Overview of Moderna's Investigational Next Generation COVID-19 Vaccine, mRNA-1283, in Individuals ≥12 Years of Age

ACIP

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COVID-19 Remains a Leading Cause of Hospitalization among Respiratory Viruses in the US

Risk Factors for Severe COVID Infection in the US[1]

Advancing Age

Adults ≥65 years account for:

- >60% of COVID-19 hospitalizations *(since 2023)*[2]
- ~76% of deaths *(since 2020)*[3]

Pre-Existing Chronic Conditions[4]

- 95% of adults hospitalized with COVID-19 have ≥1 underlying medical condition

Effective prophylactic approaches to address the burden of disease in vulnerable populations remain a high priority

1. https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html
2. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network
3. https://covid.cdc.gov/covid-data-tracker/#demographics
4. https://www.cdc.gov/pcd/issues/2021/21_0123.htm

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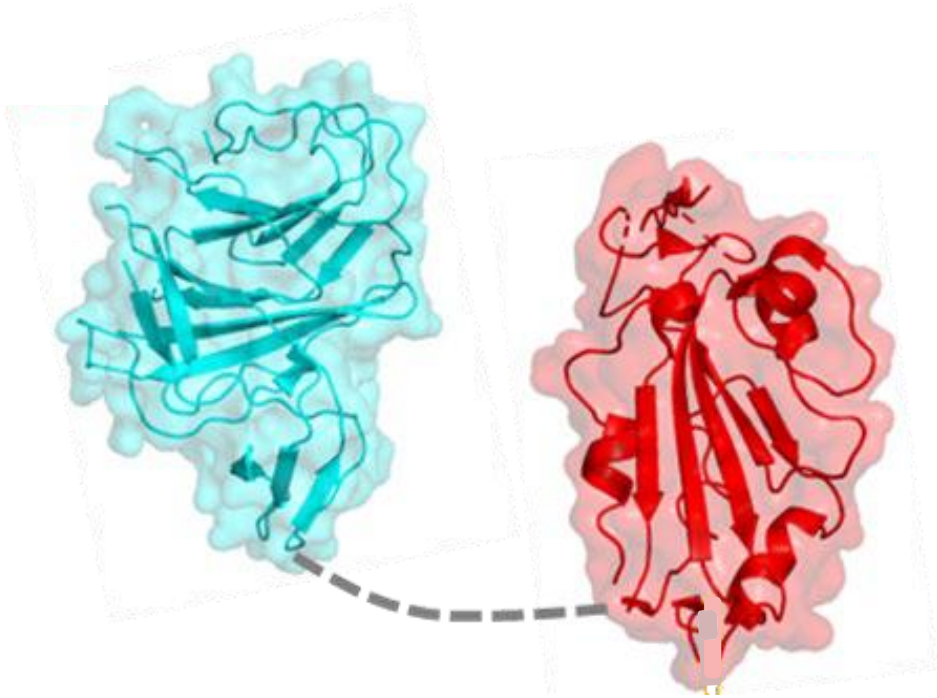
Design of mRNA-1283
Investigational Next Generation COVID-19 Vaccine

N-terminal Domain (NTD)



Receptor Binding Domain (RBD)

7-amino acid flexible linker

Lower mRNA dose (10 µg; 1/5th of dose of Spikevax)

1. Piccoli et al, Cell 2020 doi: 10.1016/j.cell.2020.09.037
2. Dejnirattisai et al, Cell 2021 doi: 10.1016/j.cell.2021.03.055
3. Cerutti et al, Cell Host Microbe 2021 doi: 10.1016/j.chom.2021.03.005

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Pivotal Safety, Immunogenicity and Relative Vaccine Efficacy Study

Study 301

Chalkias et al. *Lancet ID*, in press, 2025

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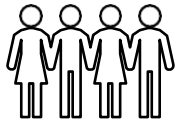
Study Design & Primary Objectives

Randomized, blinded, active-controlled phase 3 trial



Participants ≥12 years

1:1

N = 5,728

mRNA-1283 (10 µg)

Original: Omicron BA.4/BA.5 Bivalent Vaccine

N = 5,726

SPIKEVAX (mRNA-1273 - 50 µg)

Original: Omicron BA.4/BA.5 Bivalent Vaccine

Stratified randomization:
Age groups (12-17, 18-64, and ≥65)

Primary Objectives

Safety and Reactogenicity
mRNA-1283 & SPIKEVAX

Non-Inferior Immunogenicity
mRNA-1283 vs SPIKEVAX

Non-Inferior Relative Vaccine Efficacy (rVE)
mRNA-1283 vs SPIKEVAX
(based on CDC COVID-19 definition)

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Demographics and Baseline Characteristics Balanced Between Groups

Study 301 - Safety Set

	mRNA-1283 (10 µg) N = 5706	SPIKEVAX (50 µg) N = 5711
Mean age, years (range)	**51.1 (12, 96)**	**51.2 (12, 90)**
Median age, years	**56**	**55**
Age subgroup, % (n)		
12-17 years	**8.7%** (497)	**8.7%** (495)
18-64 years	**62.7%** (3575)	**62.6%** (3576)
≥65 years	**28.6%** (1634)	**28.7%** (1640)
Race/Ethnicity, % (n)		
White	**81.8%** (4670)	**82.5%** (4711)
Black or African American	**11.2%** (640)	**11.1%** (635)
Asian	**3.9%** (225)	**3.2%** (183)
Hispanic or Latino	**13.5%** (769)	**13.0%** (741)
≥1 pre-existing COVID-19 comorbidity (CDC definition)	**46.0%** (2626)	**46.6%** (2664)

Race/ethnicity generally representative of US population

https://www.cdc.gov/covid/risk-factors/index.html;; https://www.census.gov/quickfacts/fact/table/US/RHI225223

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Prior SARS-CoV-2 Infection and Time Since Last COVID-19 Vaccination Balanced Between Groups

Study 301 - Safety Set

- **Eligibility criteria:**
  - All study participants previously received primary series of COVID-19 vaccine
  - Adults ≥18 years received ≥1 dose beyond primary series

	mRNA-1283 (10 µg) N = 5706	SPIKEVAX (50 µg) N = 5711
Prior SARS-CoV-2 Infection[1]	**73.8%**	**74.8%**
Months since last COVID-19 vaccination, median (Q1, Q3)	**9.8** (7.6, 16.9)	**9.8** (7.7, 16.7)

1. Evidence of SARS-CoV-2 infection pre-study vaccination (defined by a positive RT-PCR test, and/or a positive serology test based on binding antibody specific to SARS-CoV-2 nucleocapsid)
2. Q - quartile

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Safety Results

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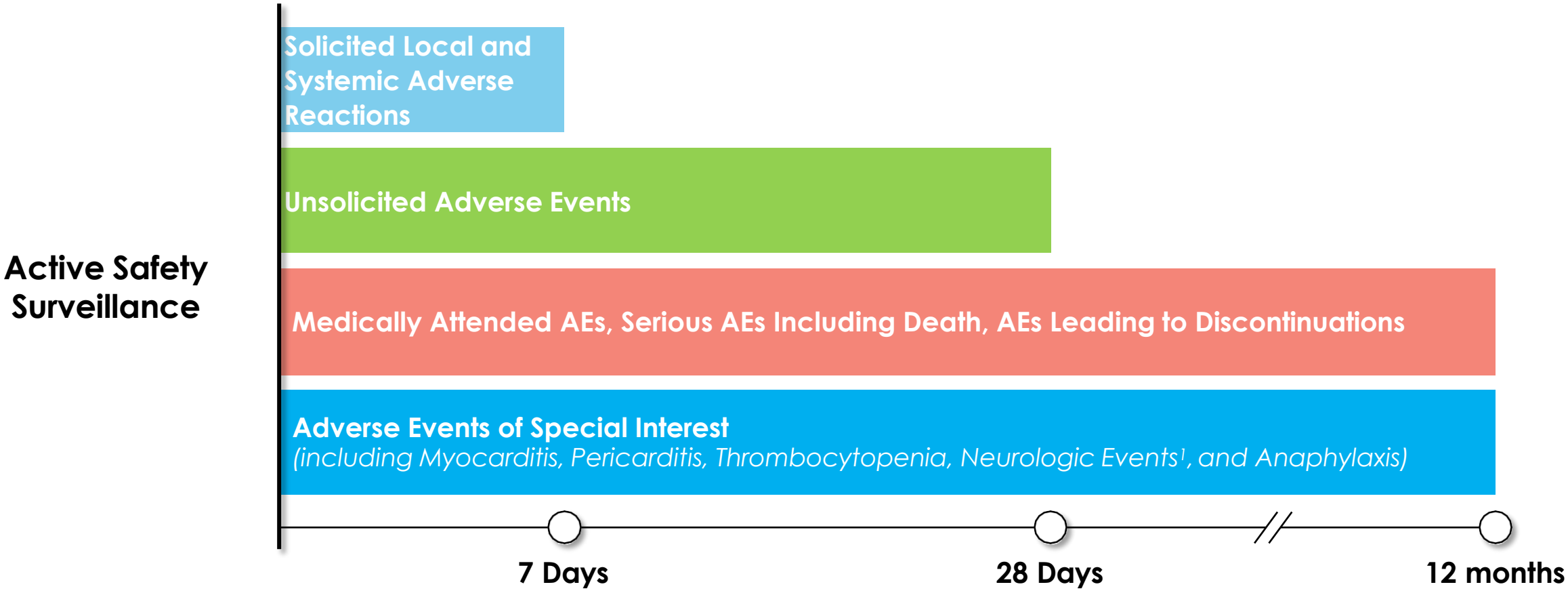
Primary Safety Endpoints and Duration of Follow-up

Study 301 Safety Set – Median 8.8 Months Follow-up

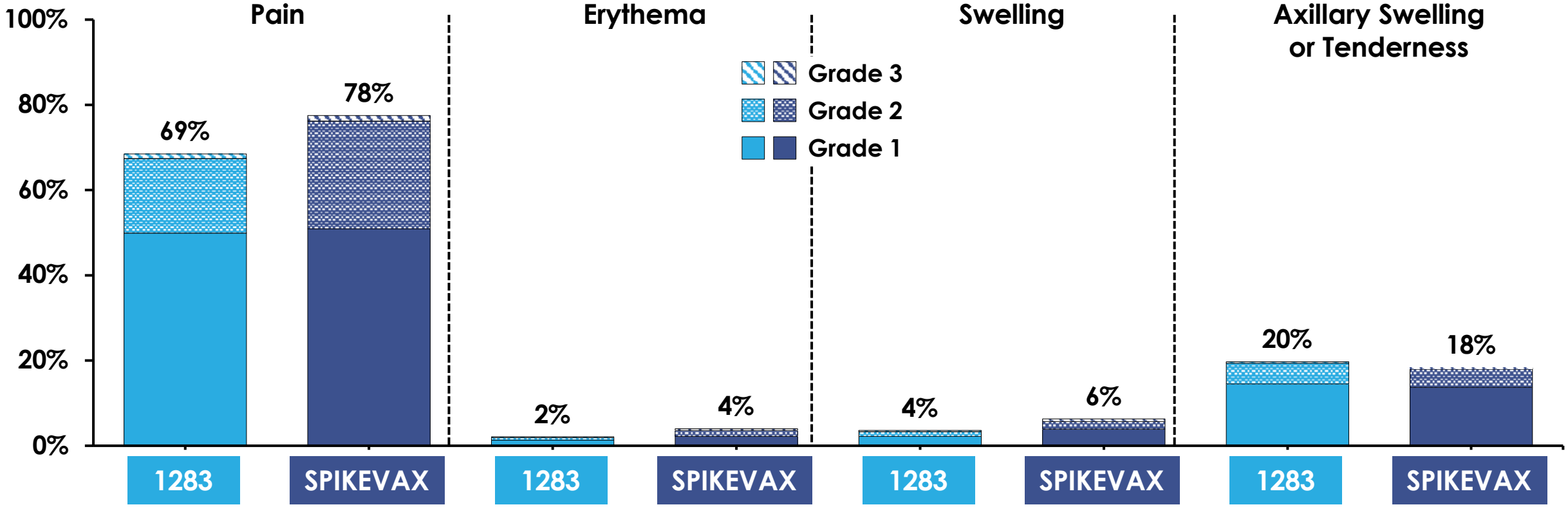


Trial overseen by independent Data and Safety Monitoring Board (DSMB)

1. Neurologic events of interest include Guillain-Barre syndrome, acute disseminated encephalomyelitis, Bell's palsy, and seizures; 2. AE – adverse event

Solicited Local Adverse Reactions within 7 Days of Vaccination with mRNA-1283 and SPIKEVAX

Study 301 – Solicited Safety Set



- Pain at the injection site was most frequently observed solicited local adverse reaction for both groups
- 1 – 2 days median duration for local adverse reactions

Feb 23, 2024 data cutoff; mRNA-1283, N = 5702; mRNA-1273, N = 5706; no grade 4 reactions

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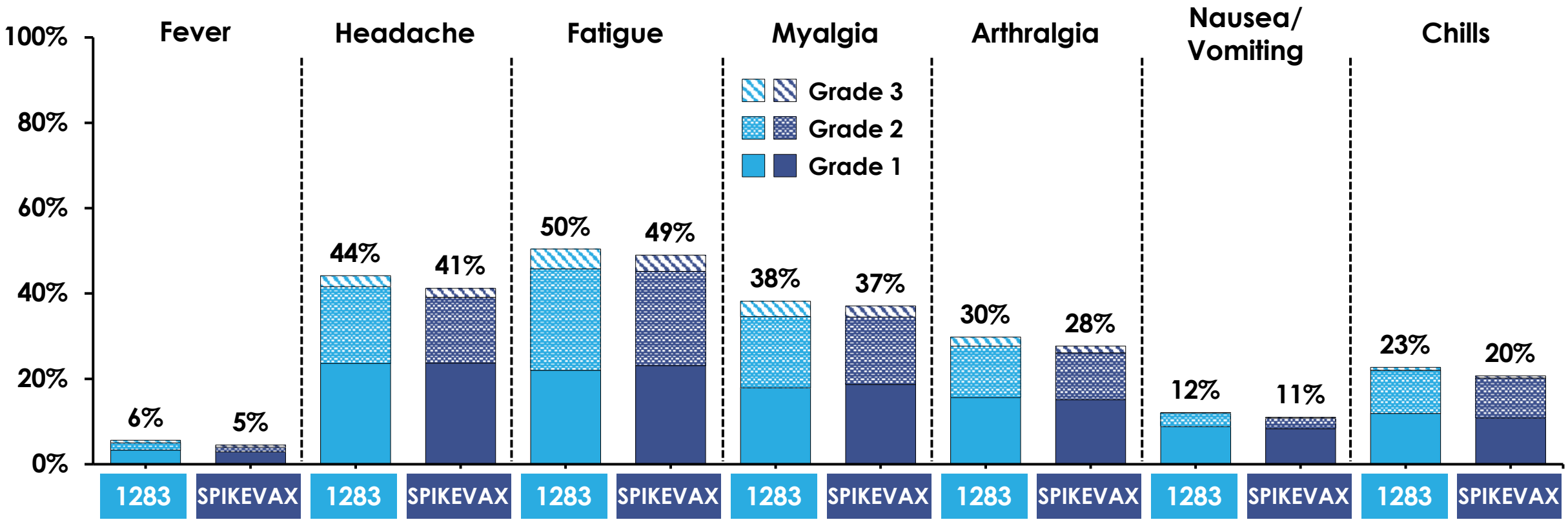
Solicited Systemic Adverse Reactions within 7 Days of Vaccination with mRNA-1283 and SPIKEVAX

Study 301 – Solicited Safety Set



- Fatigue, headache, and myalgia most frequently observed solicited systemic adverse reactions for both groups
- 1-2 days median duration for systemic adverse reactions

Feb 23, 2024 data cutoff; mRNA-1283, N = 5702; mRNA-1273, N = 5706. One participant in the mRNA-1273 group had a grade 4 fever. No grade 4 reactions.

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Similar Frequency of Unsolicited AEs Within 28 Days After Injection, Regardless of Relationship to Vaccine, Between mRNA-1283 and SPIKEVAX

Study 301 – Safety Set

	mRNA-1283 (10 µg) N = 5706	SPIKEVAX (50 µg) N = 5711
All, % (n)	**12%** (701)	**12%** (680)
Serious	**0.2%** (13)	**0.3%** (18)
Fatal	**0%** (0)	**0.02%** (1)
Medically-Attended	**7%** (425)	**7%** (422)
Leading to Study Discontinuation	**0%** (0)	**0.02%** (1)
Any Adverse Event of Special Interest (AESI)	**0.05%** (3)	**0.1%** (6)
Myocarditis/Pericarditis	**0%** (0)	**0%** (0)

Feb 23, 2024 data cutoff

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Safety Summary through Median 8.8 Months of Follow-up

- No imbalances in any adverse events between the vaccine groups
- No myocarditis or pericarditis in recipients of mRNA-1283
- No safety concerns identified

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Immunogenicity

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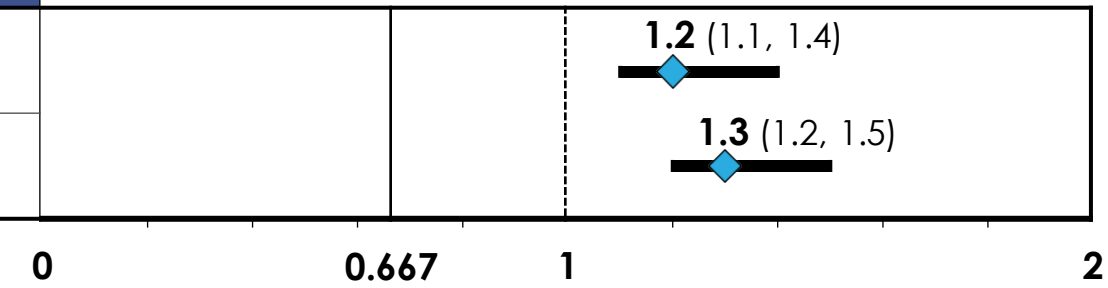
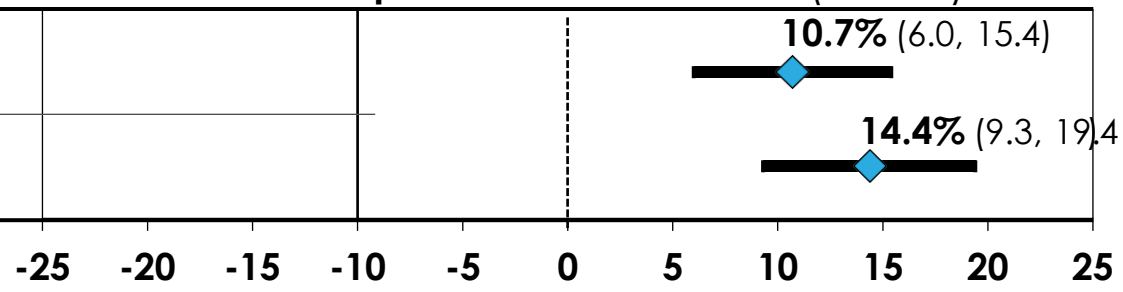
mRNA-1283 Elicited Higher Antibody Response at Day 29 Compared to SPIKEVAX

Study 301 – Per-Protocol Immunogenicity Set (Randomly Selected Subset)

GMC (95% CI)[1]	mRNA-1283 (10 µg) N = 621	SPIKEVAX (50 µg) N = 568
Original SARS-CoV-2	**10632** (9960, 11349)	**8577** (8013, 9180)
BA.4/BA.5	**2341** (2167, 2529)	**1754** (1618, 1901)



Seroresponse Rate, % (95% CI)		
Original SARS-CoV-2	**83.6%** (80.4, 86.4)	**72.9%** (69.0, 76.5)
BA.4/BA.5	**79.9%** (76.5, 83.0)	**65.5%** (61.4, 69.4)



Noninferiority Success Criteria Met

- **GMR:** Lower 95% CI of GMR was >0.667
- **Seroresponse rate difference:** Lower 95% CI of difference >–10%

Seroresponse rate defined as antibody value change from baseline below lower limit of quantification (LLOQ) to ≥4 × LLOQ, or ≥4-fold rise if baseline ≥ LLOQ and <4 × LLOQ, or ≥2-fold rise if baseline is ≥4 × LLOQ; GMC – geometric mean concentration; GMR – geometric mean ratio

1. GMC estimated based on ANCOVA model

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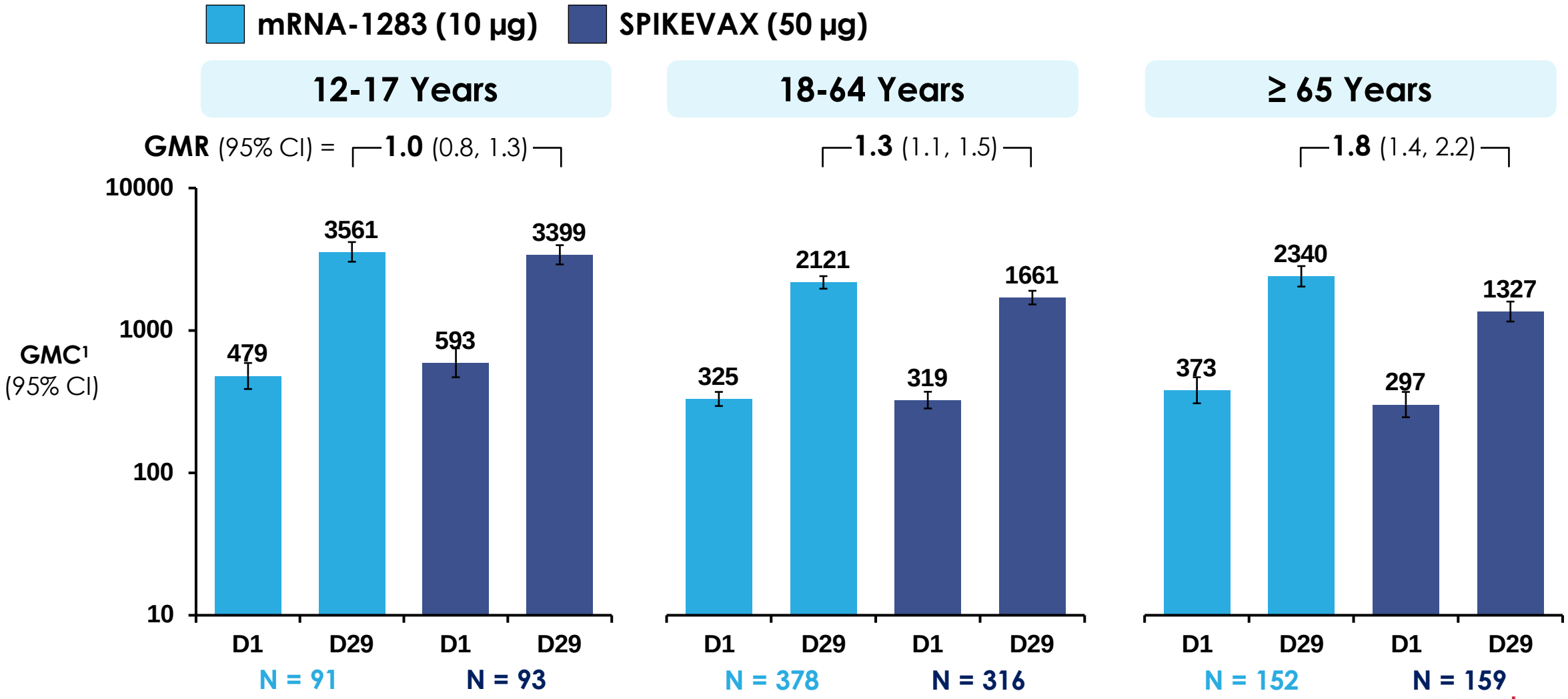
Highest BA.4/BA.5 Neutralizing Antibody Geometric Mean Ratio (GMR) at Day 29 in Adults ≥65 Years Old

Study 301 – Per Protocol Immunogenicity (Randomly Selected Subset)



1. GMC estimated based on ANCOVA model

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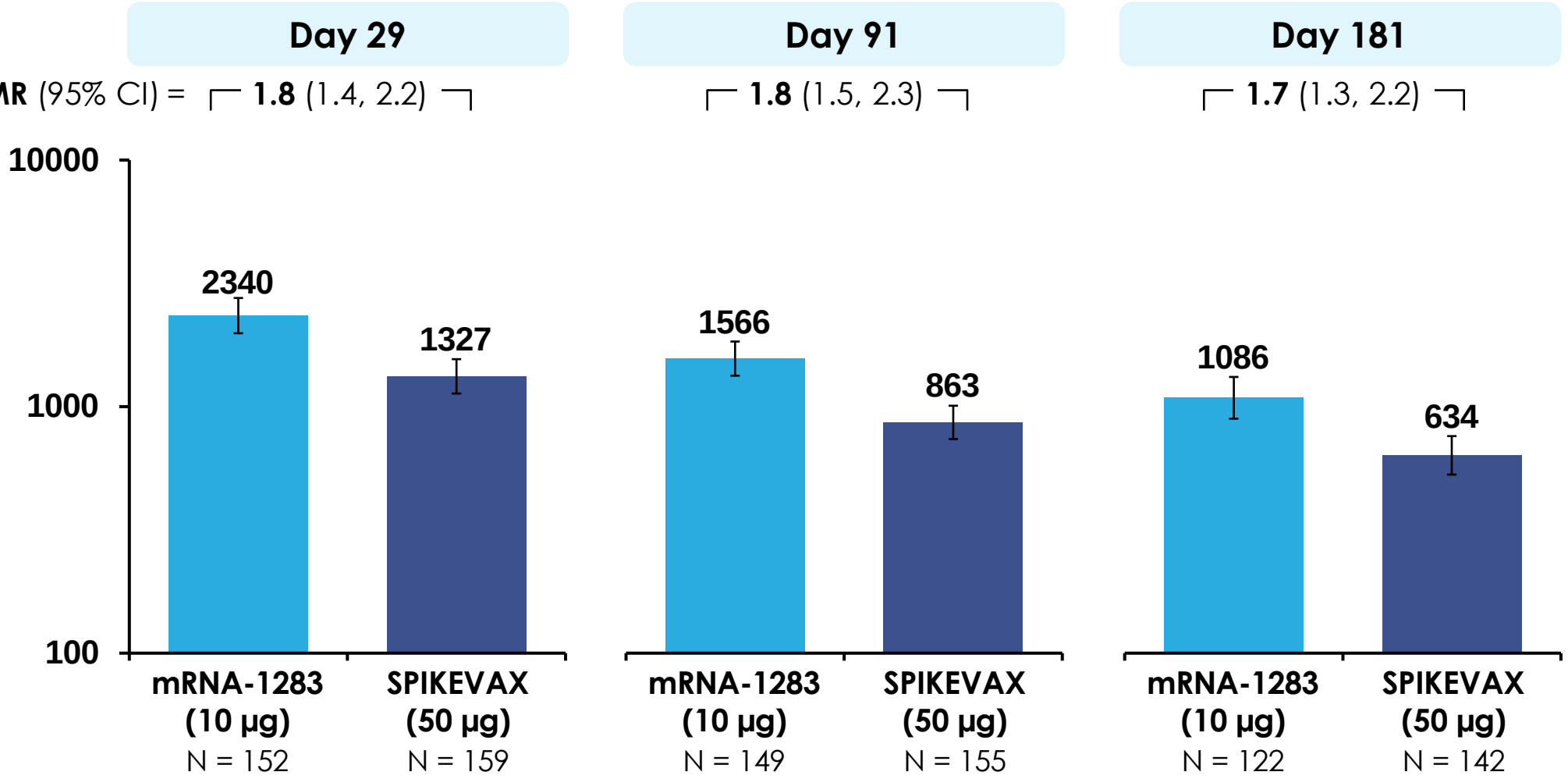
mRNA-1283 Elicited Consistently Higher Antibody Responses Compared to SPIKEVAX Over Time - Adults ≥65 Years of Age

Study 301 – Per-Protocol Immunogenicity Set (Randomly Selected Subset)

GMC[1] Against Omicron BA.4 / BA.5 (95% CI)



1. GMC estimated based on ANCOVA model

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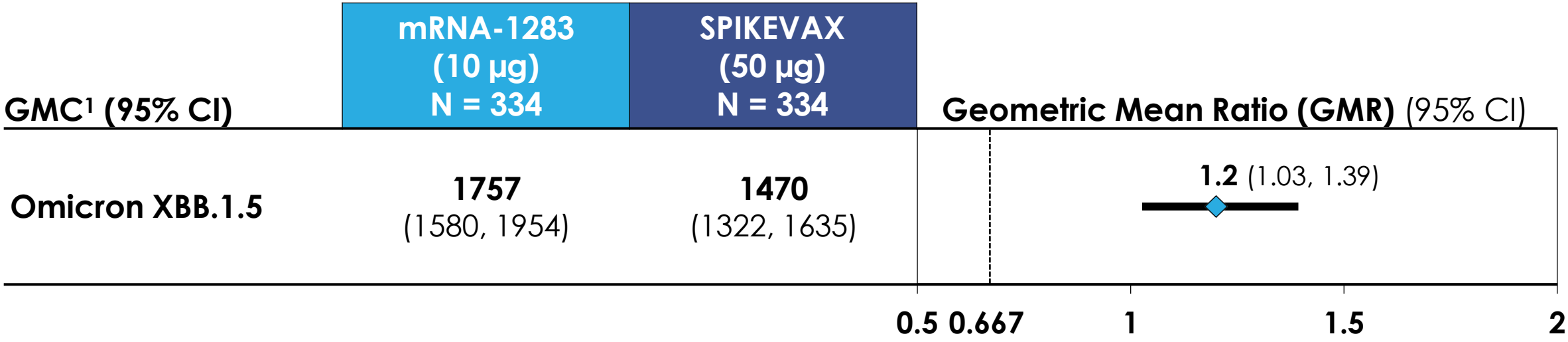
Neutralizing Antibody Responses against Omicron XBB.1.5 with mRNA-1283 Similar to SPIKEVAX

Study 301 – Per-Protocol Immunogenicity Set - Japan

- **Study assessed safety & immunogenicity of monovalent XBB.1.5 COVID-19 vaccine**



Noninferiority Success Criteria Met

- Lower 95% CI of GMR was >0.667

1. GMC estimated based on ANCOVA model

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Relative Vaccine Efficacy of mRNA-1283 vs SPIKEVAX (mRNA-1273)

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COVID-19 Case Definition and Surveillance

CDC COVID-19 Definition[1]

- Virologic confirmation of SARS-CoV-2 infection via PCR
- Presence of ≥1 symptom consistent with COVID-19 within 14 days of positive PCR
  - Fever or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body ache
  - Headache
  - Nausea or vomiting
  - Loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Diarrhea

COVID-19 Surveillance

- Biweekly symptom surveillance conducted using an electronic diary prompt
  - Participants with symptoms seen for clinical evaluation and collection of respiratory samples for SARS-CoV-2 PCR

1. https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-covid-19/

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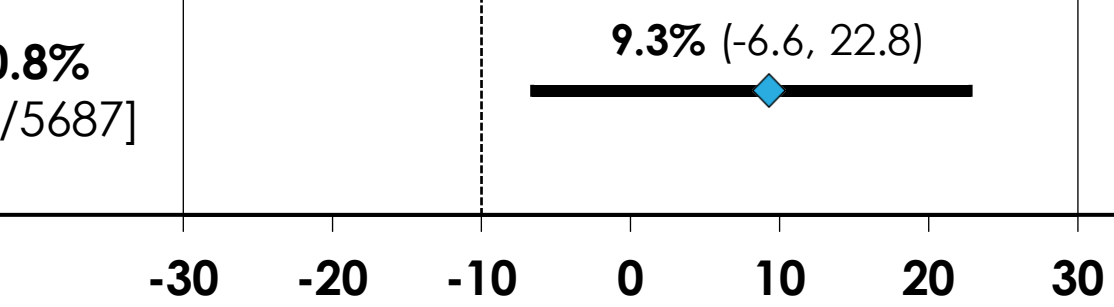
Prespecified Success Criteria Met for Relative Vaccine Efficacy of mRNA-1283 vs SPIKEVAX

Per-Protocol Set for Efficacy (Median 8 Months)

Participants with COVID-19, % [n/N]	mRNA-1283 (10 µg)	SPIKEVAX (50 µg)	Relative Vaccine Efficacy Based on Hazard Ratio (99.4% CI)[1,2]	P-value[3]
Primary rVE Objective (≥12 year)	**9.9%** [560/5679]	**10.8%** [617/5687]	**9.3%** (-6.6, 22.8)	**0.0005**



Noninferiority Success Criteria Met

- Lower bound of two-sided 99.4% (alpha-adjusted) CI of rVE > -10% (1-sided alpha spending: 0.0028)

Based on CDC COVID-19 definition
1 rVE =1-hazard ratio, hazard ratio estimated using a stratified Cox proportional hazard model (stratified by age group at randomization) and with treatment group as a fixed effect.
2 Alpha-adjusted 2-sided (99.4%) CI was calculated using the Lan-DeMets O'Brien-Fleming Spending function (nominal one-sided alpha of 0.0028)
3 P-value based on the stratified Cox proportional hazard model to test the null hypothesis log (hazard ratio)>=log(1.1)

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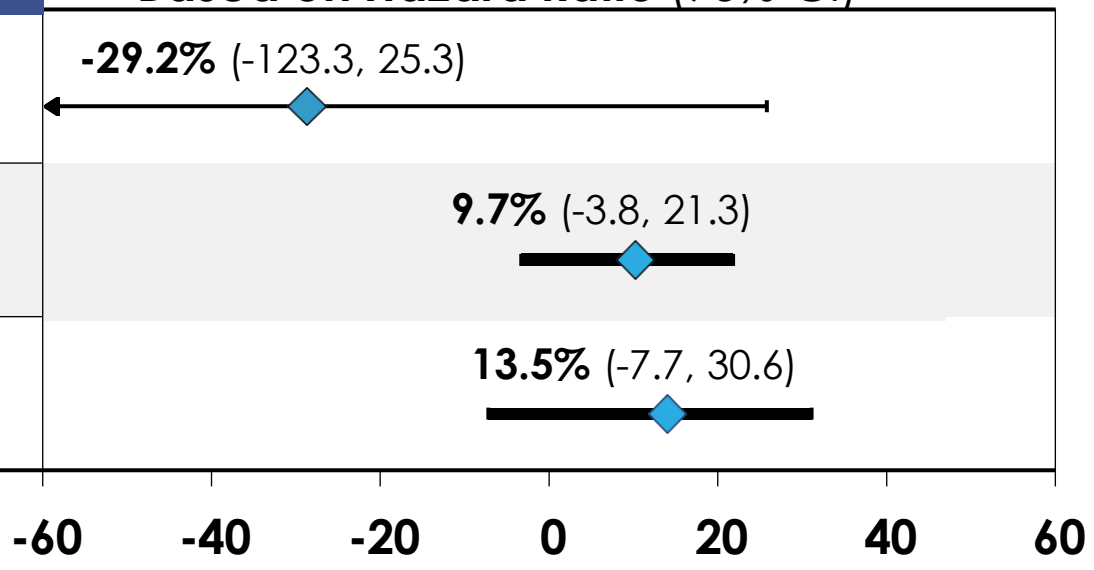
Relative Vaccine Efficacy of mRNA-1283 vs SPIKEVAX in Participants by Age

COVID-19 Events[1] through 31 Jan 2024 – Per-Protocol Set for Efficacy

Participants with COVID-19, % [n/N]	mRNA-1283 (10 µg)	SPIKEVAX (50 µg)	Relative Vaccine Efficacy Based on Hazard Ratio (95% CI)[1,2]
12-17 Years	5.9% [29/491]	4.7% [23/490]	-29.2% (-123.3, 25.3)
18-64 Years	10.7% [382/3558]	11.8% [422/3562]	9.7% (-3.8, 21.3)
≥ 65 Years	9.1% [149/1630]	10.5% [172/1635]	13.5% (-7.7, 30.6)



- Highest relative vaccine efficacy in adults ≥65 years
- Limited number of COVID-19 cases in 12-17-year-olds results in imprecise relative vaccine efficacy estimate

1.Based on CDC COVID-19 definition; 2. Posthoc analysis of RVE in ≥50-year-olds (3399 received mRNA-1283, 3431 received mRNA-1273);
rVE – relative vaccine efficacy = 1-hazard ratio, hazard ratio was estimated using a Cox proportional hazard model and with treatment group as a fixed effect.

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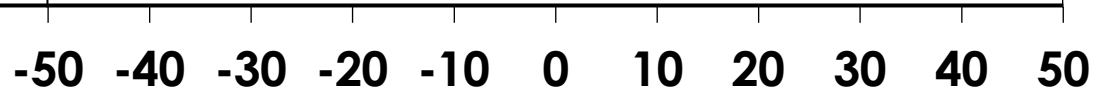
Relative Vaccine Efficacy Favorable for mRNA-1283 for Individuals with Comorbidities

Post Hoc Analysis – Based on CDC Definition for COVID-19 Risk[1]

Participants with COVID-19, % [n/N]	mRNA-1283 (10 µg)	SPIKEVAX (50 µg)	Relative Vaccine Efficacy Based on Hazard Ratio (95% CI)[1]
≥ 1 comorbidities	**10.2%** [267/2617]	**12.4%** [329/2658]	**17.5%** (3.0, 29.8)
And ≥ 50 Years	**9.6%** [169/1755]	**12.4%** [228/1833]	**23.0%** (6.1, 36.9)
And ≥ 65 years	**8.5%** [78/913]	**11.8%** [110/929]	**28.6%** (4.6, 46.6)



1. https://www.cdc.gov/covid/risk-factors/index.html

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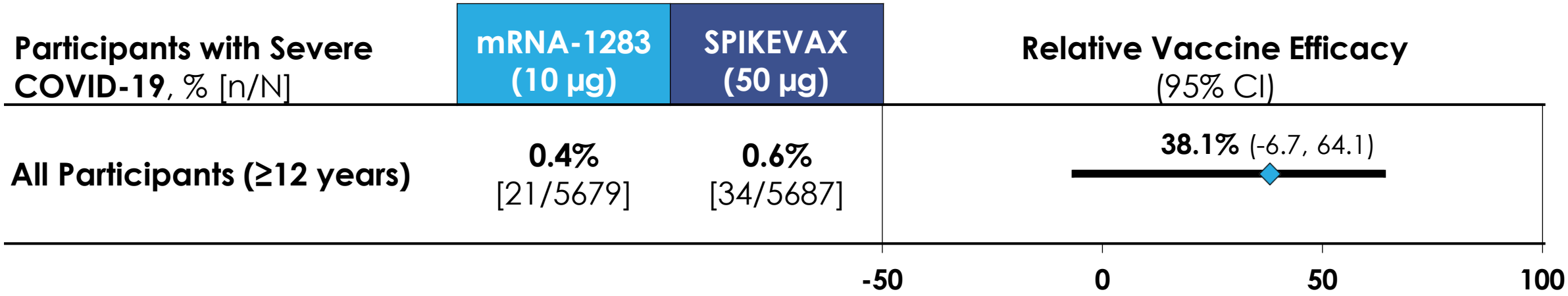
Relative Vaccine Efficacy of mRNA-1283 vs SPIKEVAX Demonstrated in Prevention of Severe COVID-19

Post Hoc Analysis – Protocol Set for Efficacy, through 31 Jan 2024

- **SPIKEVAX effective in prevention of severe COVID-19 in pivotal efficacy trial and real-world effectiveness studies[1-3]**
- **55 cases of severe COVID-19 identified in this trial**
  - Severe criteria per FDA guidance (originally used in mRNA-1273 efficacy trial)[1]
  - Majority (92.7%) of severe COVID-19 cases were due to blood pressure or oxygen saturation abnormalities



1. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19; 2. Zheng et al *Intl J Inf Dis* 2022; 3. Link-Gelles ACIP 2024.
Severe defined as respiratory failure/ARDS, renal/hepatic/neurologic dysfunction, admission to ICU/death, or vital sign abnormalities indicative of severe systemic illness or BP abnormalities indicative of shock (respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, or SpO2 ≤93% on room air at sea level or PaO2/FiO2 <300 mmHg, systolic BP <90 mmHg, diastolic BP <60 mmHg, or requiring vasopressors)

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Summary

Summary - Next Generation COVID-19 Vaccine mRNA-1283

Safety	• mRNA-1283 generally well tolerated; no safety concerns identified
Immunogenicity	• Pre-specified non-inferiority objectives met • mRNA-1283 elicited higher immune responses than SPIKEVAX • GMR highest in participants ≥65 years old (GMR 1.8; 95% CI: 1.4, 2.2)
Relative Vaccine Efficacy (rVE)	• Prespecified rVE non-inferiority objective met **9.3%** mRNA-1283 vs mRNA-1273; 99.4% CI: -6.6, 22.8 • Trend for higher rVE point estimates with advancing age and comorbidity ≥65 years old: **13.5%** mRNA-1283 vs mRNA-1273; 95% CI: -7.7, 30.6 ≥65 years old and ≥1 comorbidity* (*Post hoc*): **28.6%** mRNA-1283 vs mRNA-1273; 95% CI: 4.6, 46.6
Public Health Benefit	• mRNA-1283 has the potential to further reduce the burden of COVID-19, particularly among those most vulnerable to severe outcomes

GMR – geometric mean ratio ;
* Comorbidities associated with severe COVID-19 outcomes https://www.cdc.gov/covid/risk-factors/index.html

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THANK YOU!

- Investigators
- Study site personnel
- Laboratory personnel
- **Most importantly, the individuals who participated in these trials**

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