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Bivalent COVID Booster Ph 2/3 Interim Analysis (mRNA-1273.214)

June 8th, 2022

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COVID booster development for endemic phase

Strategic rationale for seasonal booster	• Neutralizing titers (NT) will wane, similar to endemic HCoV • Decline in NT will increase risk of breakthrough hospitalization for those at higher risk (e.g., older adults, immune compromised) • Emergence of new variants of concern (VOC) could accelerate the impact of waning and broaden risk of breakthrough
Desired features for the northern hemisphere (NH) Fall/Winter '22-23 booster	• Improve durability of protective neutralizing antibodies against Omicron to 6+ months (i.e., the full NH fall-winter infection season) • Retain high and durable protection against prior VOC and ancestral strains • Broaden cross-protective immunity to increase potential for protection against a new (emergent) VOC mid-year

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Overview Phase 2/3 (P205) study for mRNA-1273.214

All subject received mRNA-1273 primary series (100 µg) and mRNA-1273 booster (50 µg)

	4th dose			
Trial	*Booster*	*Dose*	**Subjects(n)**	**Comments**
Phase 2/3 P205 *Only showing current arms*	**mRNA-1273**	50 µg	377	Enrolled February 21 to March 8
	.214 (32 Omicron mutations)	50 µg	437	Enrolled March 8 to March 23

mRNA-1273.214 also being evaluated in study in UK (P305) with ~1,500 participants per arm and mixed primary regimen

Arms enrolled sequentially, safety follow-up of 57 days for mRNA-1273 and 43 days for mRNA-1273.214 at time of interim analysis

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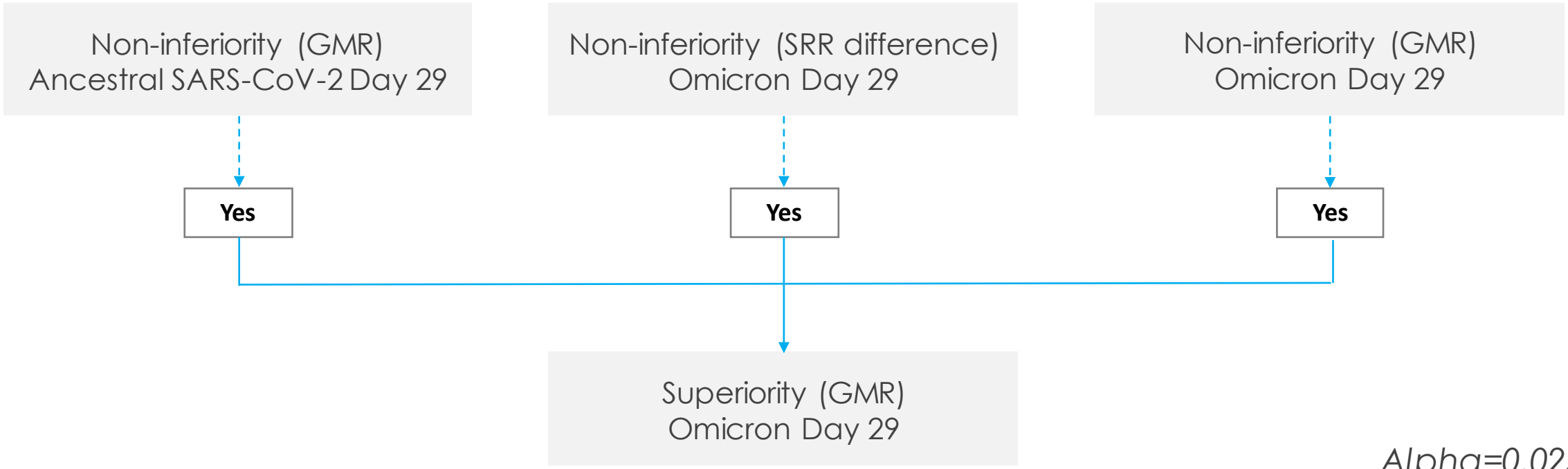
Primary immunogenecity objectives for the Phase 2/3 study (P205)

The Day 29 testing sequence for the immunogenecity endpoints is the following:



Alpha=0.025

GMR: geometric mean titer ratio; SRR: seroresponse

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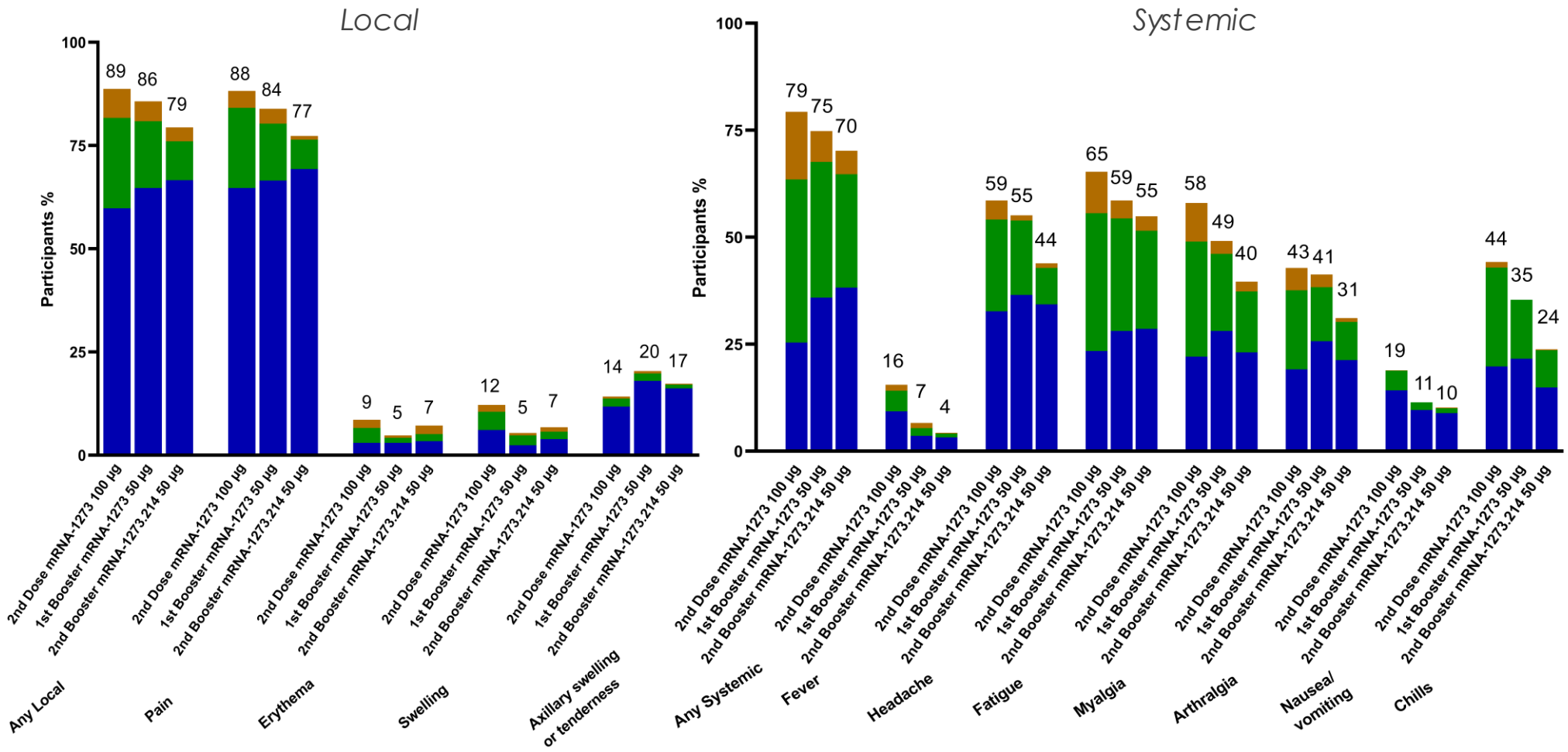
Demographics and baseline characteristics were consistent between groups

Characteristics n (%)	mRNA-1273.214 (50 µg), N=437	mRNA-1273 (50 µg), N=377
Age at Screening (yr)		
Mean (range)	57.3 (20, 88)	57.5 (20, 96)
Age subgroup		
≥18 and <65 years	263 (60.2)	227 (60.2)
≥65 years	174 (39.8)	150 (39.8)
Gender		
Male	179 (41.0)	186 (49.3)
Female	258 (59.0)	191 (50.7)
Duration between second dose of mRNA-1273 in the primary series and the first booster of mRNA-1273 (months)		
Median	8.0	8.0
Q1, Q3	(7.4, 9.0)	(7.4, 8.5)
Duration between first booster injection of mRNA-1273 and the second booster (months)		
Median	4.5	4.4
Q1, Q3	(3.9, 4.9)	3.9, 4.9
SARS-CoV-2 infection Pre-booster		
Negative	340 (77.8)	267 (70.8)
Positive*	96 (22.0)	101 (26.8)
Missing	1 (0.2)	9 (2.4)

**SARS-CoV-2 testing was performed with polymerase chain reaction (PCR) and SARS-CoV-2 nucleocapsid antibody test. A positive test (either PCR or antibody test) was needed for the SARS-CoV-2 infection positive group.*

Solicited adverse reactions were consistent with prior doses

Solicited adverse reactions within 7 days of the dose



Solicited adverse reactions trended lower for mRNA-1273.214 compared to prior doses

Frequency and types of unsolicited adverse events were also comparable, with no vaccine-related serious events in the .214 group up to 28 days after the booster dose

Source trial: P301(primary, 100 µg dose 2); P201 (50 µg booster 1); P205 (50 µg booster 2)

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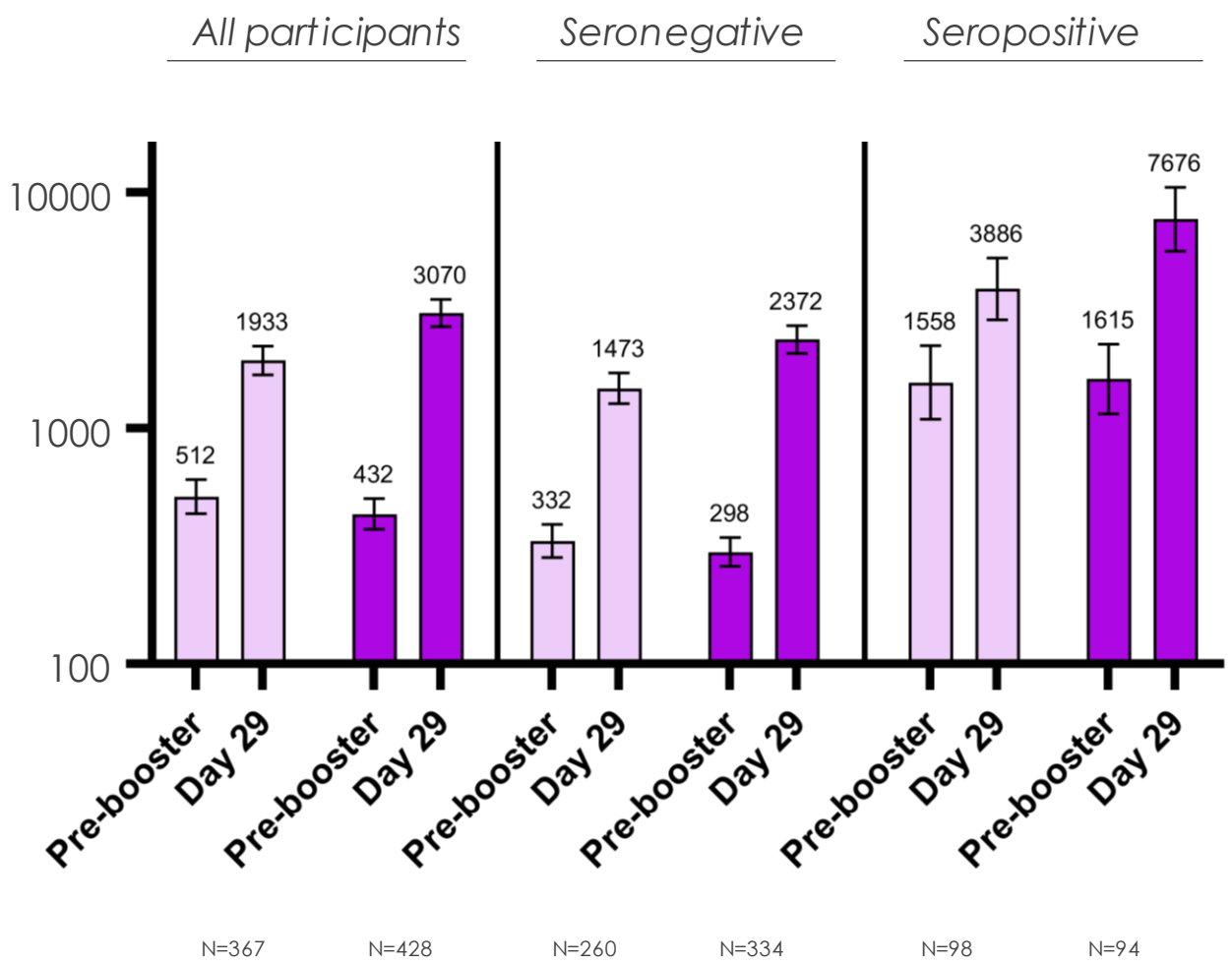
Omicron neutralizing titers (PsVNT50)

Omicron neutralizing antibody titers (PsVNT50)



Omicron neutralizing titers **were significantly higher following bivalent (.214) booster** compared to prototype for all participants and both seronegative and baseline seropositive participants

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Bivalent booster (.214) resulted in superior neutralizing GMT against Omicron

Only baseline seronegative participants

	mRNA-1273.214 50 µg (N=334)	**mRNA-1273** 50 µg (N=260)
Pre-booster GMT, 95% CI	298.13 (258.75, 343.49)	332.02 (282.05, 390.85)
Estimated GMTs (95% CI) at Day 29[a]	2479.89 (2264.47, 2715.80)	1421.24 (1282.98, 1574.41)
GMFR (95% CI) at Day 29, 95% CI	7.96 (7.18, 8.82)	4.44 (3.97, 4.96)
GMR (97.5% CI)[a]	**1.75** (1.49, 2.04)	
Seroresponse rate (95% CI) at Day 29[b]	333/333, 100 (98.9, 100)	256/258, 99.2 (97.2, 99.9)
Difference in seroresponse rates (97.5% CI)[c]	**1.5** (-1.1, 4.0)	

Primary endpoint for testing non-inferiority and superiority was seronegative participants

- **All primary and key secondary immunogenicity objectives were met**
  - mRNA-1273.214 **elicited superior neutralizing antibody response against Omicron**, compared to the prototype mRNA-1273 (50 µg) 28 days after the booster dose
  - mRNA-1273.214 **elicited a non-inferior seroresponse rate** compared to the prototype mRNA-1273 (50 µg) 28 days after the booster dose
- mRNA-1273.214 induced a **potent neutralizing antibody response against Omicron in all seronegative individuals** tested

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups.
[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.
[c] 97.5% CI was calculated using a stratified Miettinen-Nurminen method and adjusting by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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Bivalent booster (.214) resulted in superior neutralizing GMT against Omicron

All participants

	mRNA-1273.214 50 µg (N=428)	**mRNA-1273** 50 µg (N=367)
Pre-booster GMT, 95% CI	432.05 (372.47, 501.17)	511.98 (433.39, 604.84)
Estimated GMTs (95% CI) at Day 29[a]	3232.52 (2951.83, 3539.89)	1815.14 (1650.05, 1996.74)
GMFR (95% CI) at Day 29, 95% CI	7.11 (6.48, 7.79)	3.78 (3.42, 4.17)
GMR (97.5% CI)[a]	**1.78** (1.56, 2.04)	
Seroresponse rate (95% CI) at Day 29[b]	380/380, 100 (99.0, 100)	340/342, 99.4 (97.9, 99.9)
Difference in seroresponse rates (97.5% CI)[c]	**1.2** (-1.3, 3.7)	

- Bivalent booster (.214) resulted in superior neutralizing GMT against Omicron compared to mRNA-1273 for all participants (includes both **seronegative participants** and **seropositive participants)**

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, prior SARS-CoV-2 infection, pre-booster antibody titers, and age groups.
[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.
[c] 97.5% CI was calculated using a stratified Miettinen-Nurminen method and adjusting by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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Bivalent booster (.214) elicited higher neutralizing antibody titers against ancestral SARS-CoV-2 (D614G)

	SARS-CoV-2 negative pre-booster participants		*All participants*	
	mRNA-1273.214 50 µg (N=334)	**mRNA-1273** 50 µg (N=260)	**mRNA-1273.214** 50 µg (N=428)	**mRNA-1273** 50 µg (N=367)
Pre-booster GMT, 95% CI	1266.74 (1120.19, 1432.47)	1521.00 (1352.77, 1710.15)	1603.35 (1420.26, 1810.05)	1944.78 (1725.35, 2192.12)
Estimated GMTs (95% CI) at Day 29[a]	6422.32 (5990.12, 6885.71)	5286.63 (4887.07, 5718.86)	6555.69 (6122.34, 7019.72)	5301.37 (4931.77, 5698.66)
GMFR (95% CI) at Day 29, 95% CI	4.72 (4.36, 5.11)	3.71 (3.42, 4.03)	4.13 (3.84, 4.44)	3.11 (2.88, 3.36)
GMR (97.5% CI)[a]	**1.22** (1.08, 1.37)		**1.24** (1.12, 1.37)	
Seroresponse rate (95% CI) at Day 29[b]	334/334, 100 (98.9, 100)	260/260, 100 (98.6, 100)	383/383, 100 (99.0, 100)	347/347, 100 (98.9, 100)
Difference in seroresponse rates (97.5% CI)[c]	**0**		**0**	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups for SARS-CoV-2 negative pre-booster participants. For all participants, model also includes prior SARS-CoV-2 infection.

[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.

[c] 97.5% CI is calculated using a stratified Miettinen-Nurminen method and adjusting by age group for SARS-CoV-2 negative pre-booster participants. For all participants, both age group and prior SARS-CoV-2 infection are adjusted. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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Conclusions

- The **mRNA-1273.214 50 µg booster dose was well-tolerated** and the safety and reactogenicity profile was similar to that of the prototype mRNA-1273 50 µg booster dose
- **All primary and key secondary immunogenicity objectives were met:**
  - mRNA-1273.214 (50 µg) **elicited a superior neutralizing antibody response against Omicron**, compared to the prototype mRNA-1273 (50 µg) 28 days after the booster dose
  - mRNA-1273.214 (50 µg) **elicited a non-inferior neutralizing antibody response against the ancestral SARS-CoV-2** compared to the prototype mRNA-1273 (50 µg) 28 days after the booster dose
- mRNA-1273.214 (50 µg) also induced a **potent neutralizing antibody response against Omicron in all individuals** regardless of prior SARS-CoV-2 infection status pre-booster

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To deliver on the promise of mRNA science to create a new generation of transformative medicines for patients.

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