

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 vaccine¹⁻³
 - 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 Square* 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

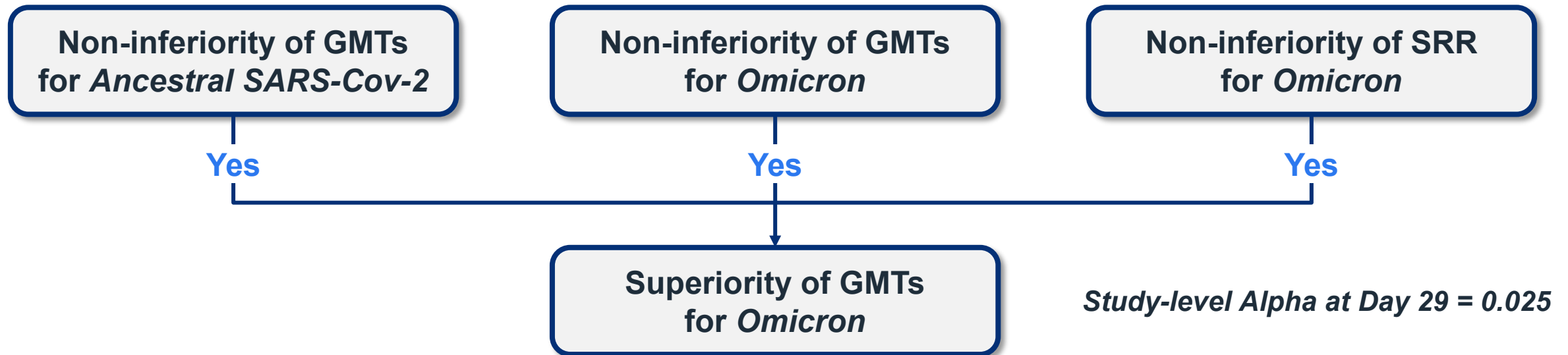
Bivalent Vaccine	Study (Part)	Dose	N	Median Follow-up
mRNA-1273.211	205 (A)	3 rd	300	245 days
mRNA-1273.214	205 (G)	4 th	437	43 days
			Total	737
Comparator				
mRNA-1273	201 (B)	3 rd	171	176 days
mRNA-1273	205 (F)	4 th	377	57 days

- 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

Study 205 Objectives Aligned with Regulatory Guidance

- Pre-specified objectives for modified vaccine vs prototype¹
 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



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

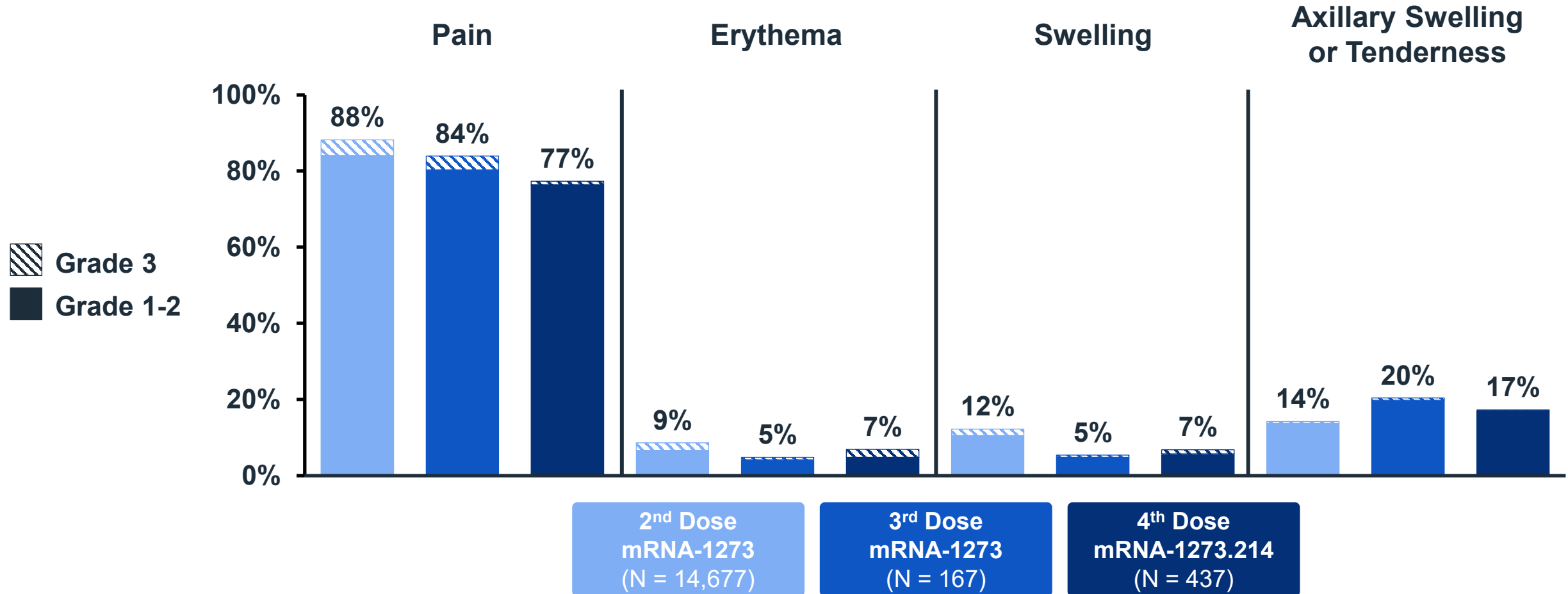
Demographics and Baseline Characteristics

Study 205, Safety Set

Characteristic	4 th Dose	
	mRNA-1273 (N = 377)	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%

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

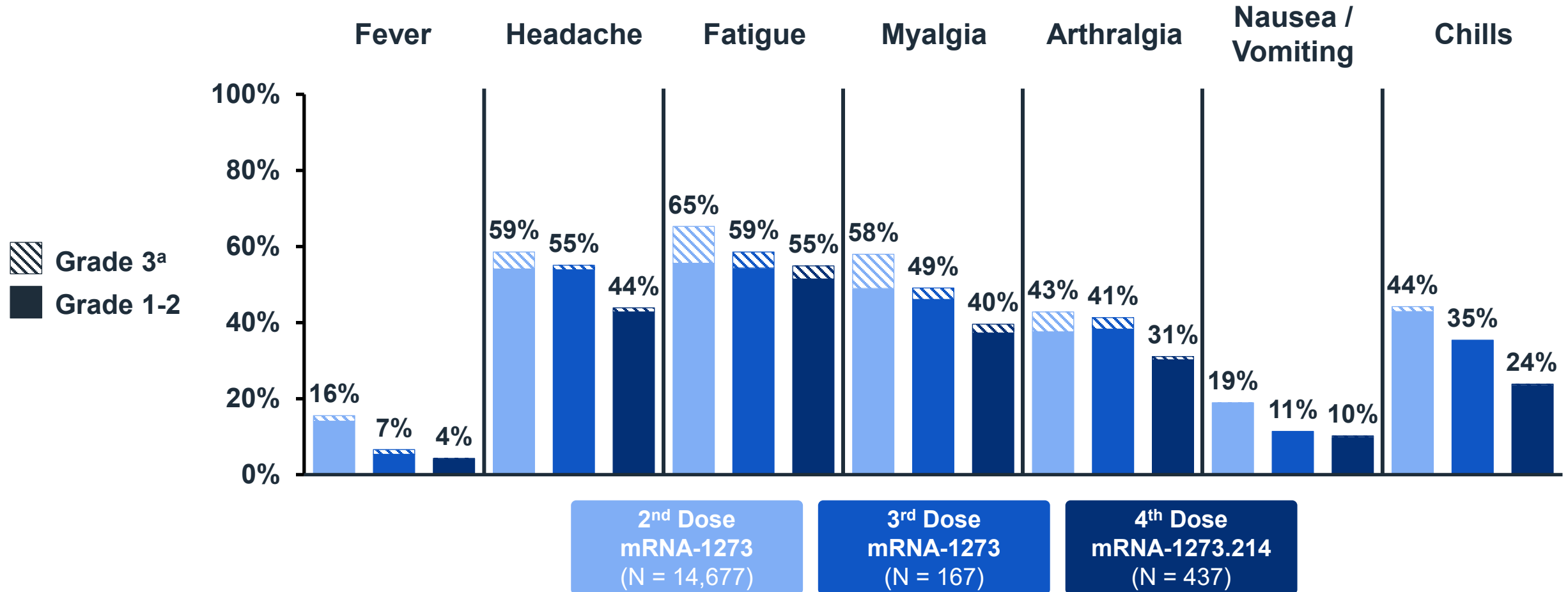


Solicited local adverse reactions within 7 Days after injection.

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

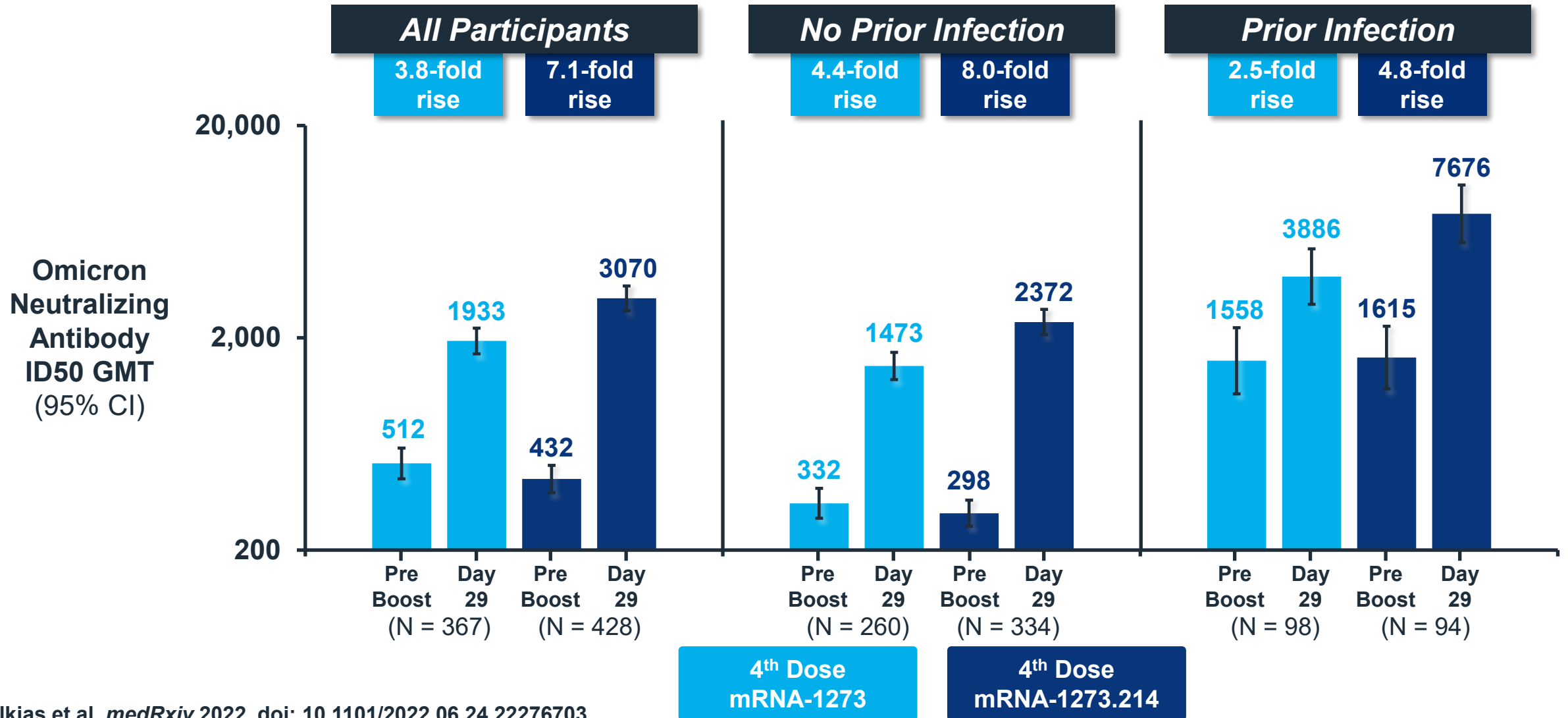


Solicited systemic adverse reactions within 7 Days after injection. a) Grade 4 systemic reactions only with 2nd dose of mRNA-1273 (<0.1%).

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



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

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

Parameter	4 th Dose	
	mRNA-1273 (N = 260)	mRNA-1273.214 (N = 334)
GMT Pre-booster	332	298
95% CI	(282, 391)	(259, 343)
GMT at Day 29¹	1421	2480
95% CI	(1283, 1574)	(2264, 2716)
GMT Ratio¹ (.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 rates²	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.

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

Parameter	4 th Dose	
	mRNA-1273 (N = 260)	mRNA-1273.214 (N = 334)
GMT Pre-booster	1521	1267
95% CI	(1353, 1710)	(1120, 1432)
GMT at Day 29¹	5287	6422
95% CI	(4887, 5719)	(5990, 6886)
GMT Ratio¹ (.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 rates²	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 $> -10\%$

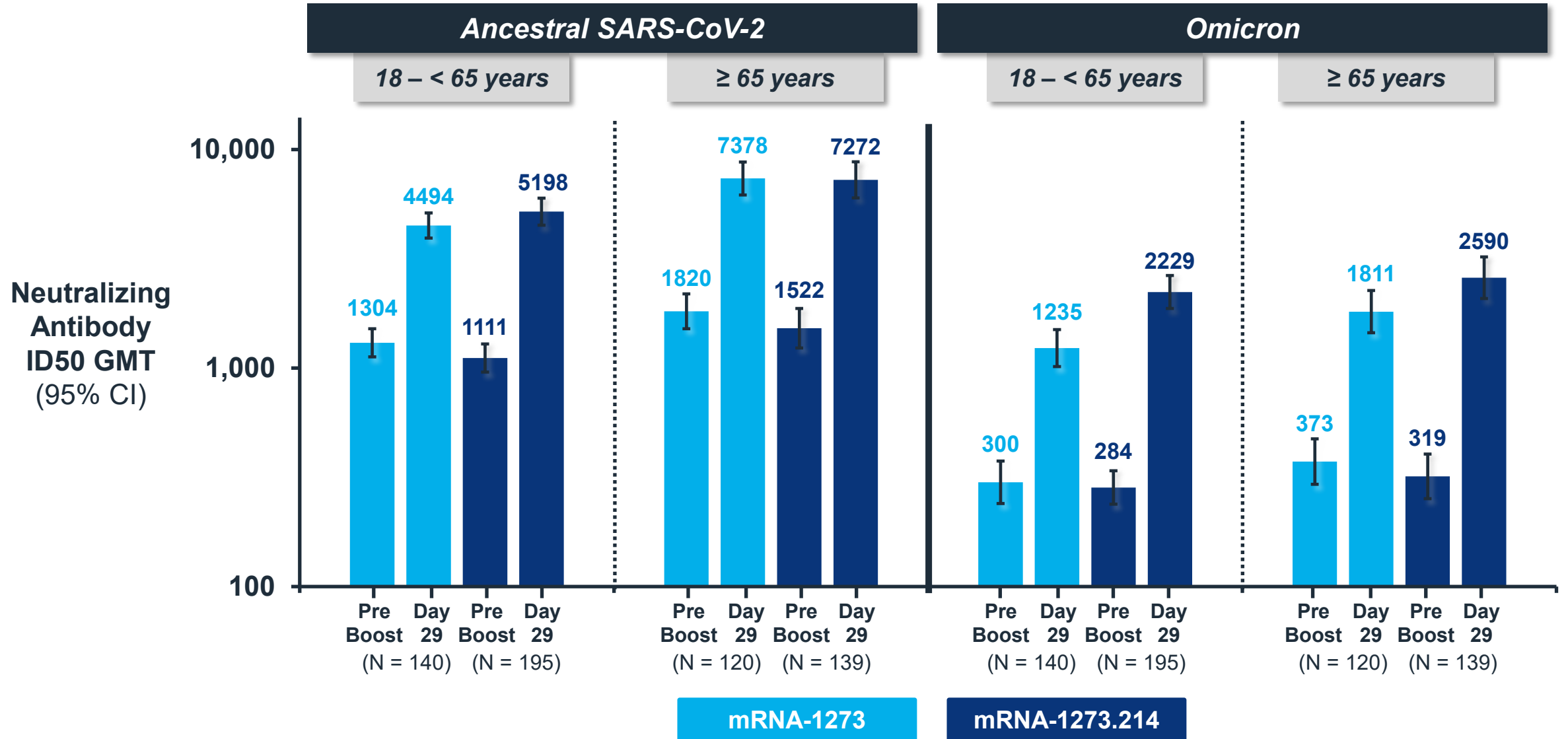
1. Based on pre-specified ANCOVA model adjusting for age group (< 65, ≥ 65 years) and pre-booster titer.

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.

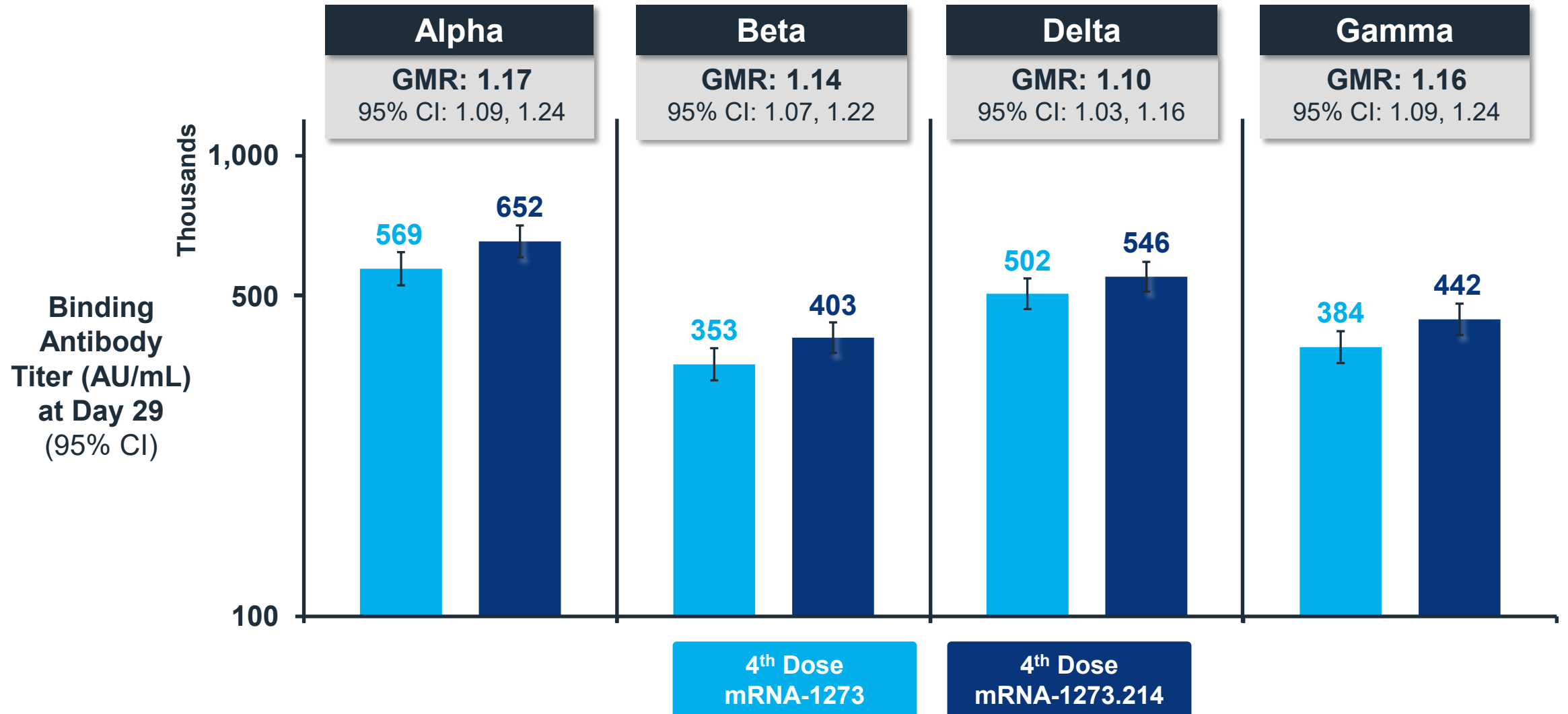
4th Dose of mRNA-1273.214 Delivered Higher Neutralizing Titers than mRNA-1273 Across Age Groups, Including Age >65

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

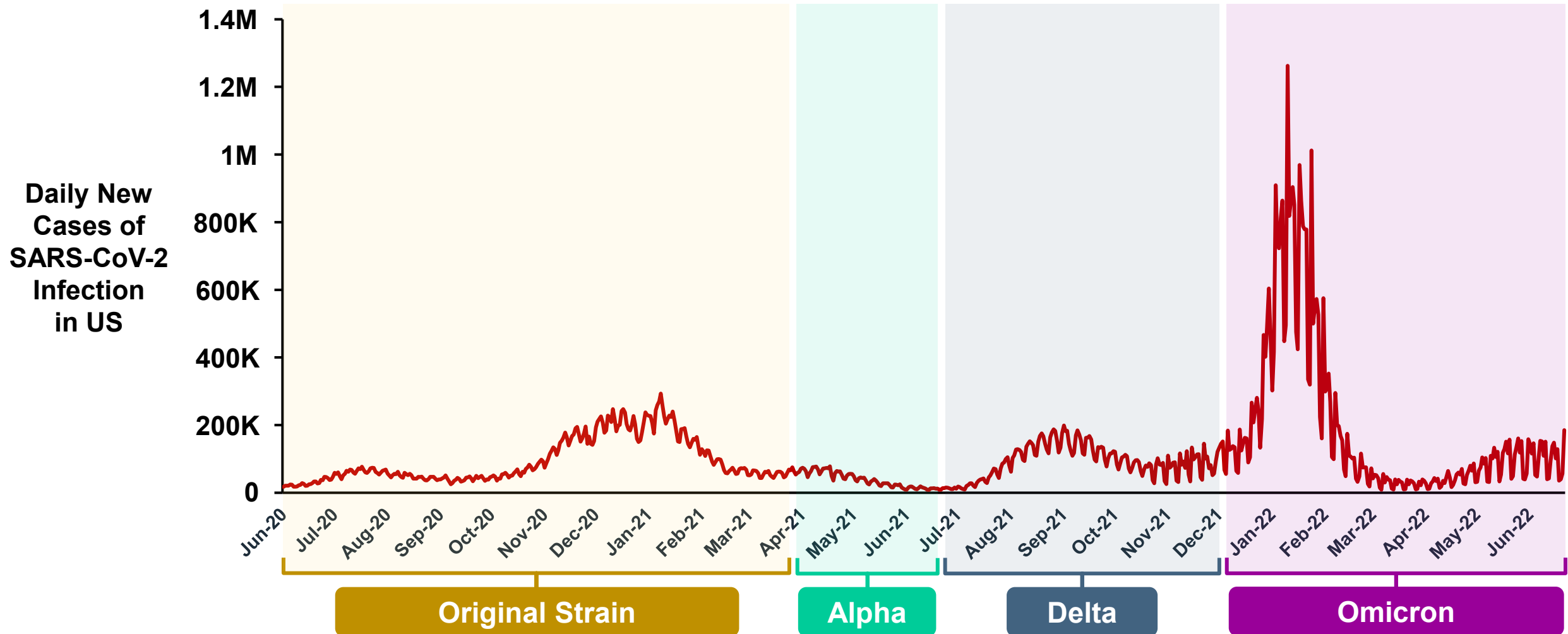
All pre-specified primary and key secondary objectives met:

- ✓ 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



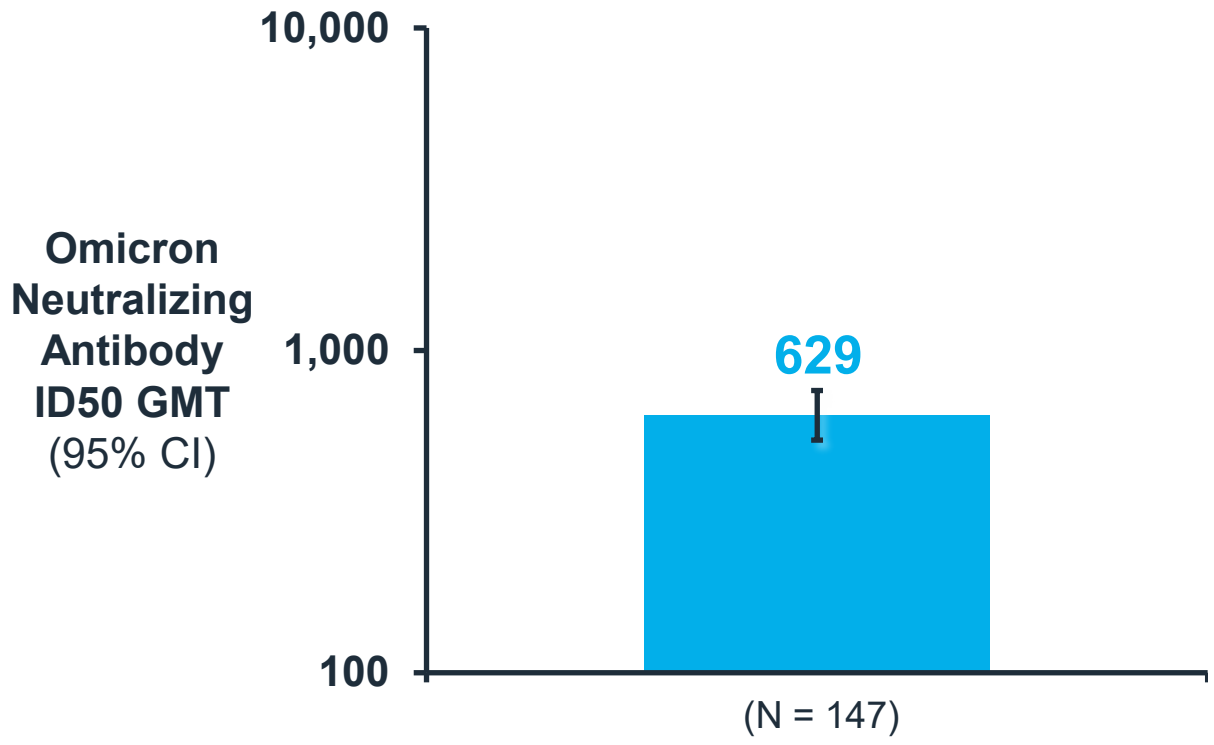
Role of mRNA-1273.214 in Addressing Emerging Variants

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

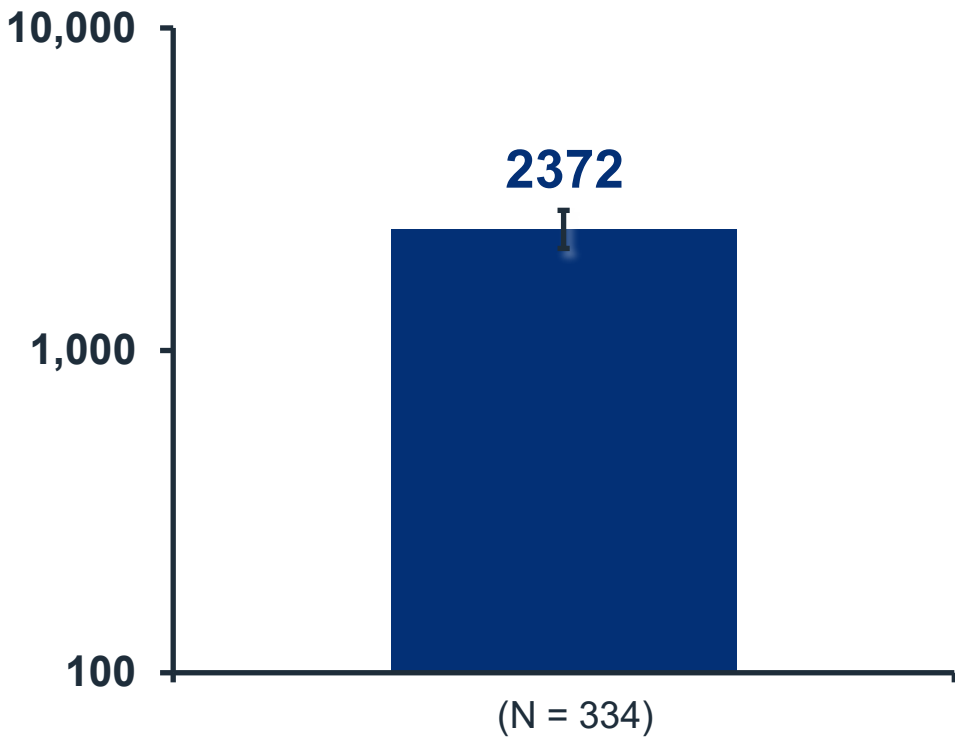


4th Dose of Bivalent mRNA-1273.214 Increases Omicron (BA.1) Neutralizing Titers

1 Month After 3rd Dose of mRNA-1273¹
Among Participants with No Prior Infection

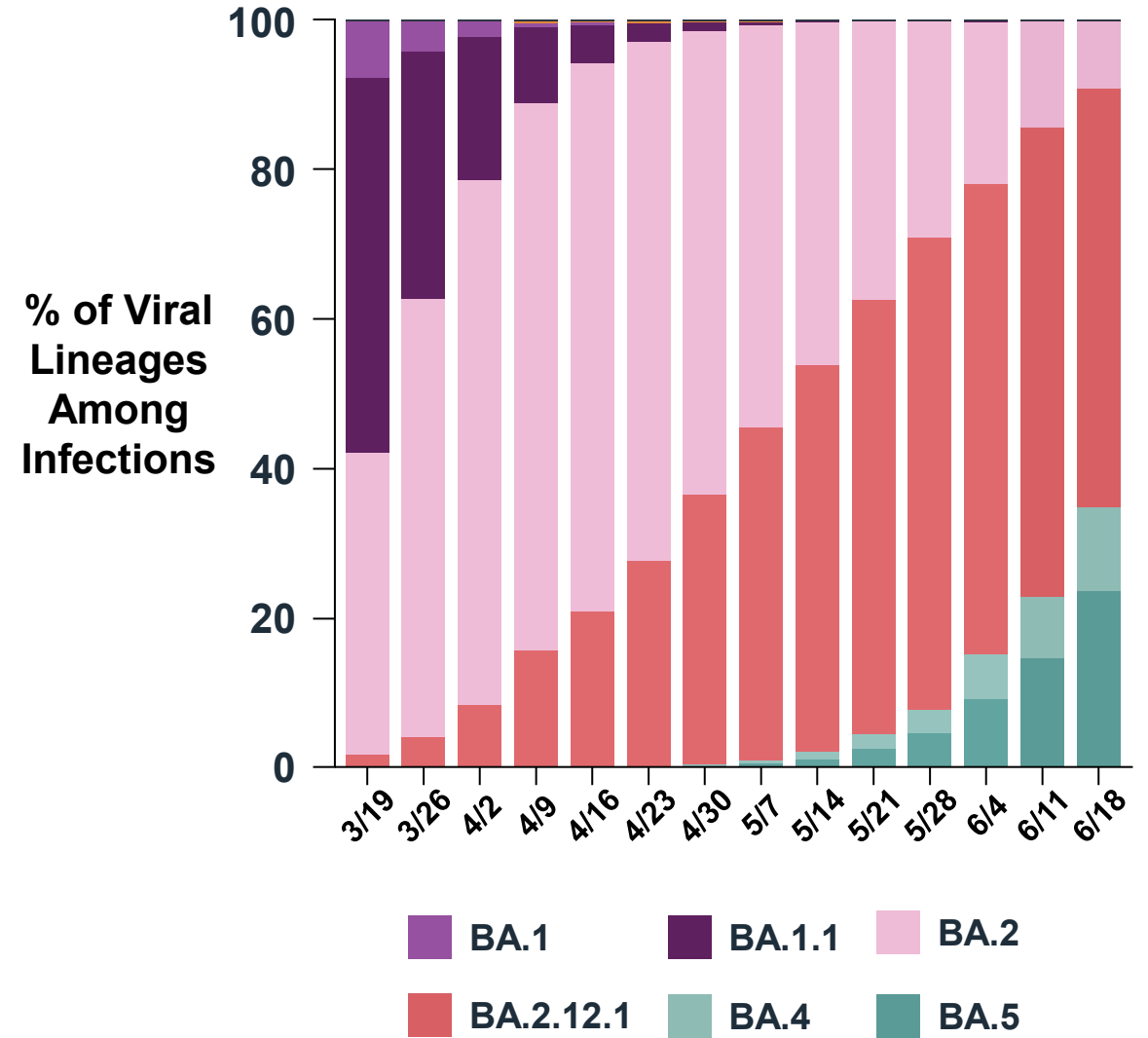
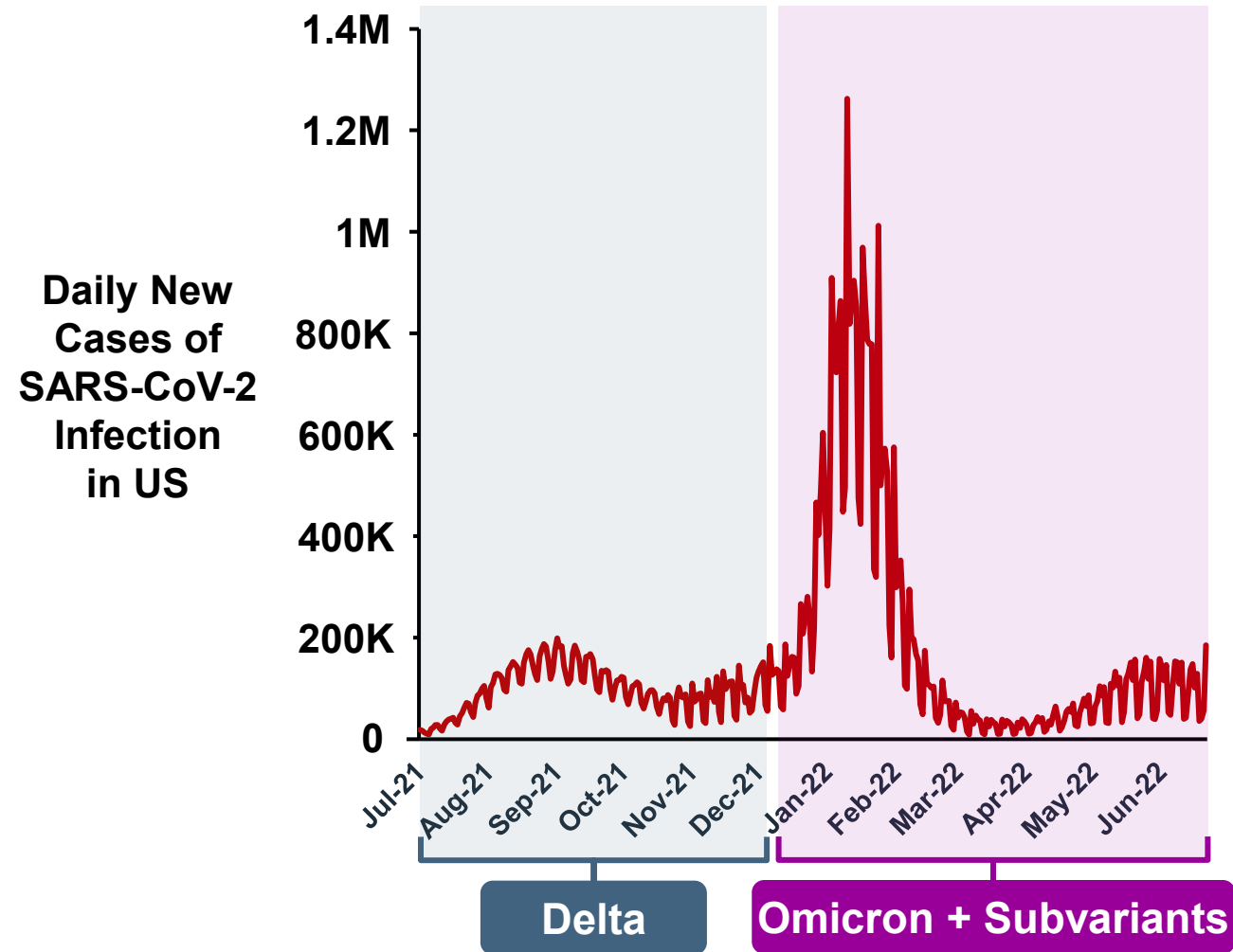


1 Month After 4th Dose of mRNA-1273.214²
Among Participants with No Prior Infection



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



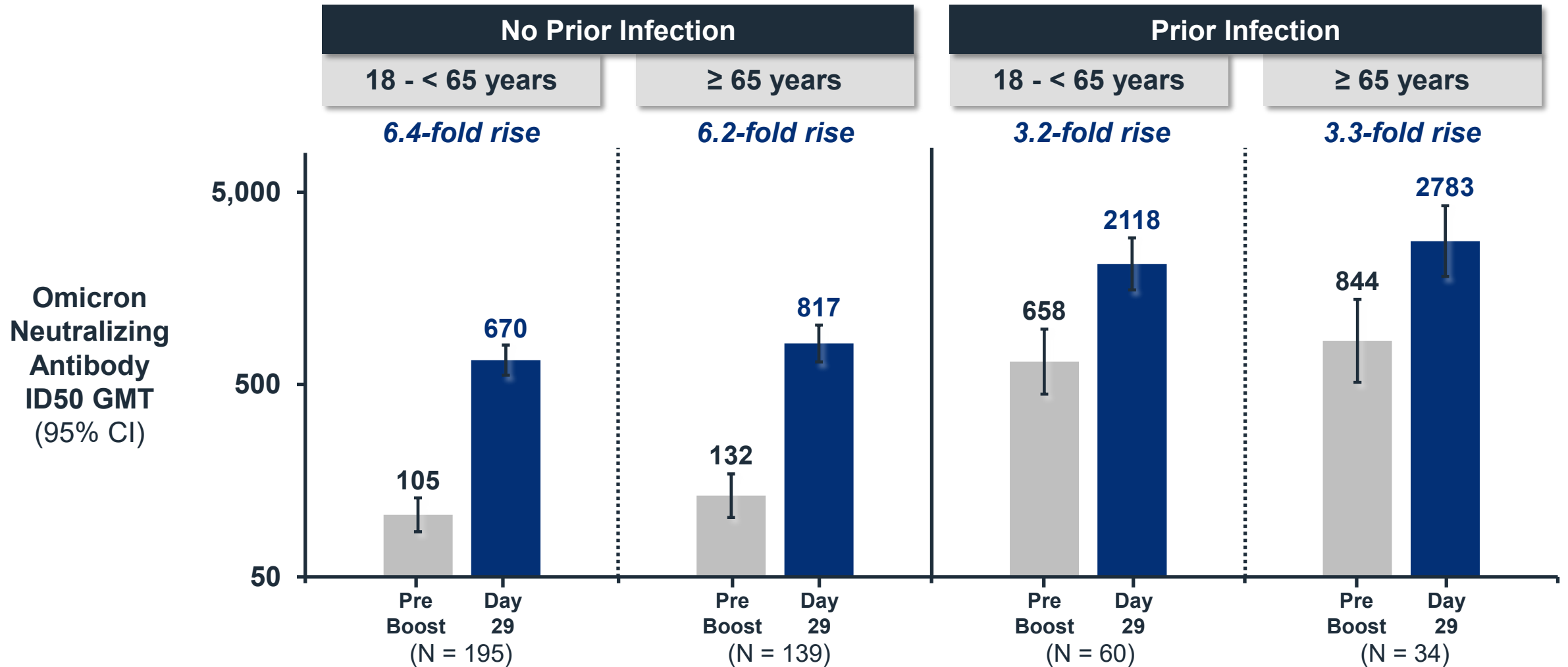
4th Dose of mRNA-1273.214 Increased BA.4/BA.5 Neutralizing Titers Regardless of Prior SARS-CoV-2 Infection

Study 205, Per-Protocol Immunogenicity Set

	4 th 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)

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

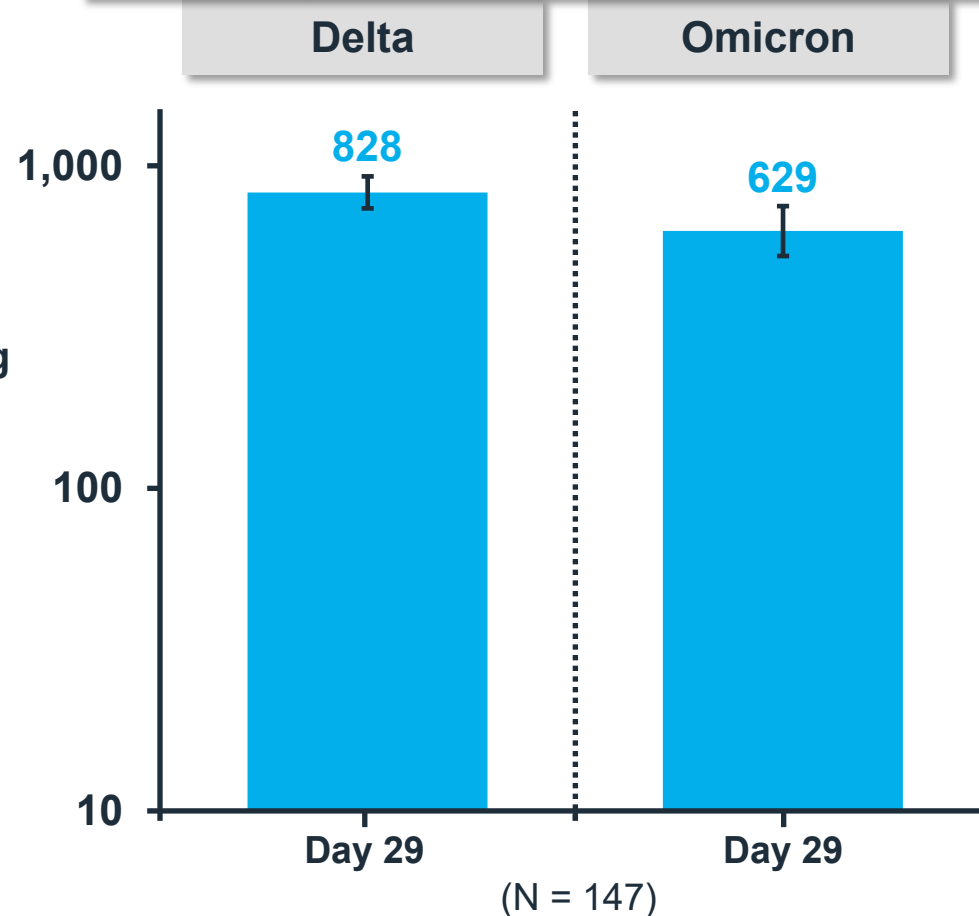


BA.4/BA.5 assay conducted at Duke/VRC (research grade, validation underway).

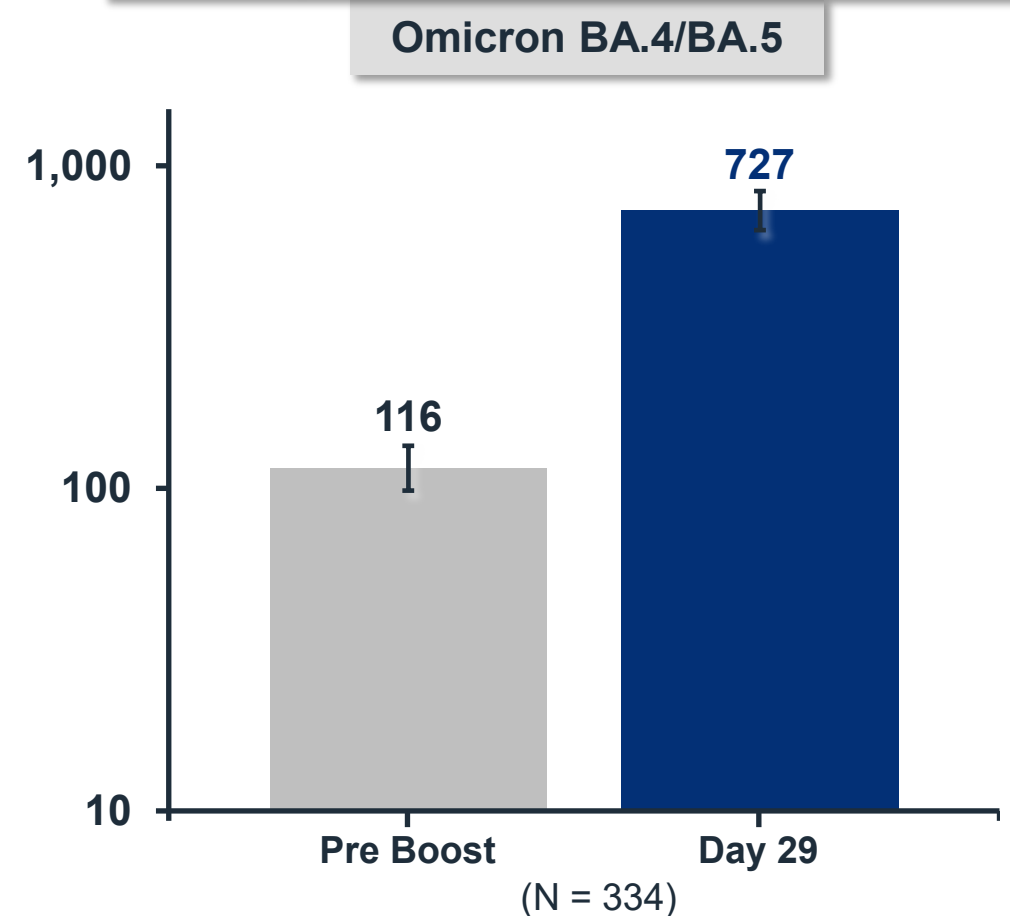
Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703.

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 Month After 3rd Dose of mRNA-1273¹
Among Participants with No Prior Infection



1 Month After 4th Dose of mRNA-1273.214²
Among Participants with No Prior Infection



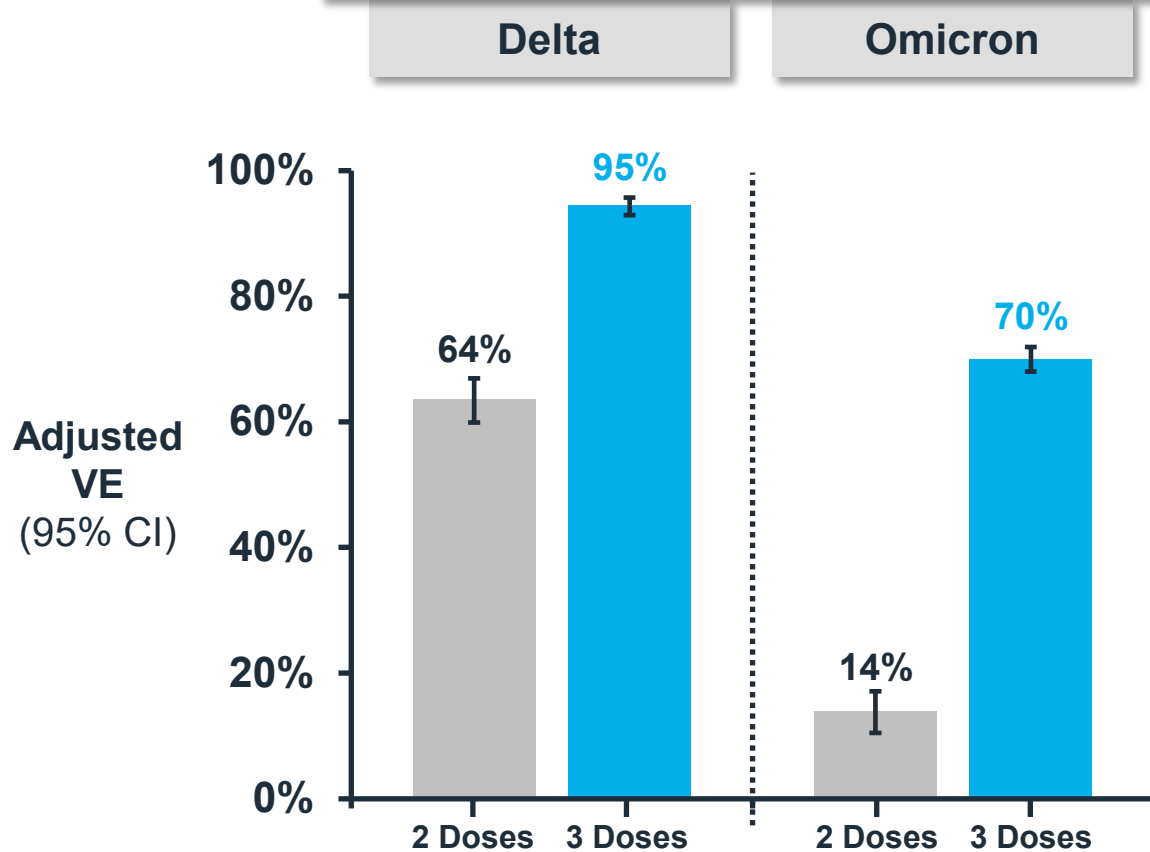
1. Chalkias et al. *Research Square* 2022, doi: 10.21203/rs.3.rs-1555201/v1.

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

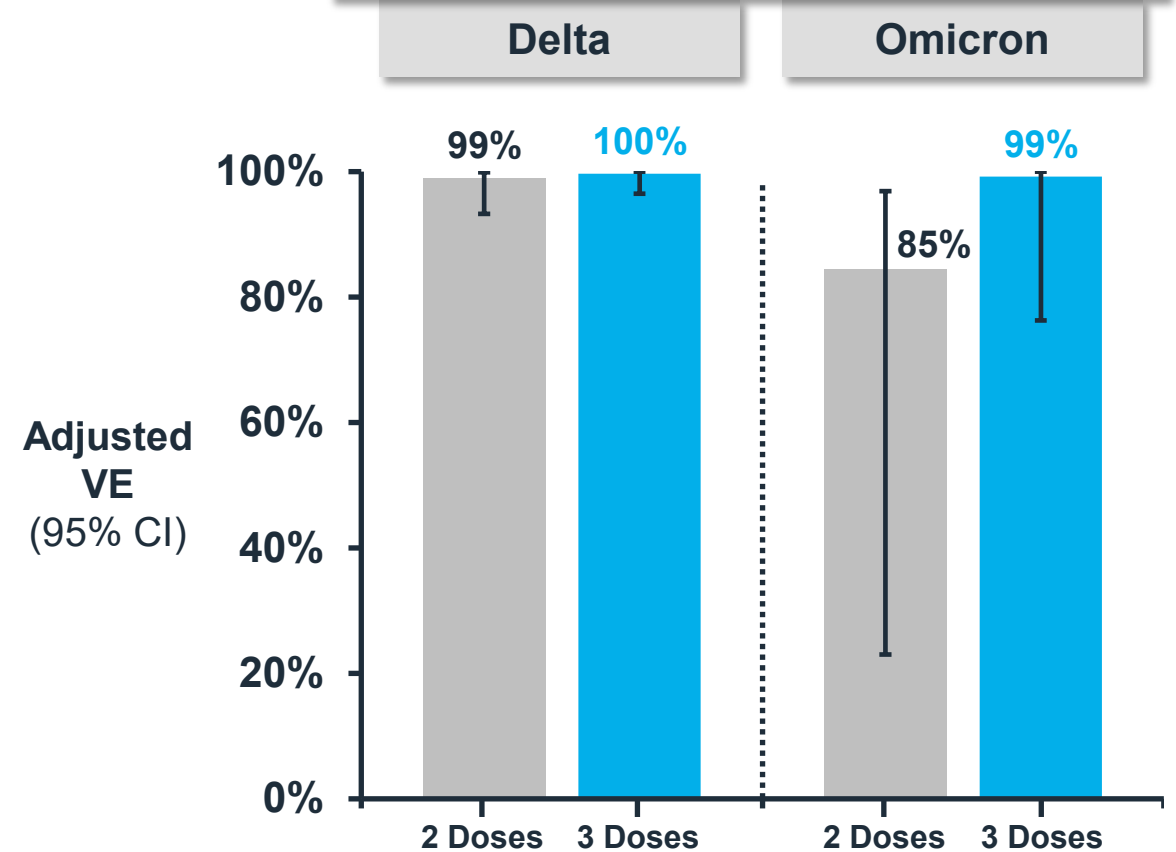
3rd Dose of mRNA-1273 Increased Real-World Effectiveness Against Delta and Omicron

Kaiser Permanente Study

Effectiveness Against Infection After 2 or 3 Doses of mRNA-1273¹



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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