dose of vaccine:
  - Is generally well-tolerated across age strata, with solicited symptoms mostly mild-to-moderate in severity and self-limited duration
  - Induces neutralizing Abs in the upper half of the range of convalescent serum across age strata, with the induction of Th-1 biased, CD4+ T-cells
- Phase 2 and the Phase 3 COVE study are underway

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Manufacturing Plans of mRNA-1273

Moderna manufacturing collaborations

United States

moderna + Lonza (US)

Pharma & Biotech

Catalent

Independent supply chains

Manufacturing scale up to supply 500 million to 1 billion doses per year

International

Lonza (Switzerland)

Pharma & Biotech

ROVI (Spain)

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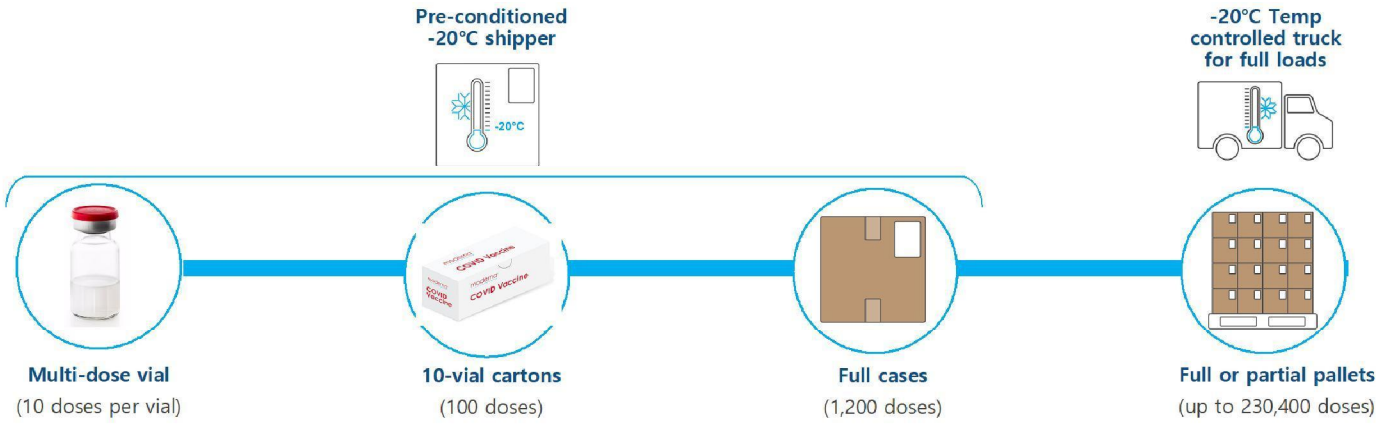
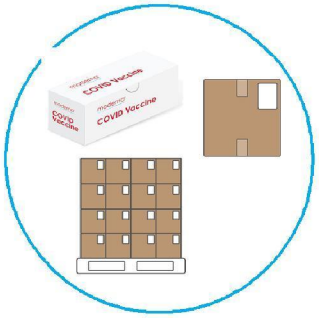
Slide

From manufacturing to distribution

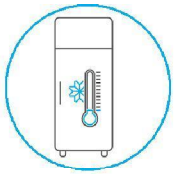


Distribution to any immunization locations using existing infrastructure



Ship any configuration using existing infrastructure

Storage Conditions*

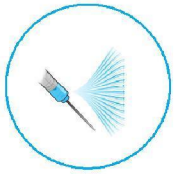


Freezer: -20°C/-4°F for 6 months

+

Fridge: 2-8°C/~36-46°F for up to 7 days

+



Room temperature: 12 hours post thaw

Flexible and adaptable supply chain

Uses standard existing vaccination infrastructure

No dilution required

*Shelf life is expected based on current data available; Product characteristics subject to regulatory review and approval

Thank you and Q&A