Vaccines and Related Biological Products Advisory Committee Meeting

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mRNA-1273.214
Moderna COVID-19 Investigational Bivalent Vaccine *(Original + Omicron)*

Moderna, Inc.

Vaccines and Related Biological Products Advisory Committee

June 28, 2022

mRNA-1273.214
Moderna COVID-19 Investigational Bivalent Vaccine *(Original + Omicron)*

Stephen Hoge, MD

President

Moderna, Inc.

Rationale for Variant-Containing Booster Vaccines

- SARS-CoV-2 variants continue to challenge public health in US and globally
- Circulating variants are antigenically distinct from the strain in current vaccines
- Current vaccine boosters increase antibody response against variants, including Omicron
  - Neutralizing antibody titers lower against variants, particularly Omicron
  - Real-world data suggest decrease in effectiveness against infection from Omicron, although effectiveness against severe disease is maintained[1,2]
- Goals of variant-containing booster vaccines[3,4]
  - Retain neutralization for ancestral SARS-CoV-2
  - Stronger immune response against current variants
  - Broader cross-neutralization against future variants
  - Extend durability of protection

1. Tseng et al. *Nature Med* 2022;28:1063-1071. 2. UK Health Security Agency. COVID-19 vaccine surveillance report, Week 13, 31 March 2022.
3. FDA Briefing Document for June 26, 2022 VRBPAC Meeting. 4. WHO Interim Statement on the Composition of Current COVID-19 Vaccines (June 17, 2022).

Moderna COVID-19 Investigational Vaccine Candidates

- Extensive evaluation of 3 monovalent and 3 bivalent variant vaccines in past year
  - >4,300 participants across all vaccines
  - Studied 50 and 100 µg dose levels
- Focus today will be on bivalent candidates at 50 µg dose level

mRNA-1273.211

25 µg
Ancestral SARS-CoV-2

+

25 µg
Beta Variant (B.1.351)

mRNA-1273.214

25 µg
Ancestral SARS-CoV-2

+

25 µg
Omicron Variant (B.1.1.529)

Summary of Results from Prior Studies on Monovalent and Bivalent Variant-Containing Vaccines

- Monovalent Beta vaccine 50 µg elicited numerically lower neutralizing GMTs than bivalent vaccine[1-3]
  - At both 1 and 6 months
  - Against ancestral SARS-CoV-2, Beta, and Delta
- Bivalent Beta-containing vaccine (mRNA-1273.211 50 µg) elicited significantly higher neutralizing antibody response than prototype (mRNA-1273 50 µg)[1]
  - At both 1 and 6 months
  - Against ancestral SARS-CoV-2, Beta, Delta, and Omicron
  - Bivalent titers more durable (Beta GMR increased at 6 months vs. 1 month)
- 50 and 100 µg dose levels evaluated for mRNA-1273 and mRNA-1273.211
  - 50 µg dose of both vaccines met all immunobridging criteria
  - 50 µg of mRNA-1273 is the currently authorized booster dose

1. Chalkias et al. *Research Squa*re 2022, doi: 10.21203/rs.3.rs-1555201/v1.
2. Choi et al. *Nature Med* 2021;27:2025-2031.
3. Moderna unpublished data.

Clinical Studies with Moderna COVID-19 Investigational Bivalent Vaccine Candidates

Bivalent Vaccine	Study (Part)	Dose	N	Median Follow-up
mRNA-1273.211	205 (A)	3rd	300	245 days
mRNA-1273.214	205 (G)	4th	437	43 days
		Total	737	
Comparator				
mRNA-1273	201 (B)	3rd	171	176 days
mRNA-1273	205 (F)	4th	377	57 days

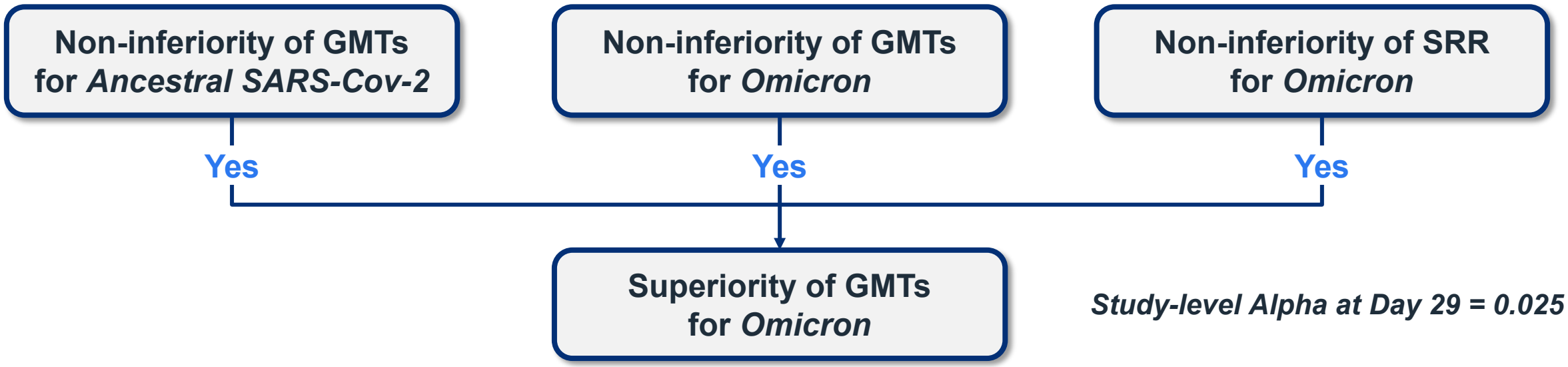
- Participants in Parts F/G previously received mRNA-1273 primary series (100 µg) and 3rd dose (50 µg)
- Parts F and G enrolled Feb 18 – Mar 23, 2022

Chalkias et al. *Research Square* 2022, doi: 10.21203/rs.3.rs-1555201/v1.
Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

Study 205 Objectives Aligned with Regulatory Guidance

- Pre-specified objectives for modified vaccine vs prototype[1]
  1. Superiority of GMTs against variant of concern (VOC)
  2. Non-inferiority of seroresponse rate (SRR) against VOC
  3. Non-inferiority of GMTs and SRR against ancestral SARS-CoV-2

Hypothesis Testing Strategy for mRNA-1273.214 at Day 29



Study-level Alpha at Day 29 = 0.025

1. FDA. Emergency Use Authorization for Vaccines to Prevent COVID-19: Guidance for Industry, 2022.

Demographics and Baseline Characteristics

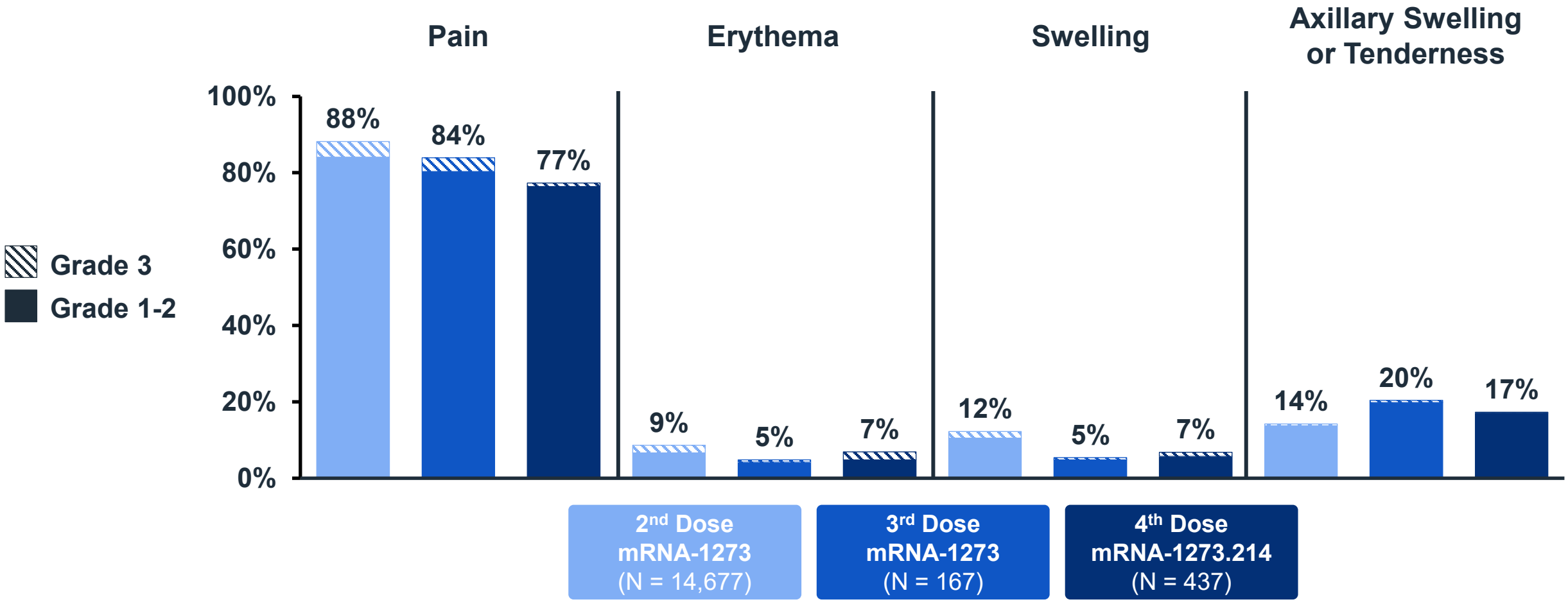
Study 205, Safety Set

Characteristic	4th Dose mRNA-1273 (N = 377)	4th Dose mRNA-1273.214 (N = 437)
Age (years) – mean (range)	**57.5** (20, 96)	**57.3** (20, 88)
≥ 65 years	**39.8%**	**39.8%**
Female	**50.7%**	**59.0%**
Non-White Race	**14.6%**	**12.8%**
Hispanic / Latino Ethnicity	**9.8%**	**10.5%**
Interval between 2nd and 3rd Dose (months) – median (range)	**8.0** (5.6, 14.4)	**8.0** (4.7, 15.0)
Interval between 3rd and 4th Dose (months) – median (range)	**4.4** (3.0, 10.2)	**4.5** (2.9, 13.4)
Prior SARS-CoV-2 Infection	**26.8%**	**22.0%**

Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

Local Reactogenicity After 4th Dose of mRNA-1273.214 Similar to 2nd Dose of Primary Series and 3rd Dose of mRNA-1273

Study 205, Safety Set

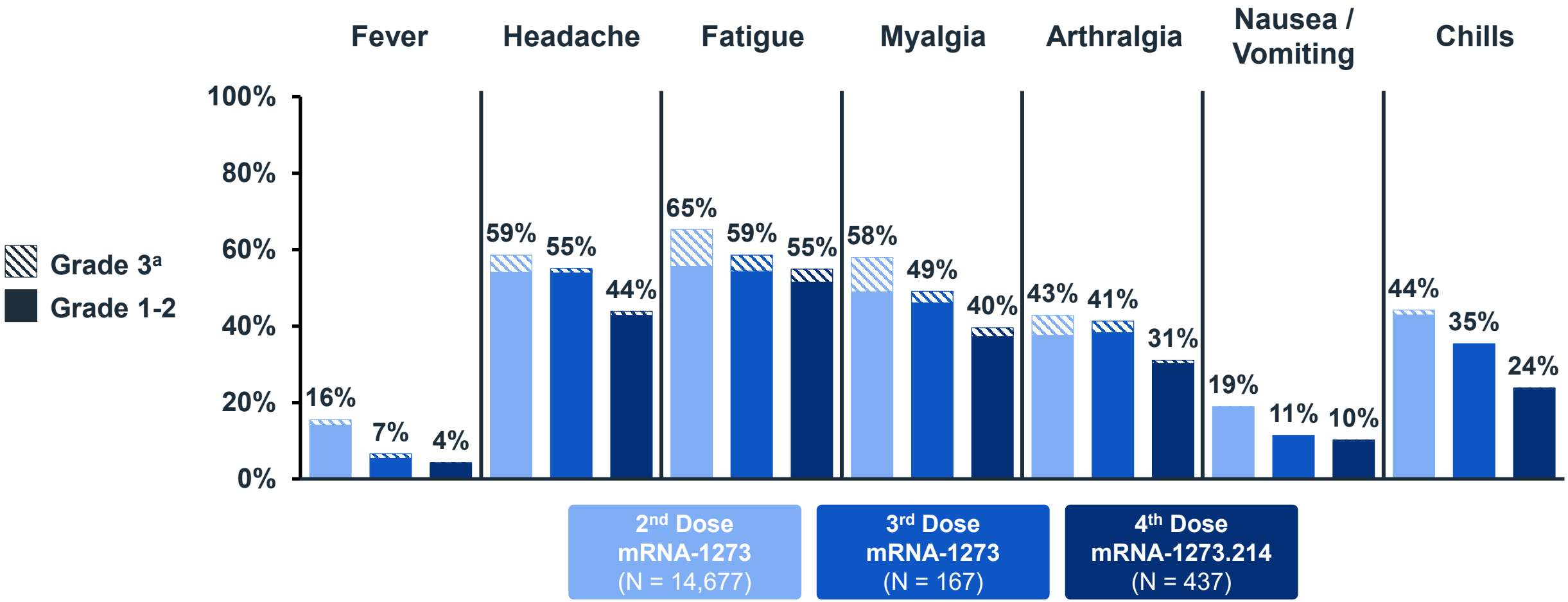


Solicited local adverse reactions within 7 Days after injection.

Sources: 2nd dose mRNA-1273 (Baden et al, *NEJM* 2021); 3rd dose mRNA-1273 (Choi et al, *Nat Med* 2022); 4th dose mRNA-1273.214 (Chalkias et al. *medRxiv* 2022).

Systemic Reactogenicity After 4th Dose of mRNA-1273.214 Similar to 2nd Dose of Primary Series and 3rd Dose of mRNA-1273

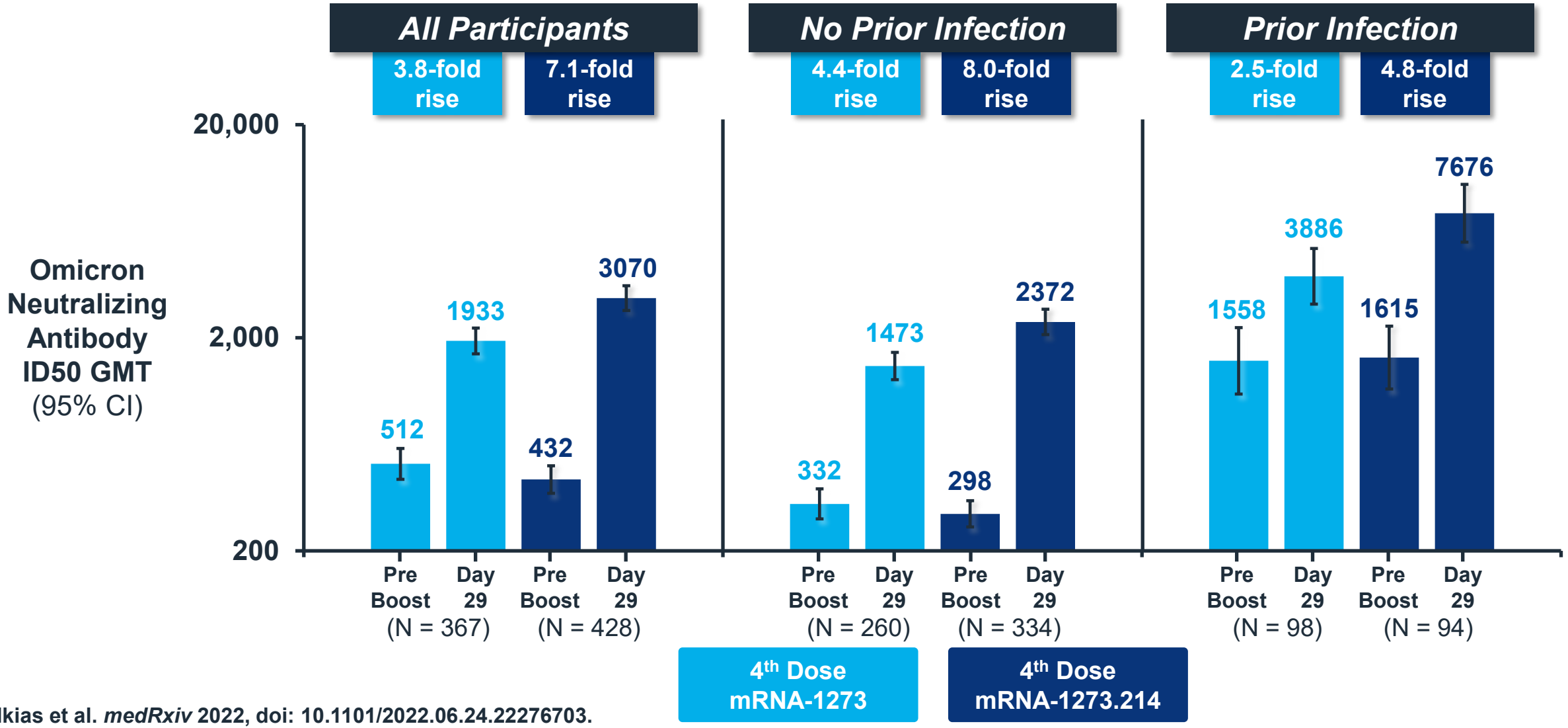
Study 205, Safety Set



Solicited systemic adverse reactions within 7 Days after injection. a) Grade 4 systemic reactions only with 2nd dose of mRNA-1273 (<0.1%).
Sources: 2nd dose mRNA-1273 (Baden et al, *NEJM*, 2021); 3rd dose mRNA-1273 (Choi et al, *Nat Med*, 2022); 4th dose mRNA-1273.214 (Chalkias et al. *medRxiv,* 2022).

Omicron Neutralizing Titers After 4th Dose Significantly Higher with mRNA-1273.214 than mRNA-1273

Study 205, Per-Protocol Immunogenicity Set



Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

Omicron Neutralizing Titers After 4th Dose with mRNA-1273.214 Superior to mRNA-1273

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection

	4th Dose	
Parameter	mRNA-1273 (N = 260)	mRNA-1273.214 (N = 334)
GMT Pre-booster	**332**	**298**
95% CI	(282, 391)	(259, 343)
GMT at Day 29[1]	**1421**	**2480**
95% CI	(1283, 1574)	(2264, 2716)
GMT Ratio[1] (.214 vs Prototype)	**1.75**	
97.5% CI	(1.49, 2.04)	
Seroresponse rate at Day 29	**99.2%**	**100%**
95% CI	(97.2, 99.9)	(98.9, 100)
Difference in seroresponse rates[2]	**1.5**	
97.5% CI	(-1.1, 4.0)	

Success Criteria Met

Superiority of GMTs: Lower 97.5% CI of GMT Ratio ≥ 1.0

Non-inferiority of Seroresponse Rates: Lower 97.5% CI of difference > -10%

1. Based on pre-specified ANCOVA model adjusting for age group (< 65, ≥ 65 years) and pre-booster titer.
2. Common risk difference and 97.5% CI were calculated using stratified Miettinen-Nurminen method adjusting for age group.

Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

Ancestral SARS-CoV-2 (D614G) Neutralizing Titers After 4th Dose Significantly Higher with mRNA-1273.214 than mRNA-1273

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection

	4th Dose	
Parameter	mRNA-1273 (N = 260)	mRNA-1273.214 (N = 334)
GMT Pre-booster	**1521**	**1267**
95% CI	(1353, 1710)	(1120, 1432)
GMT at Day 29[1]	**5287**	**6422**
95% CI	(4887, 5719)	(5990, 6886)
GMT Ratio[1] (.214 vs Prototype)	**1.22**	
97.5% CI	(1.08, 1.37)	
Seroresponse rate at Day 29	**100%**	**100%**
95% CI	(98.6, 100)	(98.9, 100)
Difference in seroresponse rates[2]	**0**	
97.5% CI		

Success Criteria Met

Non-inferiority of GMTs: Lower 97.5% CI of GMT Ratio ≥ 0.67

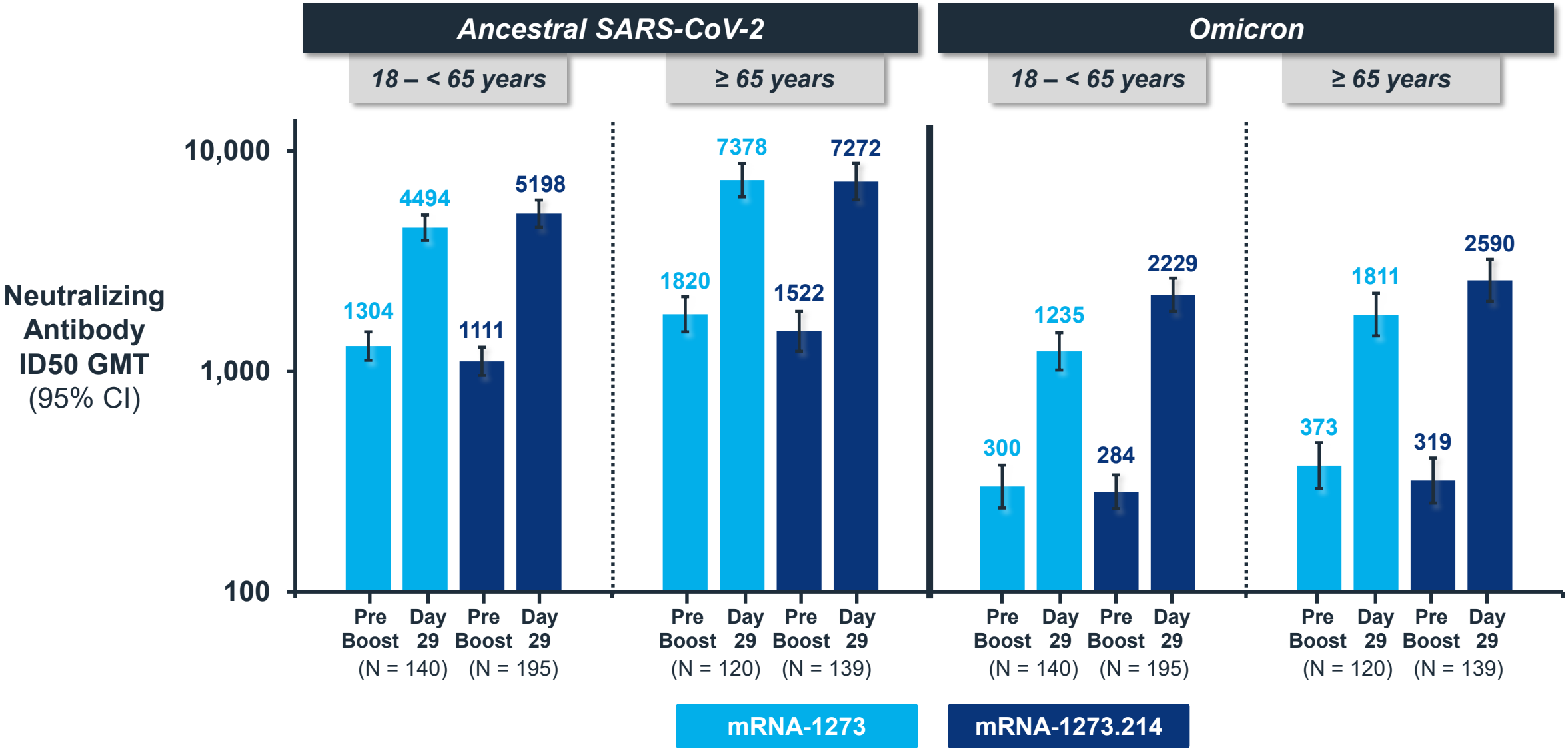
Non-inferiority of Seroresponse Rates: Lower 97.5% CI of difference > -10%

1. Based on pre-specified ANCOVA model adjusting for age group (< 65, ≥ 65 years) and pre-booster titer.
2. Common risk difference and 97.5% CI can not be estimated between two seroresponse rates of 100%.

Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

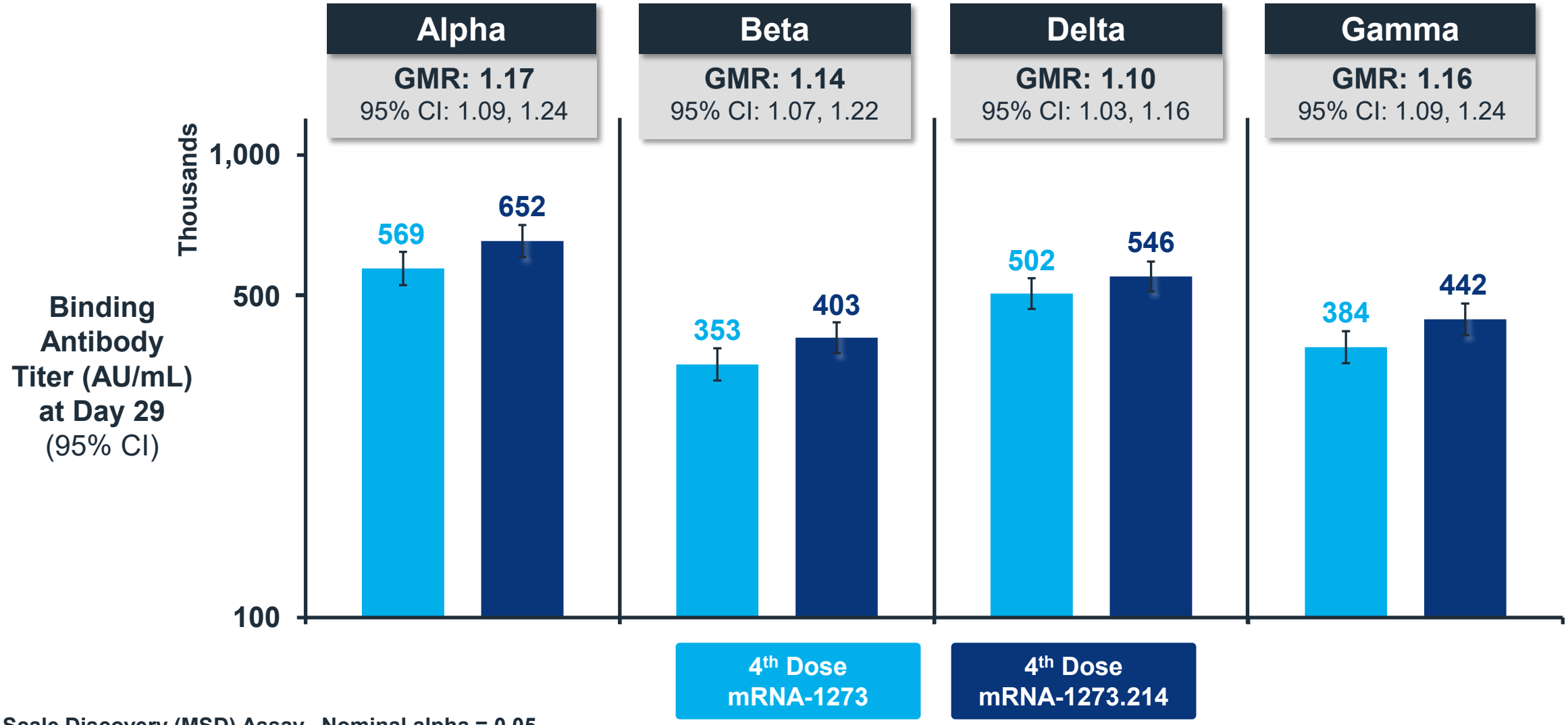
4th Dose of mRNA-1273.214 Delivered Higher Neutralizing Titers than mRNA-1273 Across Age Groups, Including Age >65

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection



Binding Antibody Titers Against Prior VOC Are Significantly Higher with mRNA-1273.214 than mRNA-1273

Study 205, Per-Protocol Immunogenicity Set



Meso Scale Discovery (MSD) Assay. Nominal alpha = 0.05.
mRNA-1273 N = 350-351; mRNA-1273.214 N = 398-402.

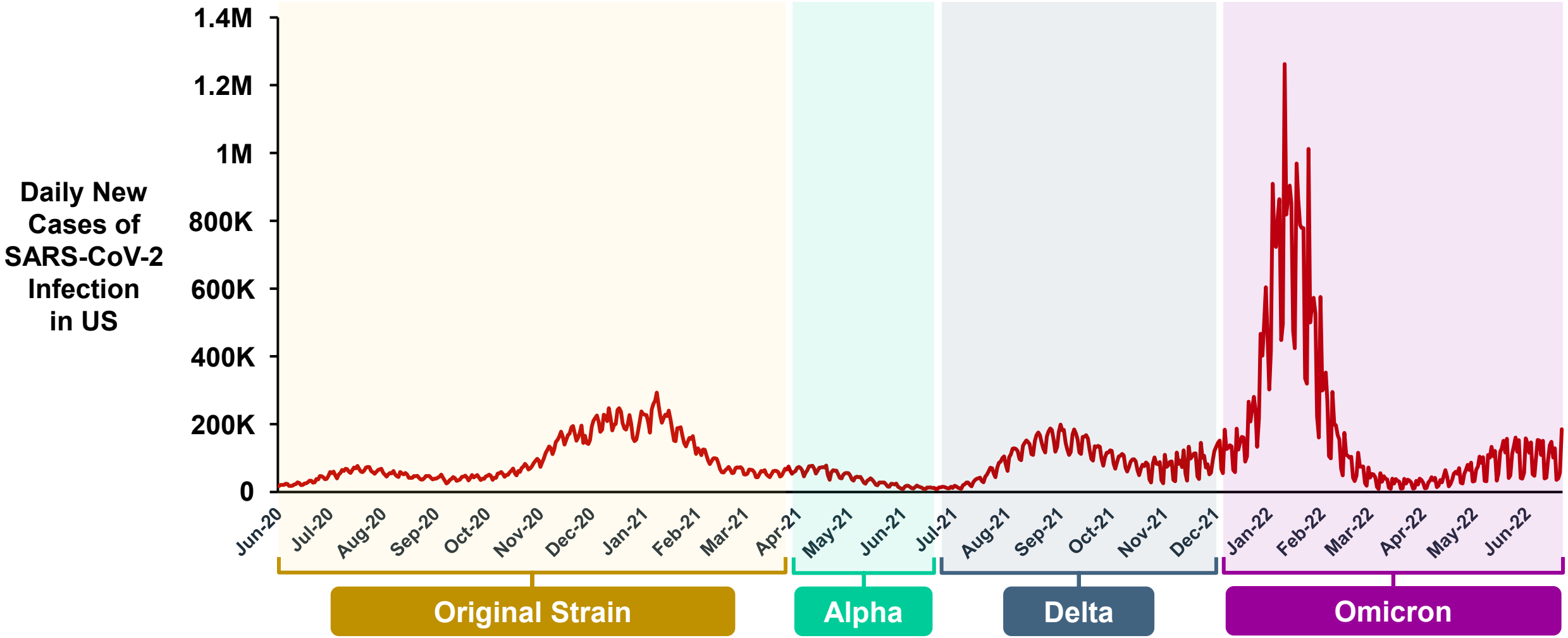
Investigational Bivalent mRNA-1273.214 Vaccine Met All Regulatory Criteria for a Variant-Containing Vaccine

All pre-specified primary and key secondary objectives met:

- ✓ Superiority of GMTs and non-inferiority of SRRs for Omicron *(Primary)*
- ✓ Non-inferiority of GMTs for Ancestral SARS-CoV-2 *(Primary)*
- ✓ Non-inferiority of SRRs for Ancestral SARS-CoV-2 *(Key Secondary)*
- ✓ Safety and tolerability profile consistent with mRNA-1273 booster

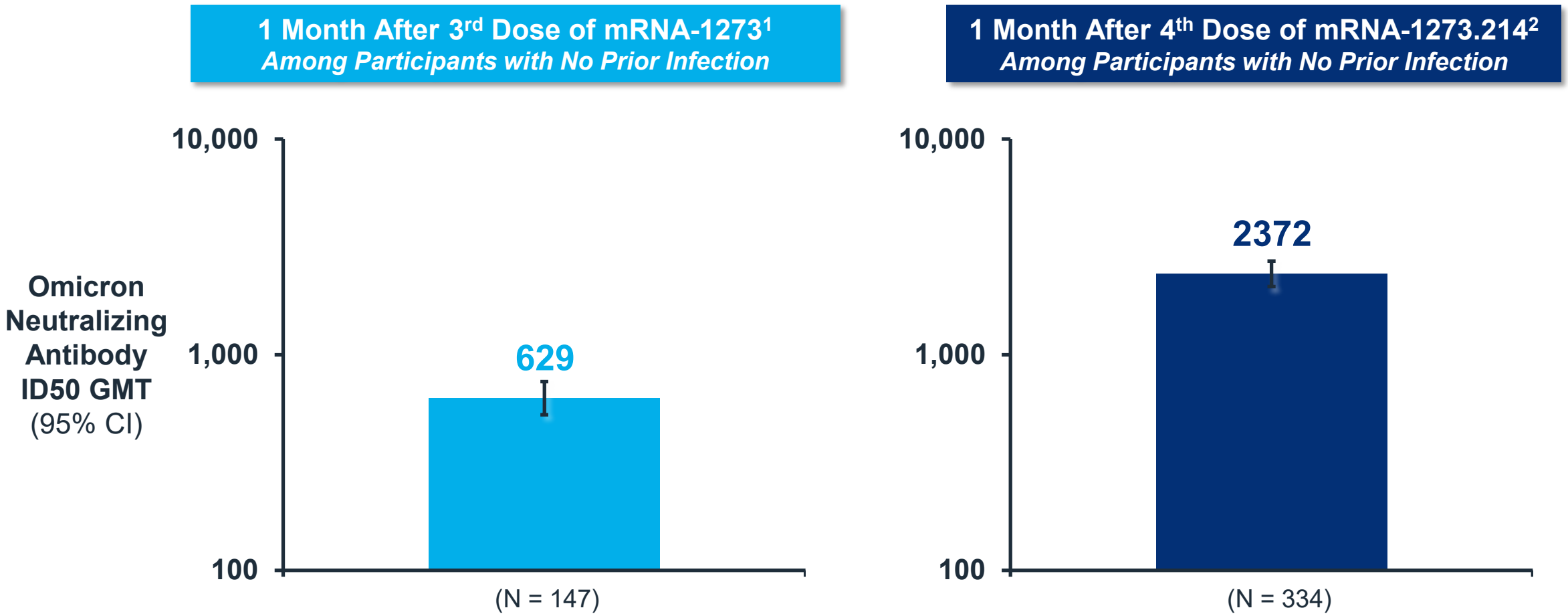
Role of mRNA-1273.214 in Addressing Emerging Variants

Predominant SARS-CoV-2 Strains in the US Have Changed During Different Periods of the COVID-19 Pandemic



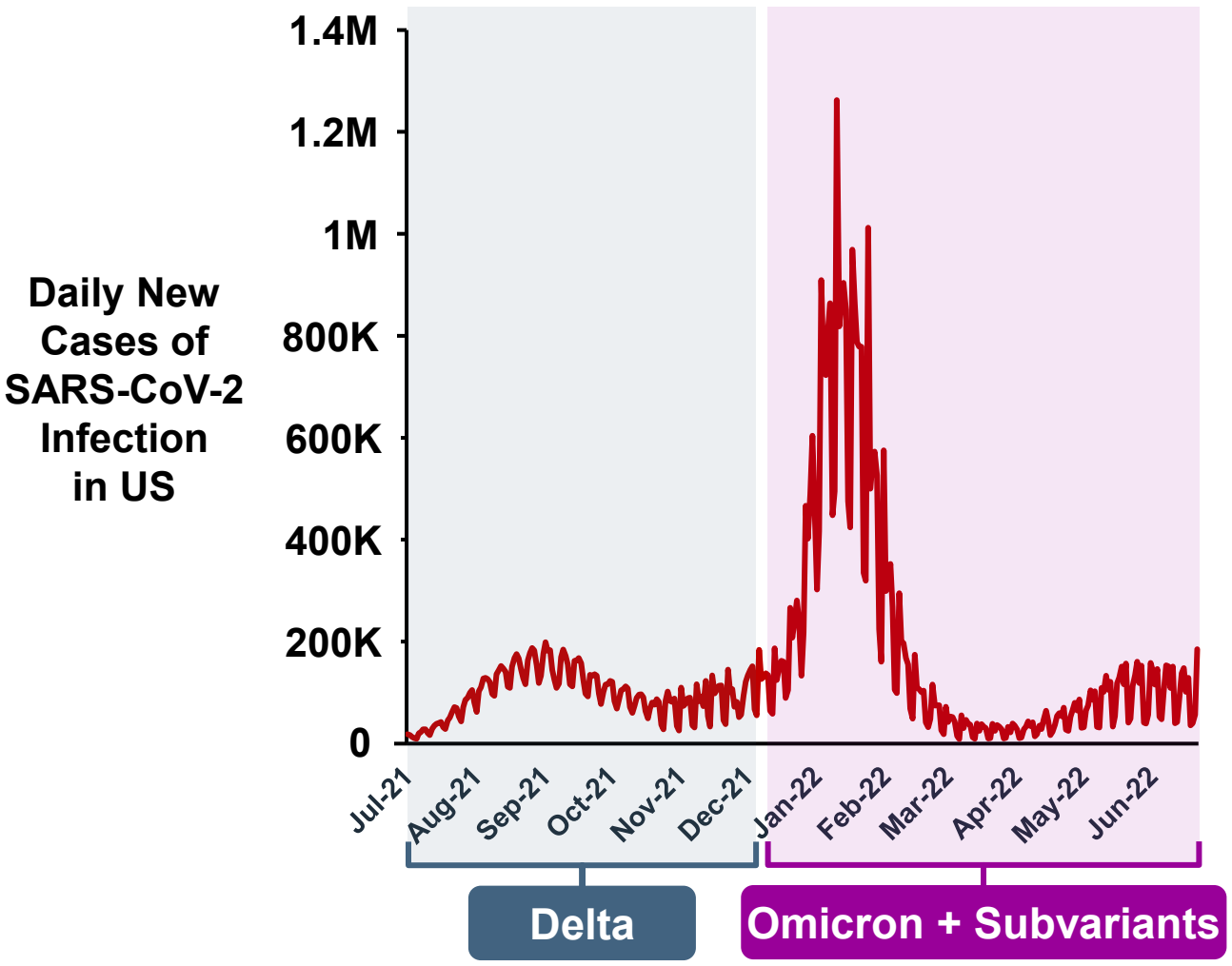
https://covid.cdc.gov/covid-data-tracker/

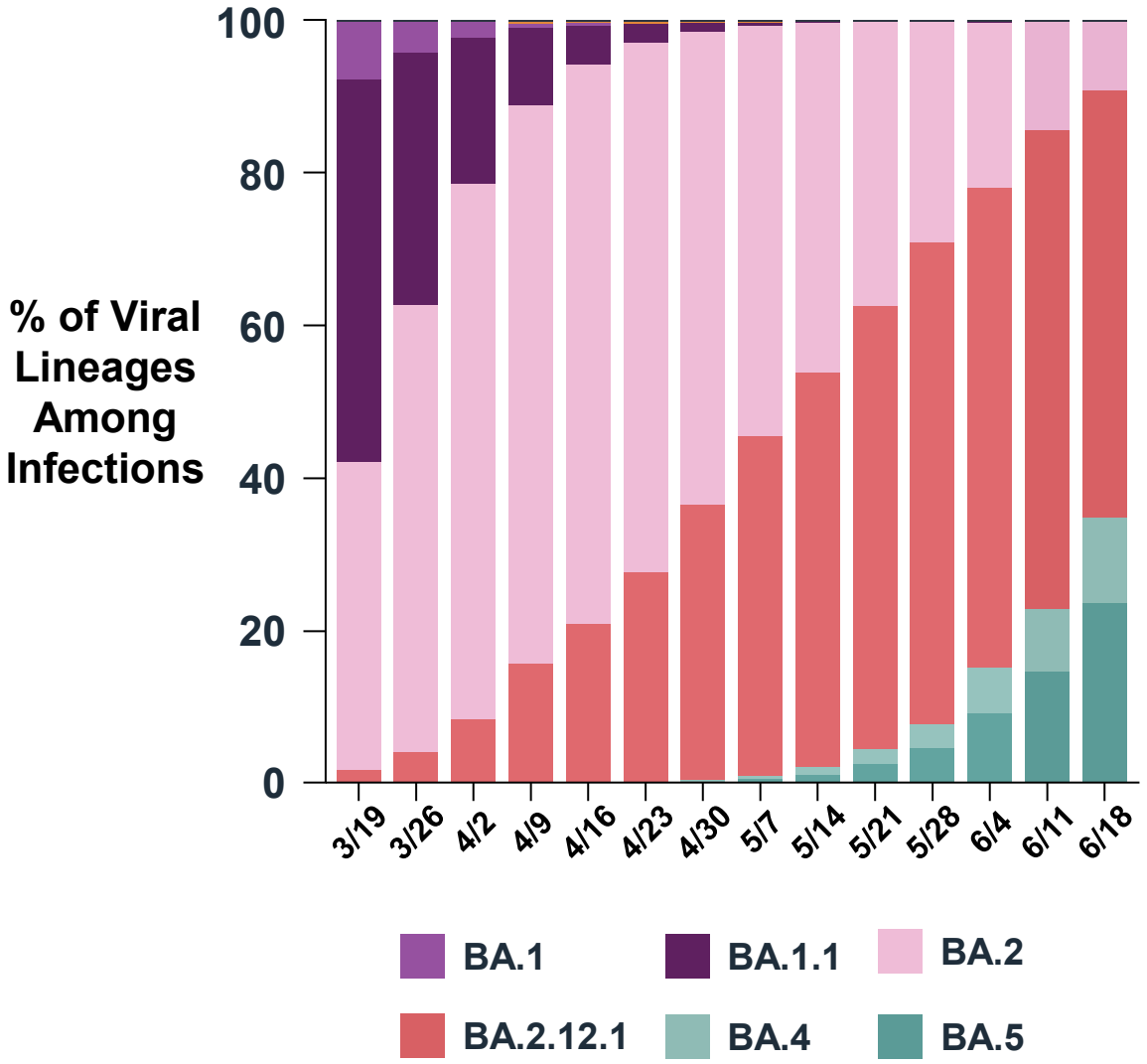
4th Dose of Bivalent mRNA-1273.214 Increases Omicron (BA.1) Neutralizing Titers



1. Chalkias et al. *Research Square* 2022, doi: 10.21203/rs.3.rs-1555201/v1.
2. Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

Omicron Subvariants Continue to Emerge





https://covid.cdc.gov/covid-data-tracker/

4th Dose of mRNA-1273.214 Increased BA.4/BA.5 Neutralizing Titers Regardless of Prior SARS-CoV-2 Infection

Study 205, Per-Protocol Immunogenicity Set

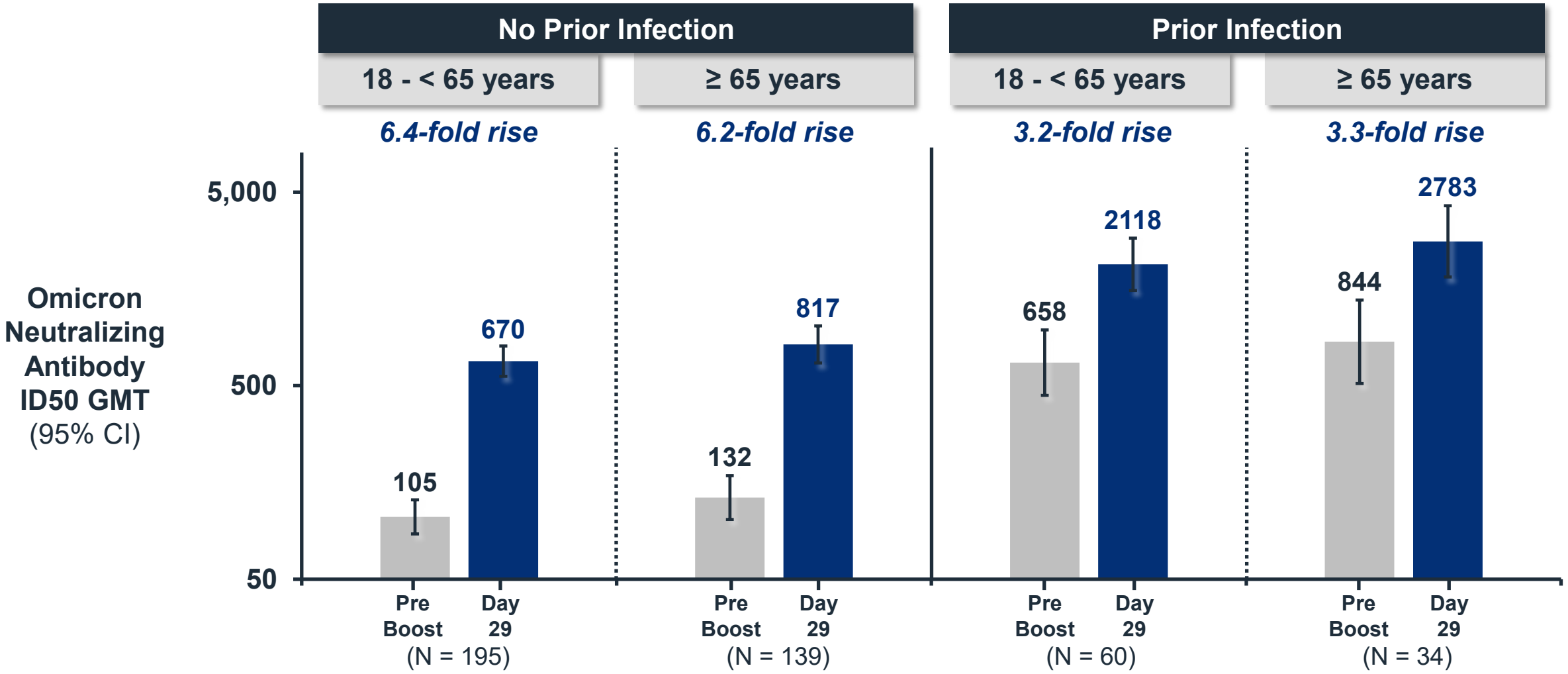
	4th Dose		
	All Participants (N = 428)	**No Prior Infection** (N = 334)	**Prior Infection** (N = 94)
Pre-Booster GMT (95% CI)	**173** (147, 202)	**116** (99, 136)	**720** (532, 974)
Observed GMTs at Day 29 (95% CI)	**941** (826, 1071)	**727** (633, 836)	**2337** (1826, 2993)
Geometric Mean Fold Rise at Day 29 (95% CI)	**5.44** (5.01, 5.92)	**6.30** (5.74, 6.91)	**3.25** (2.78, 3.80)

BA.4/BA.5 assay conducted at Duke/VRC (research grade, validation underway).

Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

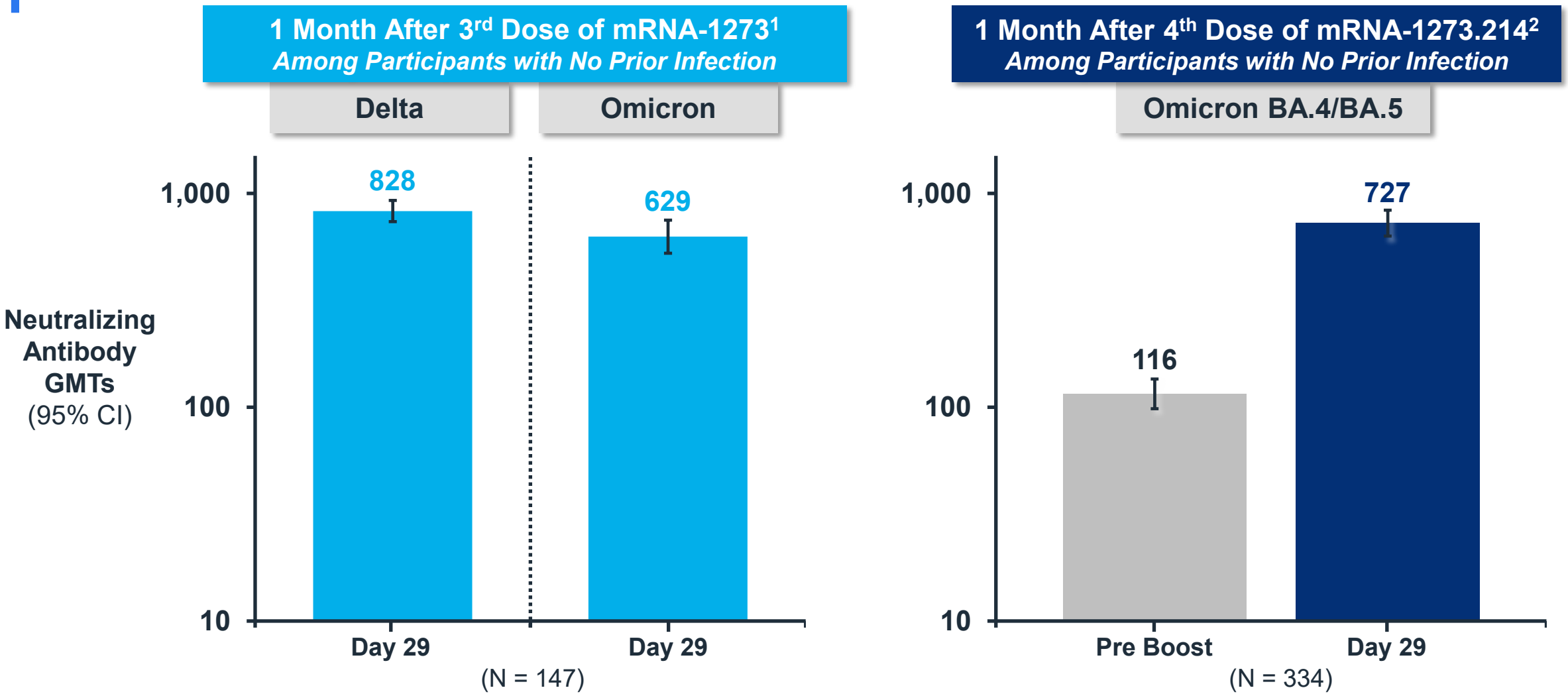
4th Dose of mRNA-1273.214 Increased BA.4/BA.5 Neutralizing Titers Regardless of Prior SARS-CoV-2 Infection or Age

Study 205, Per-Protocol Immunogenicity Set



BA.4/BA.5 assay conducted at Duke/VRC (research grade, validation underway).
Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

4th Dose of mRNA-1273.214 Increased BA.4/BA.5 Neutralizing Titers to Levels Observed Against Delta and Omicron After 3rd Dose of mRNA-1273

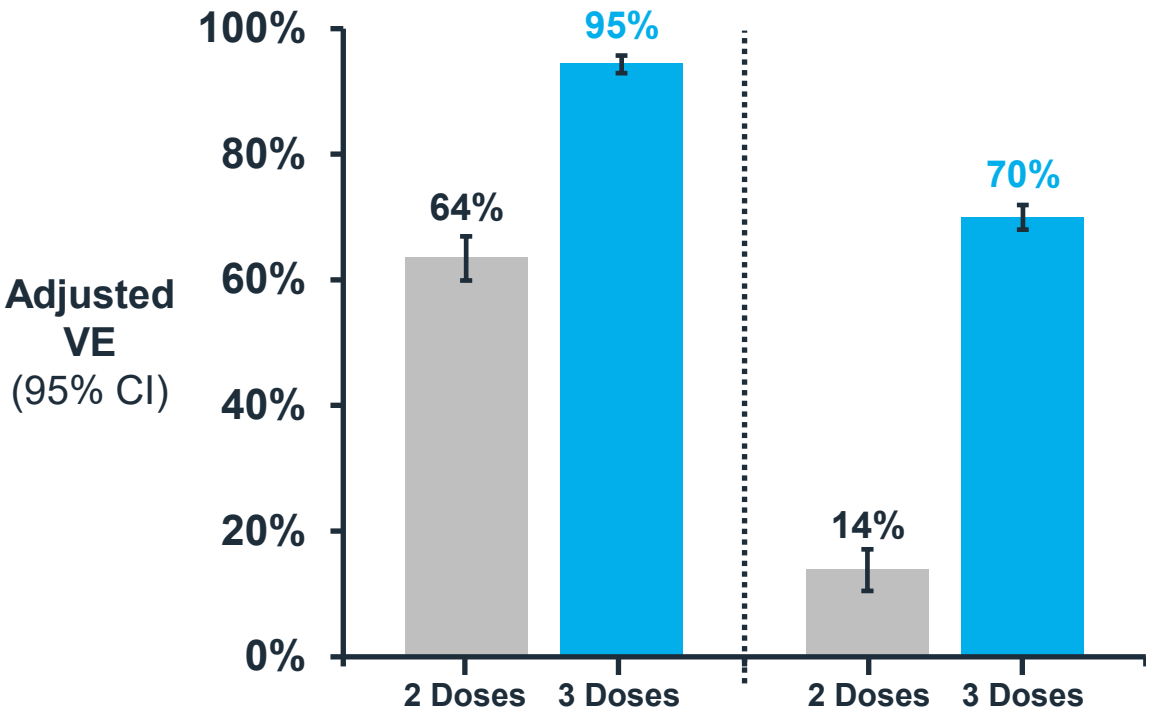


1. Chalkias et al. *Research Square* 2022, doi: 10.21203/rs.3.rs-1555201/v1.
2. Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

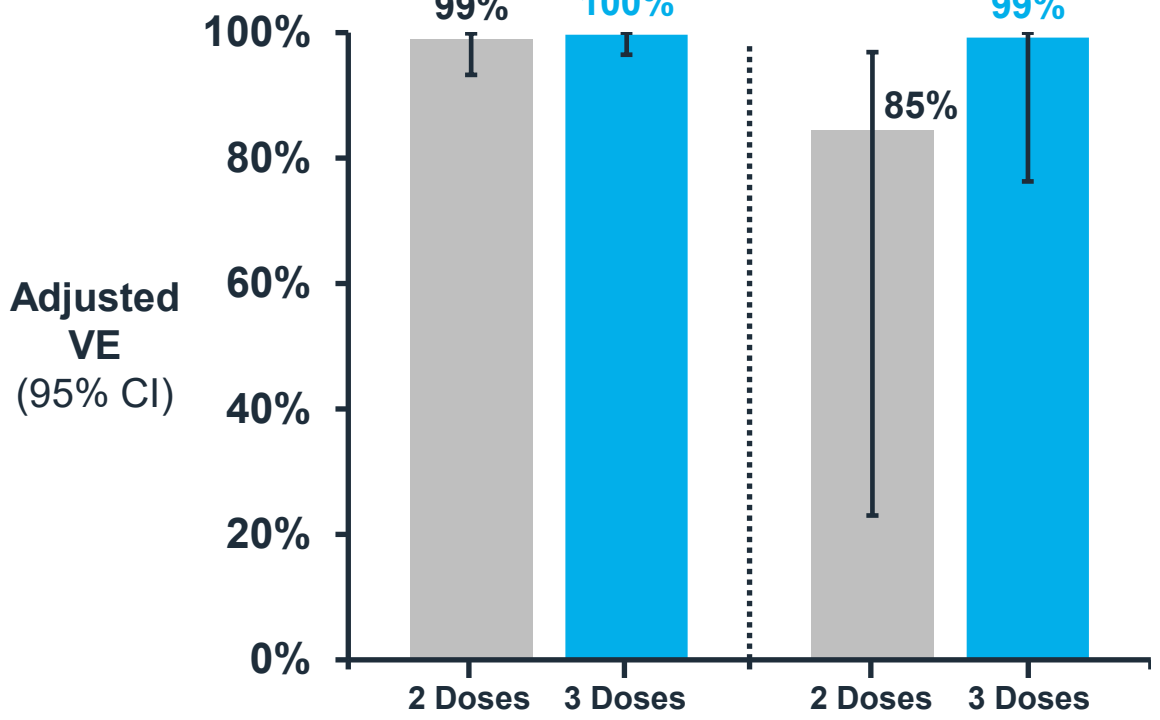
3rd Dose of mRNA-1273 Increased Real-World Effectiveness Against Delta and Omicron

Kaiser Permanente Study

Effectiveness Against Infection After 2 or 3 Doses of mRNA-1273[1]



Effectiveness Against Hospitalization After 2 or 3 Doses of mRNA-1273



1. 3-dose regimen excludes immunocompromised. Follow-up time for 2-doses >270 days, 3-doses >60 days.
Tseng et al. *Nature Med* 2022;28:1063-1071.

Upcoming Data and Plans for mRNA-1273.214

Additional Data Collection Ongoing for mRNA-1273.214

- Immunogenicity for BA.4/BA.5 after 4th dose of mRNA-1273 to provide comparator for mRNA-1273.214
- Durability of immune response with mRNA-1273.214 at 3 and 6 months after the 4th dose
- mRNA-1273.214 in infants and children, 6 months – 5 years of age
  - Primary series study ongoing
  - Booster study ongoing
- Continued safety follow-up of mRNA-1273.214 booster recipients

mRNA-1273.214 Has the Potential to Provide Improved Protection Against COVID-19

- Met pre-specified primary and key secondary objectives
  - Superior neutralizing titers against Omicron
  - Significantly higher neutralizing titers against ancestral strain
  - Favorable safety and tolerability profile
- Significantly higher binding antibodies against Alpha, Beta, Gamma, and Delta
- Robust neutralizing titers against BA.4/BA.5, including adults ≥ 65
- More durable antibody responses demonstrated with bivalent platform

Regulatory submissions completed within next 2 weeks
Pending authorization, vaccine available in late July / early August

THANK YOU to Our Study Collaborators, Investigators, and Participants

- *All investigators*
- *Study site personnel*
- *Most importantly, the individuals who participated in these trials*

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