



mRNA-1273 Clinical Development Program

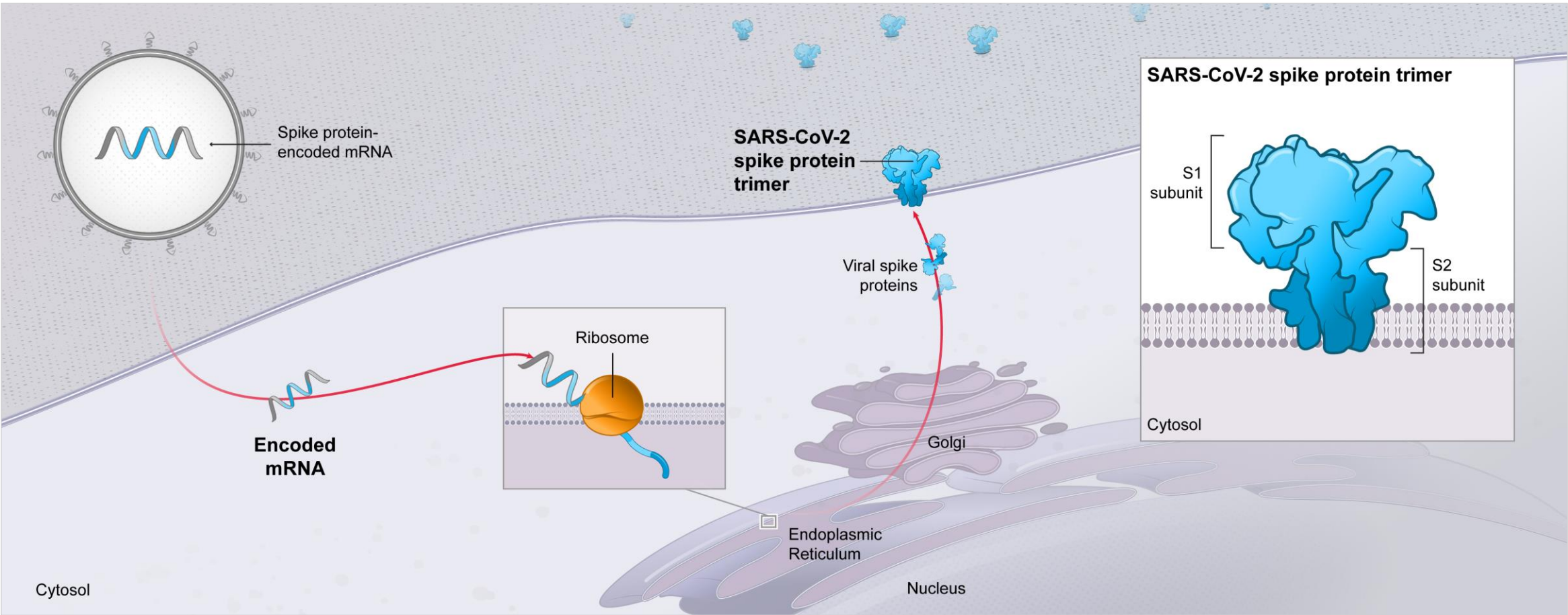
Jacqueline M. Miller, M.D., F.A.A.P.

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



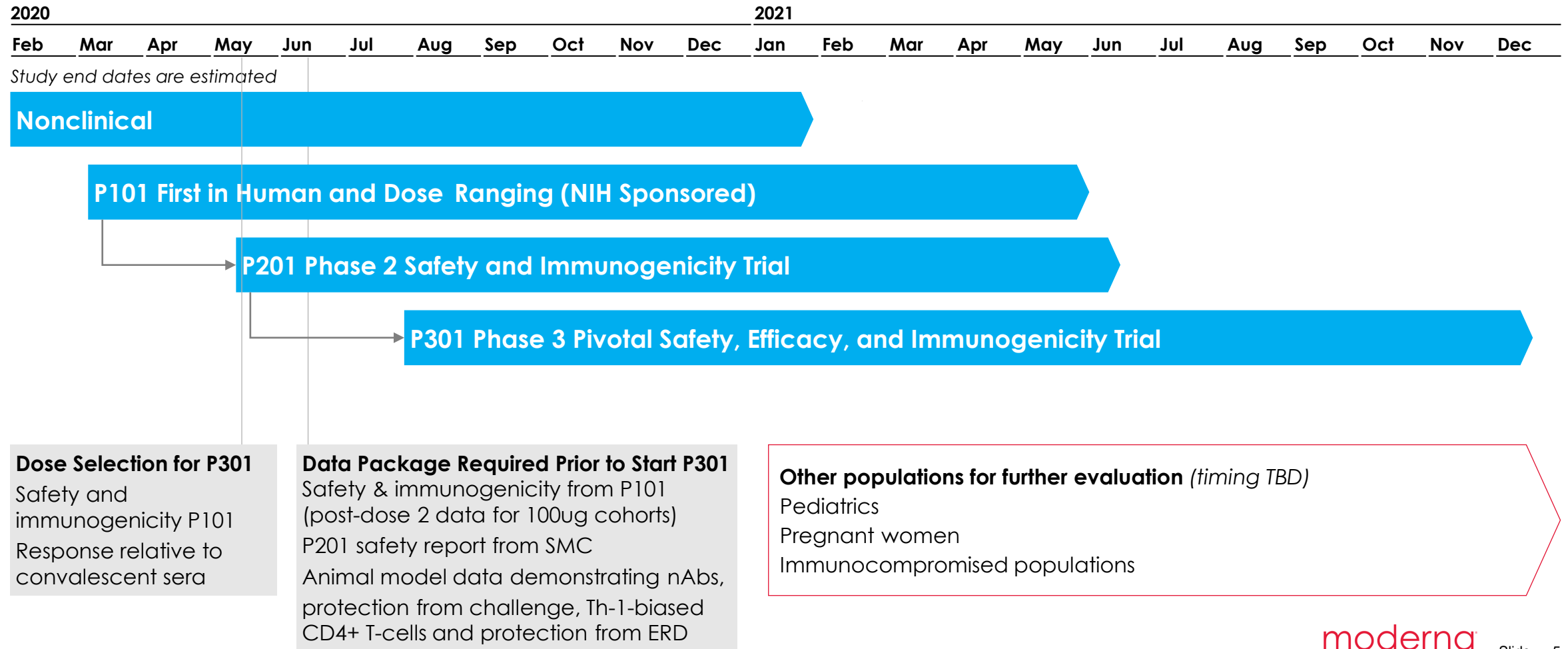
Pre-clinical data support human clinical trials with mRNA-1273

- Robust neutralizing antibody responses in mice¹, aged mice, and non-human primates (NHPs)² have been induced
- mRNA-1273 demonstrated robust protection against lung challenge in mice¹, and pulmonary and nasal challenge in NHPs²
- No indication of enhanced respiratory disease after viral challenge even when subprotective doses of mRNA-1273 are used²
- A Th1-dominant phenotype of CD4+ T-cells has induced in mice¹ and NHPs²

1. Corbett KS, Edwards D, Leist SR, et al. SARS-CoV-2 mRNA vaccine development enabled by prototype pathogen preparedness. *Nature* 2020; *Nature* 2020; DOI: 10.1038/s41586-020-2622-0

2. Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primate. *N Engl J Med*. 28 July 2020; DOI: 10.1056/NEJMod2024671.

mRNA-1273 Clinical Development Plan



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 | Cohorts¹ | 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)

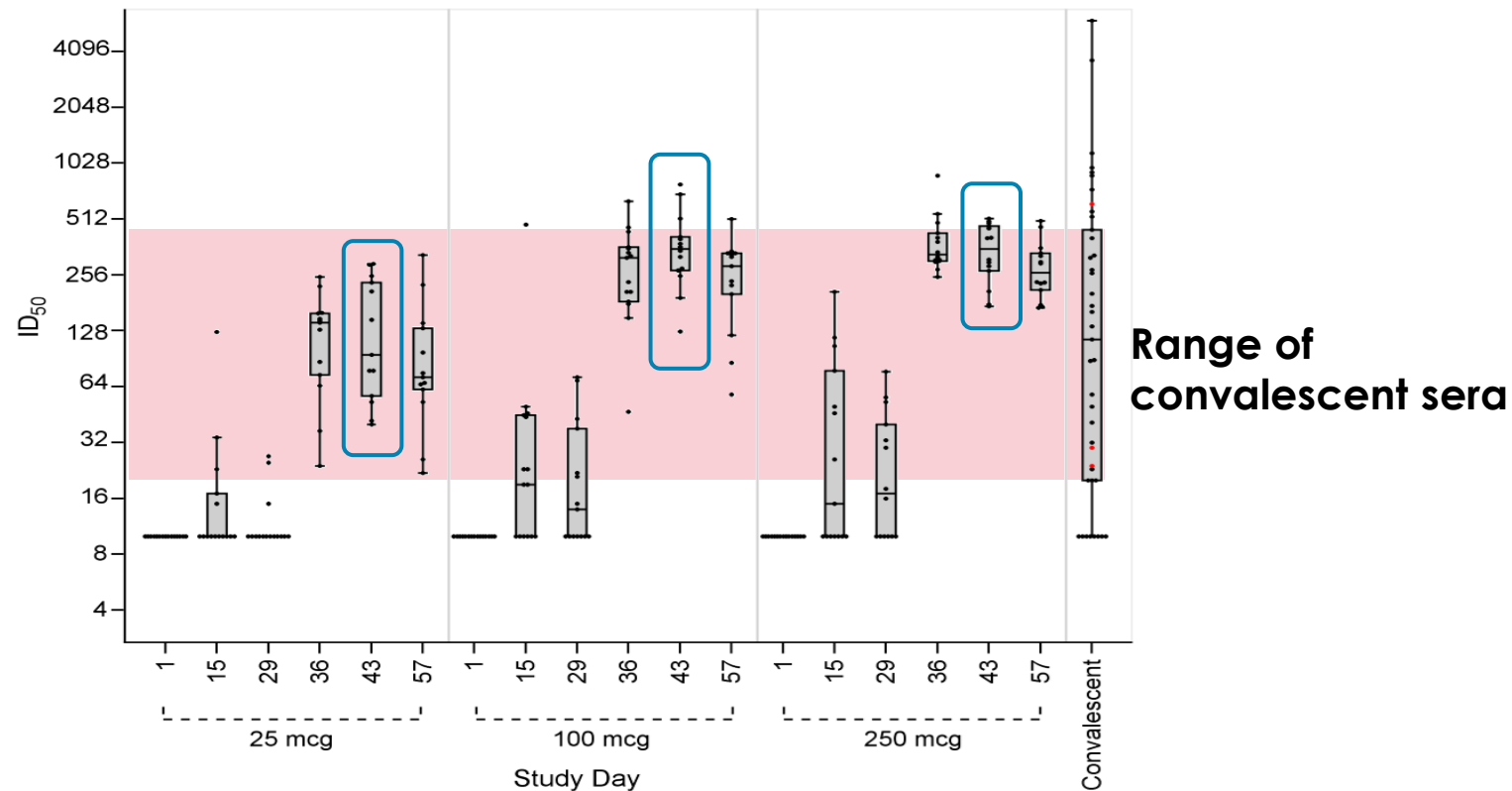
Study Endpoints Safety (solicited AR x 7 days post each injection; unsolicited AE 28 days post-vaccination; SAE and MAAE)
Immunogenicity (e.g., ELISA, pseudoneutralization, live virus neutralization and intracellular cytokine staining assay)

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, Roupael 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 (ID₅₀): age 18 – 55 Years



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

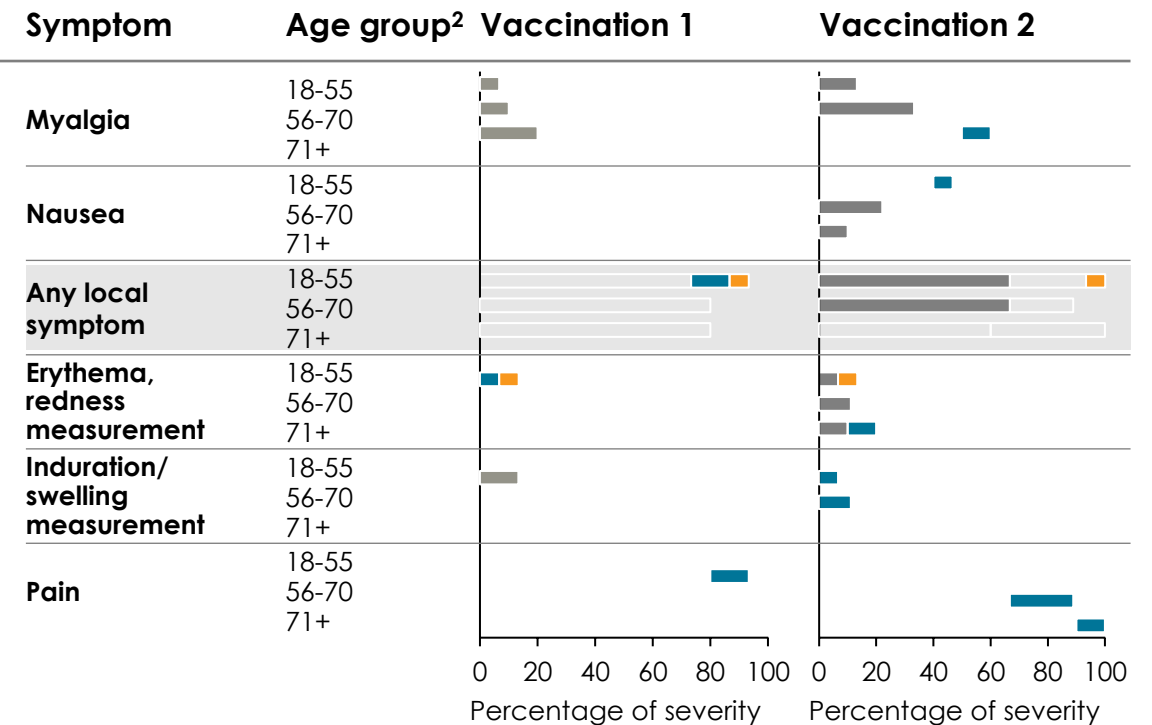
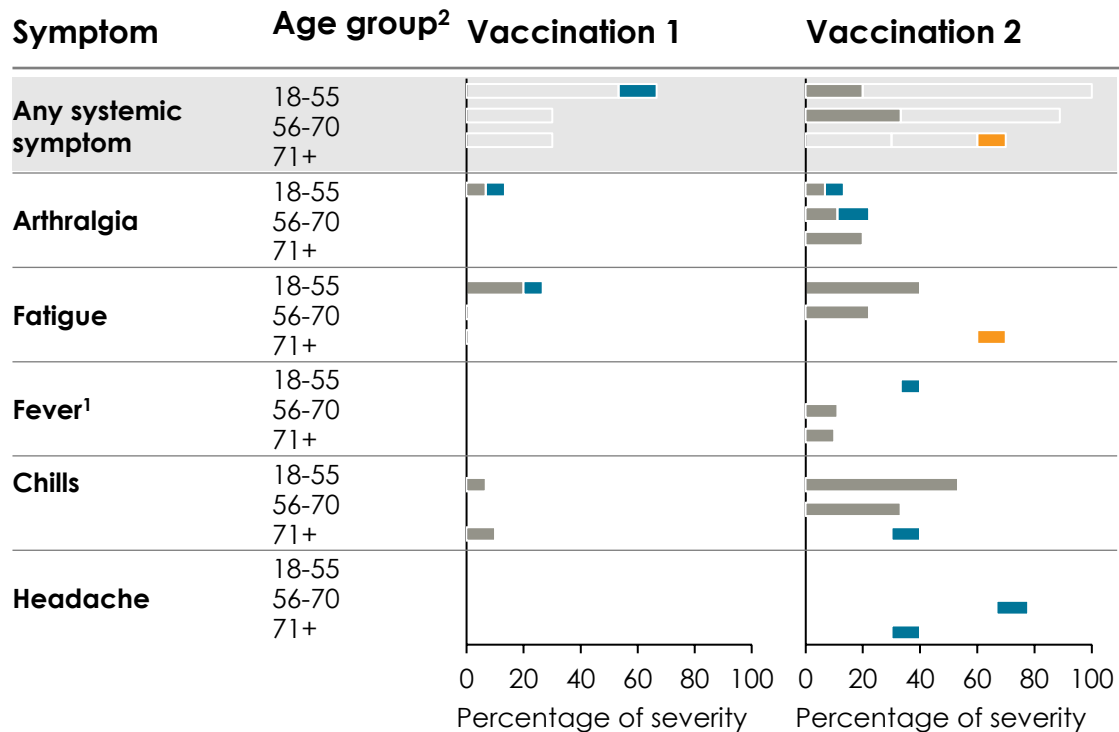
100 mcg mRNA-1273 Well-Tolerated Across Age Groups

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

■ Grade 1 (mild) ■ Grade 2 (moderate) ■ Grade 3 (severe)

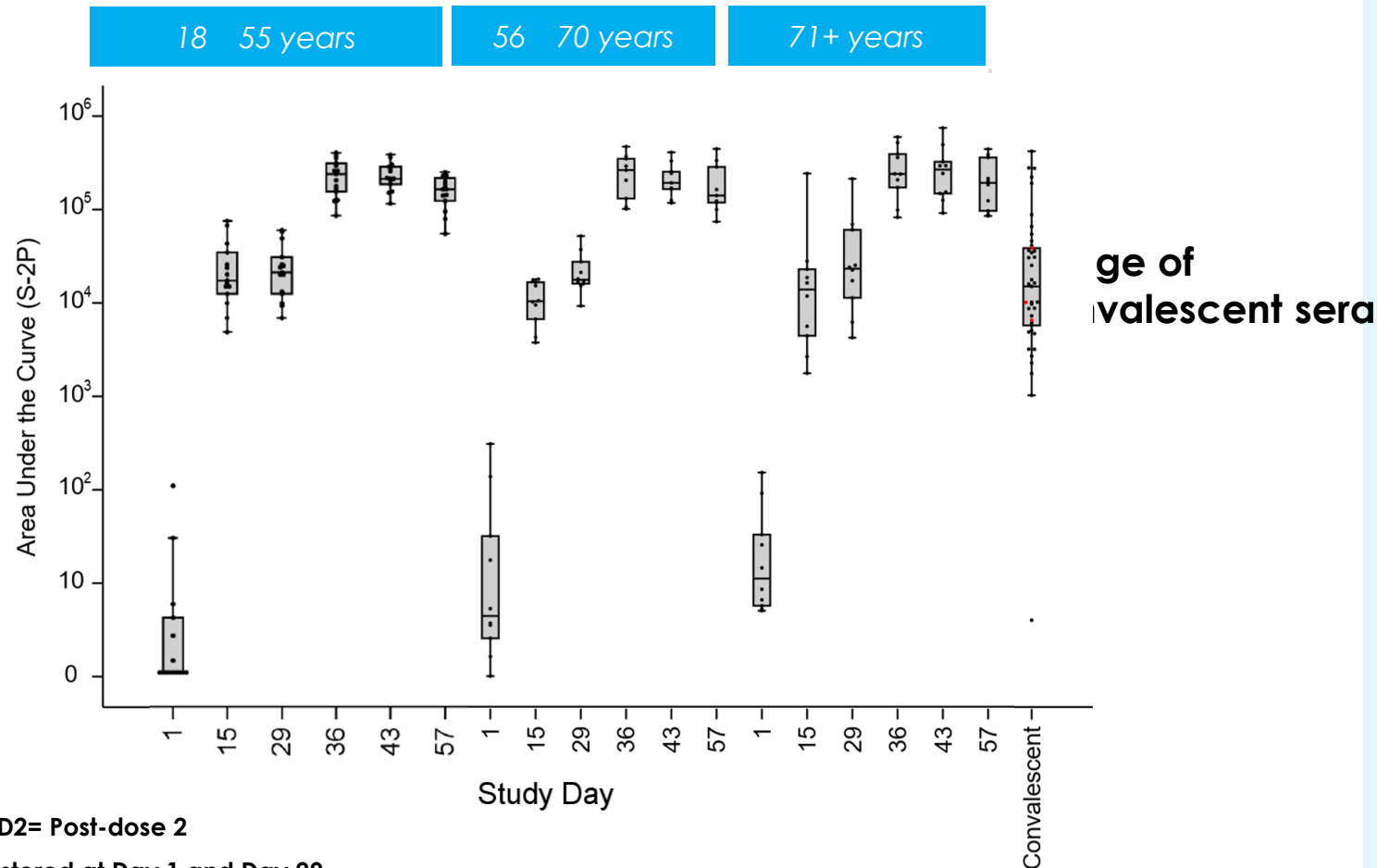


1. Fever percentages reflect the number of subjects with at least one measurement available in the data system as the denominator. This denominator may differ from other systemic symptoms, which are solicited in-clinic at the post-dose assessment

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

Anti-S-2P Binding Ab (ELISA) Comparable Across Age Strata and to Convalescent Sera at one month PD2

S-2P binding antibodies (ELISA)- 100 µg at Day 1 and Day 29



PD1= Post-dose 1; PD2= Post-dose 2

Vaccination administered at Day 1 and Day 29

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

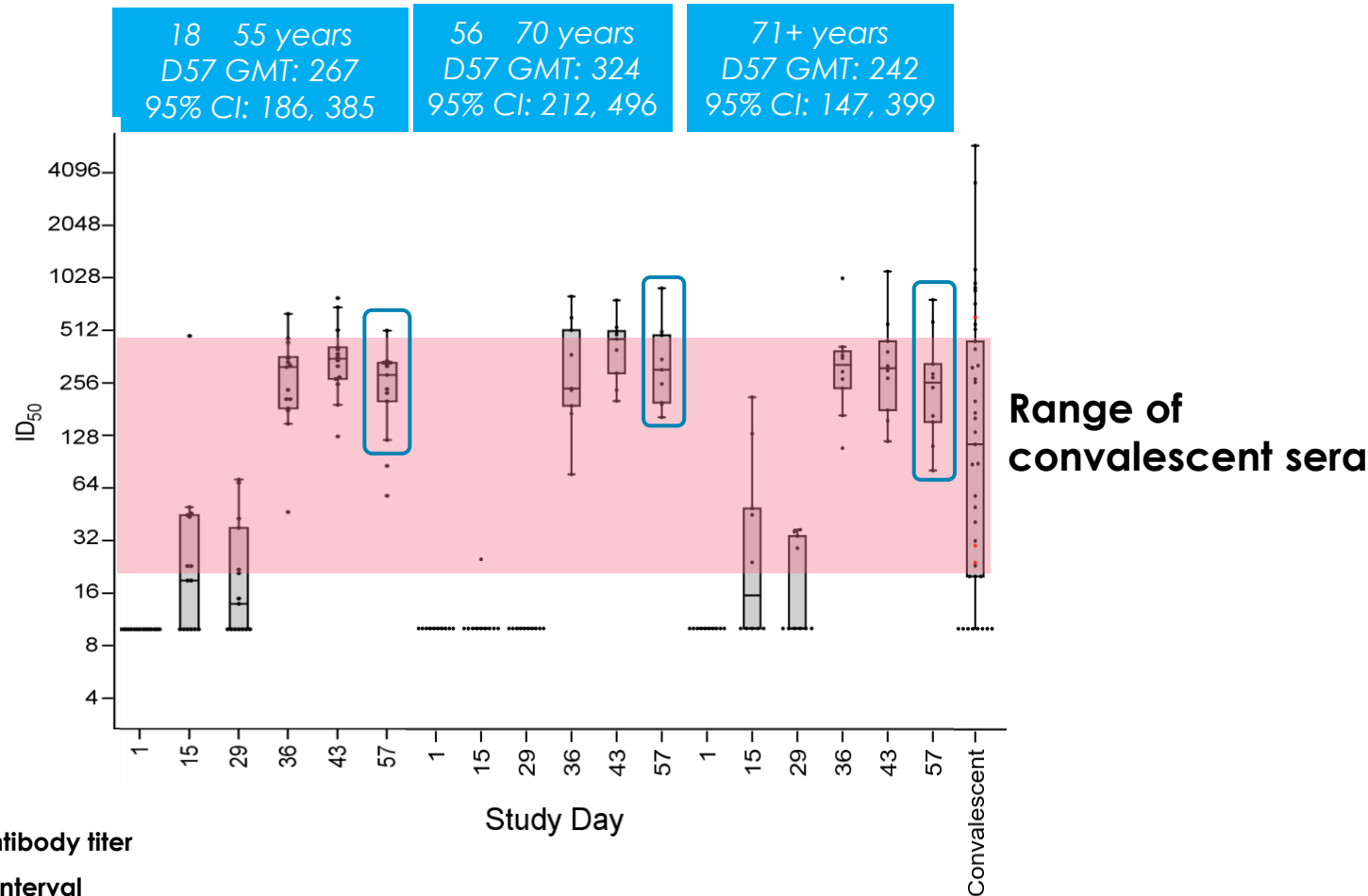
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Key Takeaways

- 100 mcg two-dose series seroconverted all participants PD1
- PD1 AUC for all age groups exceeded the median of convalescent sera
- PD2 all age groups is equivalent to high-titer convalescent sera (i.e., upper quartile)

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



D57: one month post-dos

GMT: geometric mean antibody titer

95% CI: 95% confidence interval

PD2= Post-dose 2

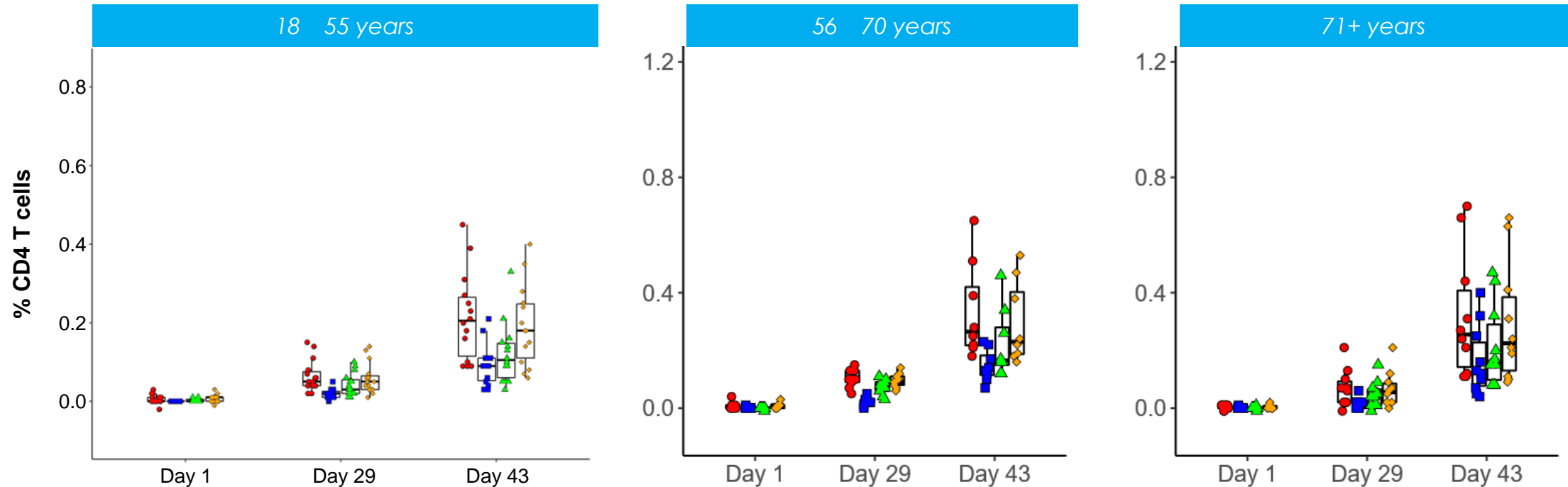
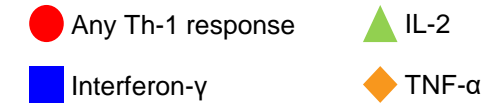
Vaccination administered at Day 1 and Day 29

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

mRNA-1273 induces CD4+ T-cells of the Th-1 Phenotype 14 days PD2

Th1 CD4+ T cell response, S1 peptide pool (100 µg at Day 1 and 29)



Key Takeaways

- Vaccination with 100 mcg mRNA-1273 led a Th1-biased CD4+ T-cell response across all age groups
- Th2 phenotype was rare (data not shown)

mRNA-1273 Phase 2 Study will Evaluate Safety and Immunogenicity of 50 mcg and 100 mcg (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

Primary Efficacy Endpoint: COVID-19 Disease Case Definition

To be considered a case of COVID-19 for the evaluation of the Primary Efficacy Endpoint, two criteria must be met:

- 1 The participant must have experienced:
 - At least **TWO** of the following systemic symptoms: fever ($\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s)
- OR**
- At least **ONE** of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia
- AND**
- 2 The participant must have at least one NP swab, nasal swab or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR

Primary analysis set is seronegative and negative NP swab at baseline without major PD (Per Protocol)

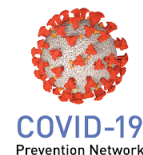
COVE D&I Advisory Committee

Remit and Role of Advisory Committee:

1. Review enrollment, race, and ethnicity demographics on a weekly basis
2. Review current outreach activities and outcomes
3. Review strategies to ensure participation of individuals from communities significantly impacted by COVID-19
4. Support the development and implementation of retention strategies



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- National Institute on Allergy and Infectious Diseases
- National Institute on Minority Health and Health Disparities
- NIH, Tribal Health Research Office
- NHLBI

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Slide

Limitations of Research

- Limited safety and immunogenicity data in a fairly homogeneous population
- Further evaluation needed in terms of vaccine use in:
 - Pediatric subjects
 - Pregnant women
 - Immunocompromised patients
- The ongoing COVE Study will provide significantly more data

Summary

- mRNA-1273 encodes the pre-fusion-stabilized Spike protein (S-2P) in a Lipid Nanoparticle designed for delivery to the APCs of the lymph node
- Pre-clinical data have demonstrated induction of neutralizing Abs and protection against viral challenge in mice and NHPs
- 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

APC – Antigen presenting cells

NHP – Nonhuman primate

Thank you to our collaborators

P101

- Division of Microbiology and Infectious Diseases, NIAID
- Vaccine Research Center (VRC), NIAID
- Coalition for Epidemic Preparedness Innovation
- Principal Investigators, Drs. Lisa Jackson (Kaiser Permanente Washington), Evan Anderson (Emory University School of Medicine), Nadine Rouphael (Emory University School of Medicine), Alicia Widge (VRC)
- The Emmes Company
- Denison Lab, Vanderbilt University
- Baric Lab, University of North Carolina
- Suthar Lab, Emory University
- Vaccine Immunology Program, NIAID
- Study sites, investigators and subjects

P201

- BARDA
- Study sites, investigators, and subjects

COVE Study (P301)

- BARDA
- Operation Warp Speed
- NIAID and the COVID-19 Prevention Network
- Members of Diversity and Inclusion Panel
- Principal Investigators, Drs. Brandon Essink (Meridian Clinical Research), Lindsey Baden (Brigham and Women's Hospital), Hana El Sahly (Baylor College of Medicine)
- Study sites, investigators, and subjects