Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Moderna COVID-19 Bivalent Vaccines Primary Series and Booster

Moderna, Inc.

Vaccines and Related Biological Products Advisory Committee

January 26, 2023

Moderna COVID-19 Bivalent Vaccines Primary Series and Booster

Antonella Lozito, PharmD

Executive Director

Regulatory Affairs Strategy, Infectious Diseases

Moderna, Inc.

Omicron-Containing mRNA-1273 Bivalent Vaccines

- >278 million doses of Moderna bivalent vaccines distributed worldwide[1]
  - No new safety signals identified
- Bivalent vaccines protect against infection and severe disease/hospitalizations as demonstrated in real-world studies[2]
- Consistent safety and immunogenicity data observed in preclinical and clinical trials with bivalent vaccines
  - Primary series and booster in children (6 months to 5 years of age)
  - Booster in adults (≥18 years of age)
- Cross-neutralization observed for emerging Omicron subvariants

1. >128.9 million doses of BA.1 and >149.7 million doses of BA.4/BA.5 (as of 1/18/23)
2. Link-Gelles *MMWR*, 2022; UK Health Security Agency COVID-19 Vaccine Surveillance Report, Week 48, 1 December 2022; Tenforde *MMWR* 2022; Surie *MMWR* 2022; Kaiser unpublished data, Jan 2023

Moderna Continues to Prepare as SARS-CoV-2 Variants Continue to Emerge

Moderna's Commitment

- Monitor emerging variants of concern
- Generate preclinical and clinical data accordingly
- Develop new vaccines as directed
- Ensure manufacturing capabilities to rapidly respond to public health needs

Future of COVID-19 Vaccines

- Welcome harmonized decision-making process to update COVID-19 vaccine composition
- Suggest similar model to that used as regulatory basis for approval of influenza vaccine updates

Clinical and Real-World Effectiveness Data with Omicron-Containing mRNA-1273 Bivalent Vaccines

Rituparna Das, MD, PhD
Vice President, Clinical Development
COVID-19 Vaccines
Moderna, Inc.

Preclinical Results from Authorized and Investigational Bivalent Vaccines

Darin Edwards, PhD
Senior Director of Immunology
Infectious Disease Group
Moderna, Inc.

Summary and Conclusion

Rituparna Das, MD, PhD

Clinical Evaluation of Moderna COVID-19 Bivalent Vaccines for Booster and Primary Series

Rituparna Das, MD, PhD

Vice President, Clinical Development, COVID-19 Vaccines

Moderna, Inc.

> 9700 Individuals Vaccinated in Clinical Trials with Moderna Variant-Containing Vaccines

- Two mRNA-1273 bivalent booster vaccines available worldwide

Omicron BA.4 / BA.5 + Original Strain (1:1 ratio)	Omicron BA.1 + Original Strain (1:1 ratio)
mRNA-1273.222	**mRNA-1273.214**
Authorized in 38 countries[1] (United States, EU and others)	**Authorized in 44 countries**[1] (EU and others)

1. As of 1/16/23

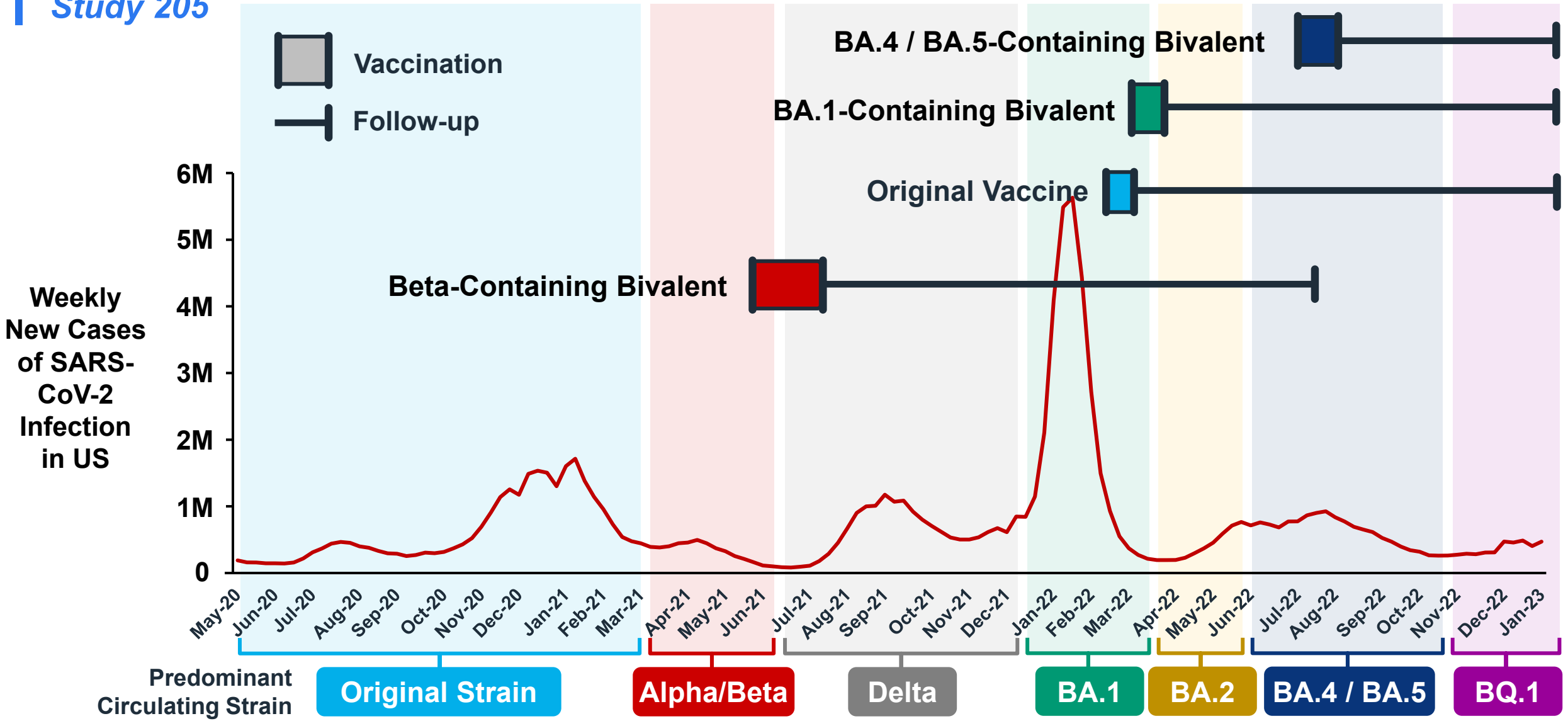
Booster of Moderna Omicron-Containing BA.4 / BA.5 Bivalent Vaccine vs Original Vaccine

Adults in United States

(Study 205H)

Open Label Phase 2/3 Safety and Immunogenicity Study of Bivalent Vaccines in Adults

Study 205



https://covid.cdc.gov/covid-data-tracker/#trends_dailycases; https://ourworldindata.org/grapher/covid-variants-area?time=2022-10-24..latest&country=~USA

Phase 2/3 Safety and Immunogenicity Study of Omicron-Containing BA.4 / BA.5 Bivalent Booster in Adults

Study 205H

	Original Vaccine (mRNA-1273) Non-Contemporaneous Control	BA.4 / BA.5 Bivalent (mRNA-1273.222)
Vaccine Composition	**50 µg** Original Strain	**25 µg** Original Strain + **25 µg** Omicron BA.4/BA.5
Enrollment	**February 18 – March 8, 2022**	**August 10 – 23, 2022**
Dose	**4th** (2nd Booster)	**4th** (2nd Booster)
Participants	**N = 376**	**N = 511**
Median Follow-up	**127 Days**	**37 Days**

All participants previously received original vaccine (mRNA-1273) primary series (100 µg) and 1st booster (50 µg)

Chalkias et al., *medRxiv,* 2022, https://doi.org/10.1101/2022.12.11.22283166

Demographics and Baseline Characteristics

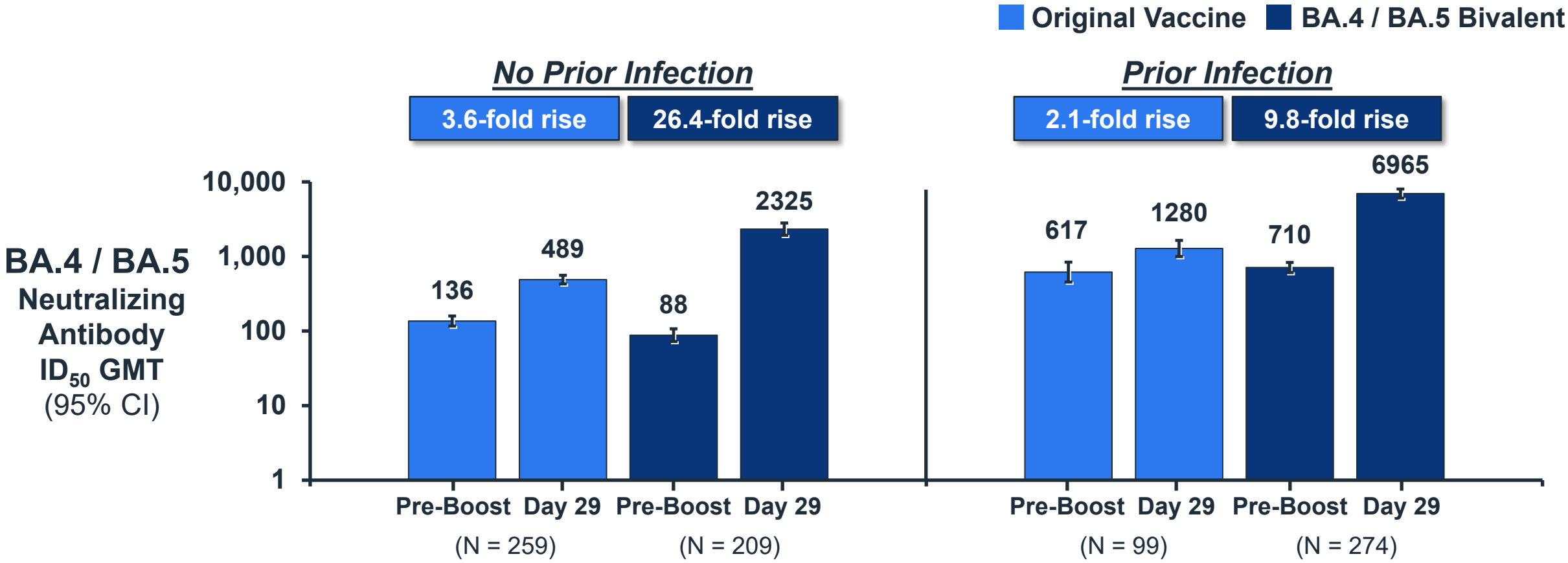
Study 205H, 4th Dose (2nd Booster)

Characteristic	Original Vaccine (mRNA-1273) N = 376	BA.4 / BA.5 Bivalent (mRNA-1273.222) N = 511
Mean Age – Years	**58**	**51**
Median Age – Years (range)	**61** (20, 96)	**50** (19, 89)
≥ 65 years	**40%**	**21%**
Non-White Race	**13%**	**16%**
Hispanic / Latino Ethnicity	**10%**	**11%**
Months between 2nd and 3rd Dose, median (range)	**8.0** (5.6, 14.4)	**8.2** (2.2, 17.5)
Months between 3rd and 4th Dose, median (range)	**4.4** (3.0, 10.2)	**9.5** (3.4, 12.2)
Prior SARS-CoV-2 Infection	**27%**	**56%**

Chalkias et al., *medRxiv,* 2022, https://doi.org/10.1101/2022.12.11.22283166

Omicron BA.4 / BA.5 Neutralizing Antibodies After 4th Dose (2nd Booster) Superior with BA.4 / BA.5 Bivalent in Adults

Study 205H, Per-Protocol Immunogenicity Set



Geometric Mean Ratio (95% CI) BA.4 / BA.5 Bivalent vs Original Vaccine	**6.3** (5.3, 7.5)	**5.1** (4.1, 6.4)

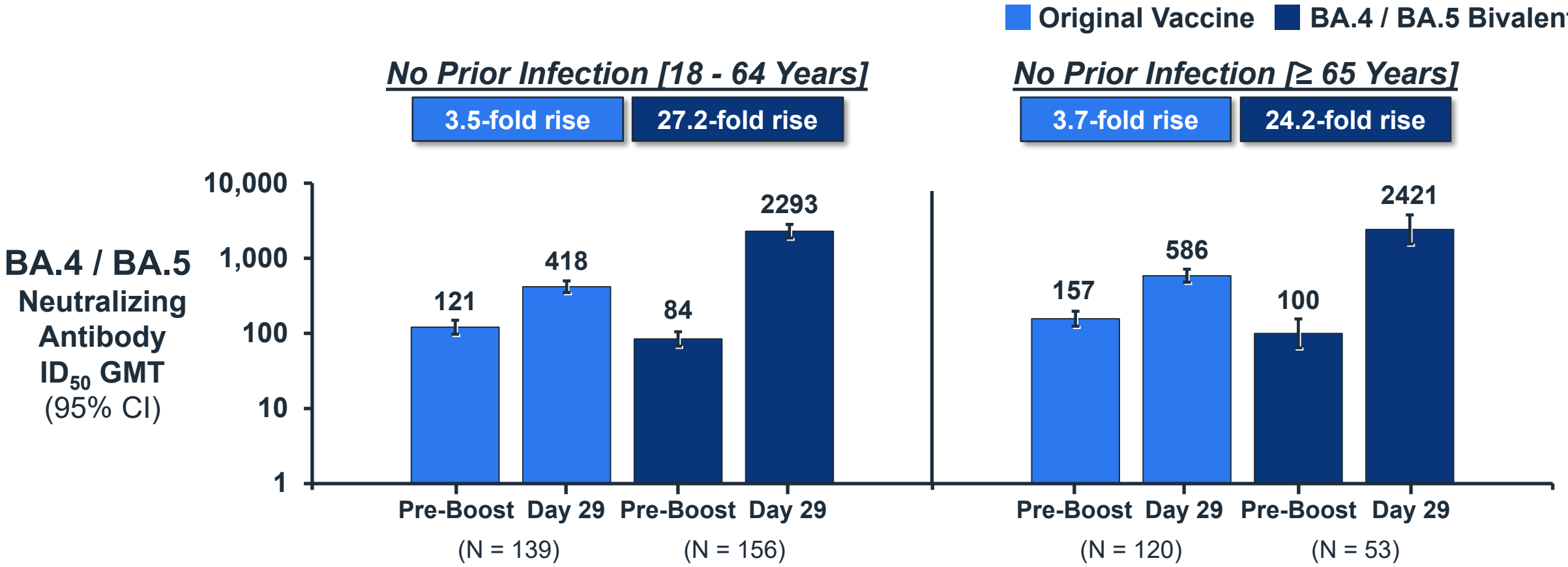
Note: Superiority of Omicron BA.4/BA.5 compared to original vaccine booster was demonstrated based on the lower bound of 95% CI >1

Chalkias et al., *medRxiv,* 2022, https://doi.org/10.1101/2022.12.11.22283166

Duke Lab – Pseudovirus Neutralization Assay

Omicron BA.4 / BA.5 Neutralizing Antibodies Higher in Adults ≥ 65 After 4th Dose (2nd Booster) with BA.4 / BA.5 Bivalent

Study 205H, Per-Protocol Immunogenicity Set



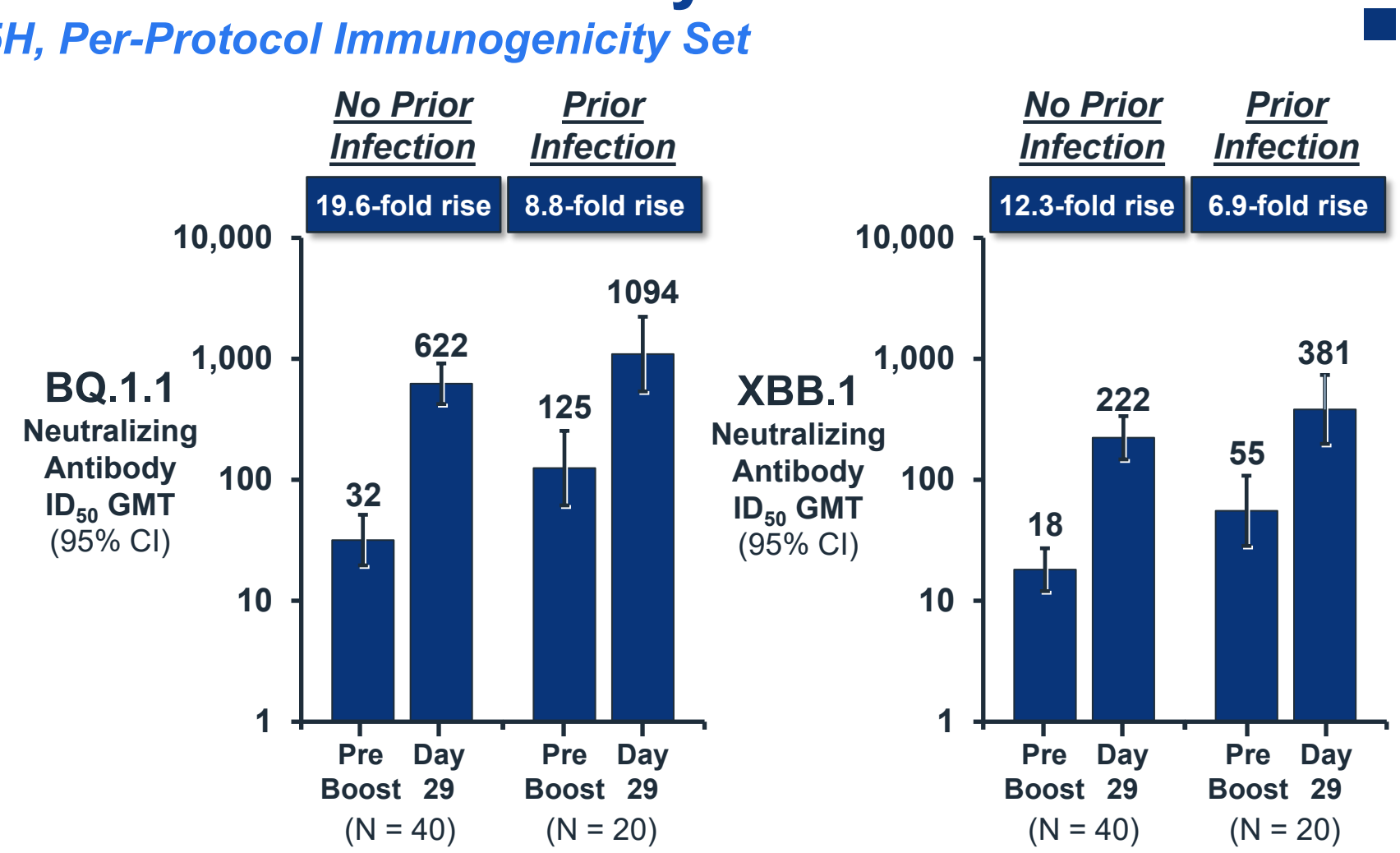
Geometric Mean Ratio (95% CI) BA.4 / BA.5 Bivalent vs Original Vaccine	**6.7** (5.4, 8.4)	**5.5** (4.0, 7.5)

Chalkias et al., *medRxiv,* 2022, https://doi.org/10.1101/2022.12.11.22283166

Neutralization Against Emerging Variants Following Receipt of Omicron Bivalent BA.4 / BA.5 Vaccine (Study 205H)

Omicron BA.4 / BA.5 Bivalent Vaccine Exhibited Cross-Neutralization at Day 29

Study 205H, Per-Protocol Immunogenicity Set



Omicron variants in US (as of Jan 14, 2023)[1] - 45% BQ.1 & BQ.1.1, 43% XBB.1.5

Chalkias et al., *medRxiv,* 2022, https://doi.org/10.1101/2022.12.11.22283166;
[1] https://covid.cdc.gov/covid-data-tracker/#variant-proportions (NOWCAST model)

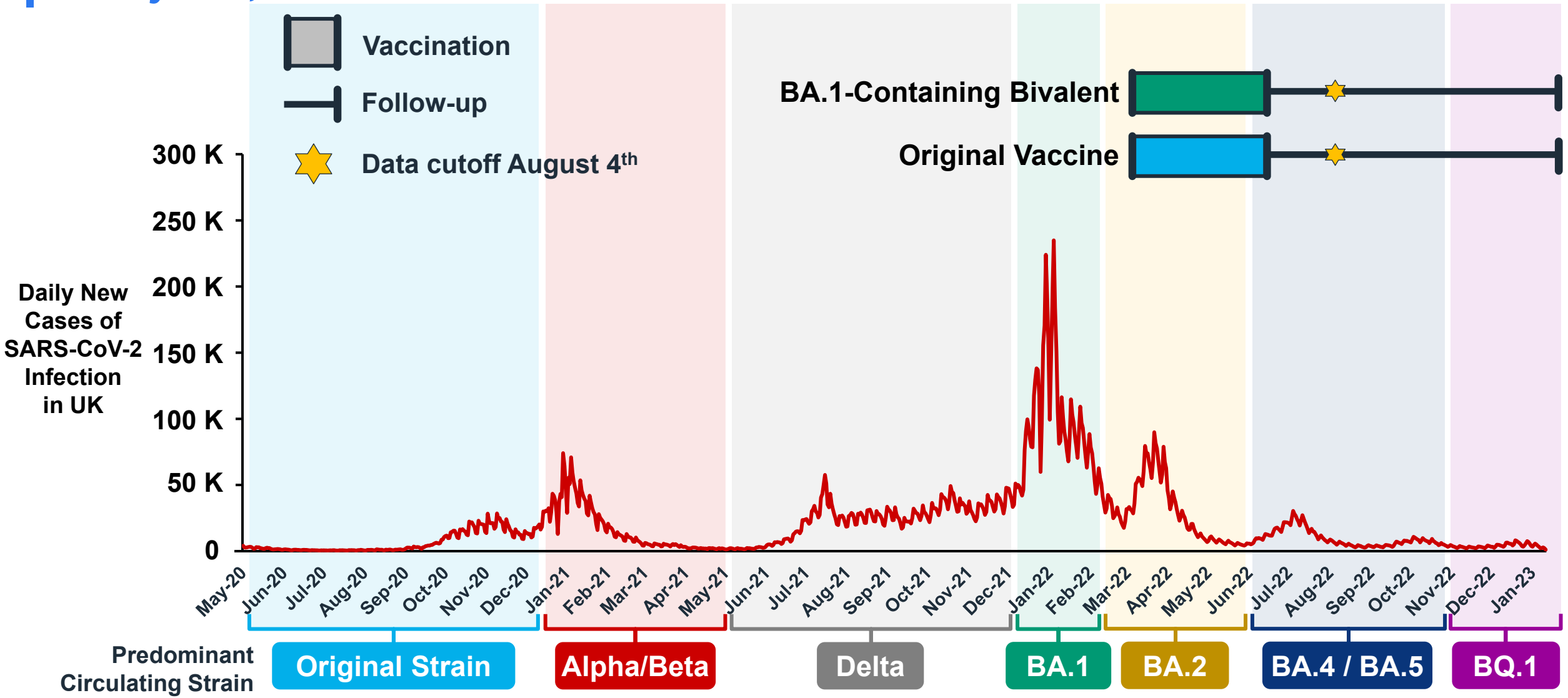
Duke Lab – Pseudovirus Neutralization Assay

Randomized, Active-Controlled Study of Moderna Omicron Containing BA.1 Bivalent Vaccine vs Original Vaccine Boosters

Individuals ≥16 Years of Age in United Kingdom (Study 305)

Phase 3 Randomized, Active-Controlled Study of Omicron BA.1 Bivalent vs Original Vaccine Boosters in ≥16 Year Olds in UK

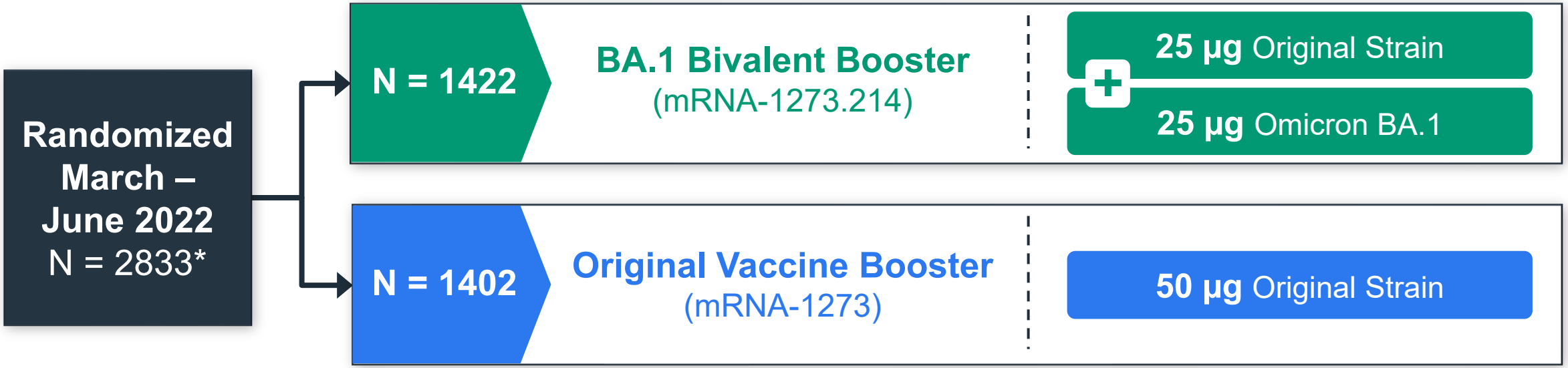
Study 305, Part 2



https://coronavirus.data.gov.uk/; https://www.gov.uk/government/collections/new-sars-cov-2-variant

Phase 3 Randomized, Active-Controlled Study of Omicron BA.1 Bivalent vs Original Vaccine Boosters in ≥16 Year Olds in UK

Study 305, Part 2



htpps://clinicaltrials.gov/ct2/show/NCT05249829

*9 individuals were randomized but did not receive a booster

Demographics and Baseline Characteristics

Study 305, Part 2

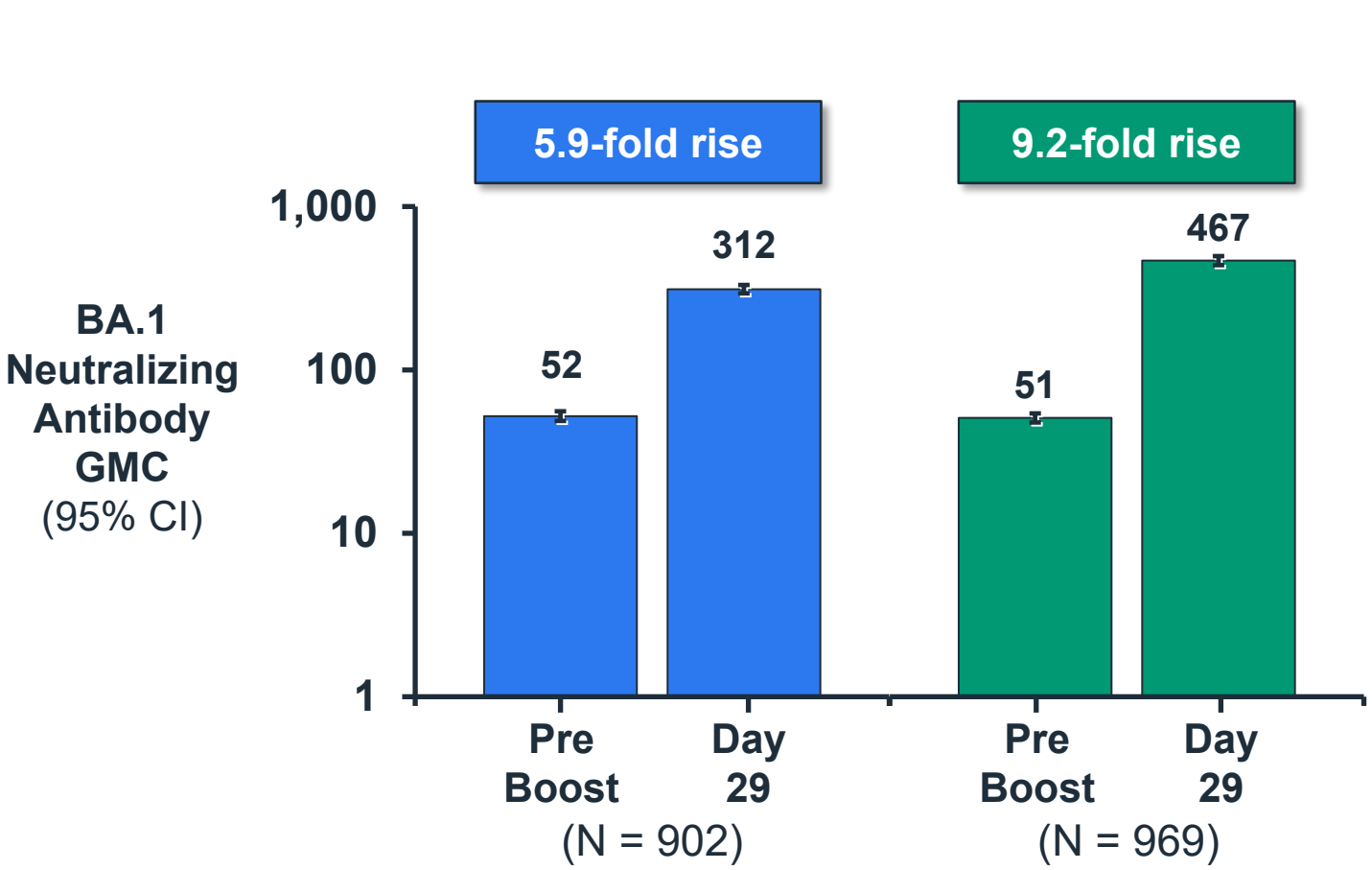
Characteristic	4th Dose (2nd Booster) Original Vaccine (mRNA-1273) N = 1395	4th Dose (2nd Booster) BA.1 Bivalent (mRNA-1273.214) N = 1418
Mean Age – Years	**57**	**58**
Median Age – Years (range)	**60 (18, 81)**	**60 (18, 89)**
≥ 65 years	**34%**	**34%**
Female (%)	**50%**	**49%**
Months between 3rd and 4th Dose, median (range)*	**5.4** (0.2, 9.9)	**5.5** (0.4, 11.2)
Prior SARS-CoV-2 Infection	**26%**	**23%**

- **Previous Vaccines:**
  - **Primary series:** 63% AstraZeneca, 34% Pfizer, 1% Moderna, Janssen 0.3%, 1% mixed
  - **Booster:** 77% Pfizer, 23% Moderna

*Participants with <3 months duration between 3rd and 4th doses were excluded from the per protocol sets

Omicron BA.1 Neutralizing Antibody After 4th Dose of Bivalent Omicron BA.1 Vaccine Compared to 4th Dose of Original Vaccine in ≥16 Year Olds

Study 305, Part 2 (Per-Protocol Immunogenicity Set – No Prior Infection)



- GMR similar to Study 205 data presented previously[1]
- Persistence of superiority for Omicron BA.1 is established for 3 months in Study 205[2]

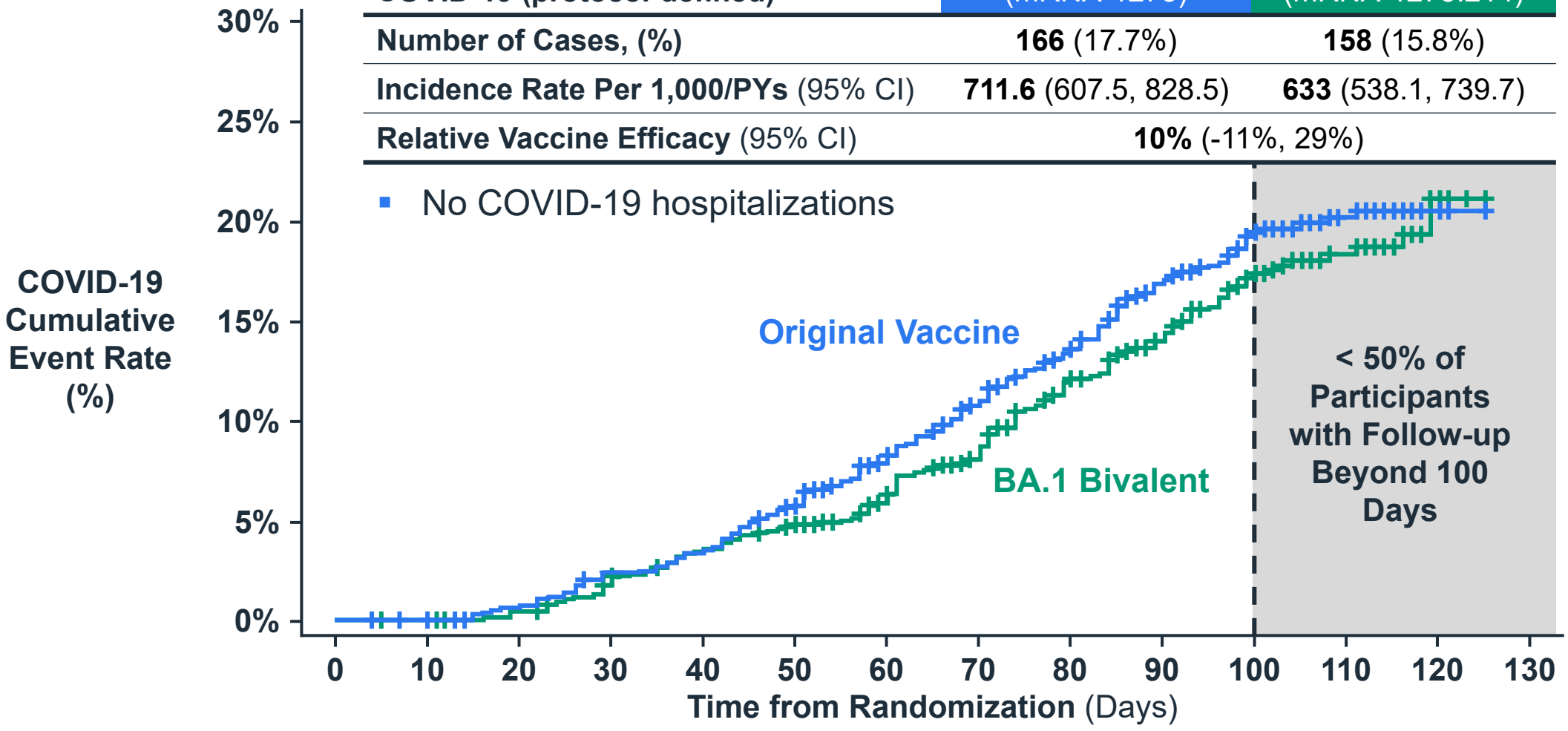
Geometric Mean Ratio (99% CI) vs Original Vaccine Booster	**1.5** (1.4, 1.7)

1. Chalkias et al, NEJM, 2022, DOI: 10.1056/NEJMoa2208343 2. Chalkias et al, Res Square, 2022, https://orcid.org/0000-0002-0817-9370 PPD - pseudovirus neut assay

Cumulative Incidence Curve of COVID-19 ≥14 Days Following Receipt of Omicron BA.1 Bivalent or Original Vaccine Booster

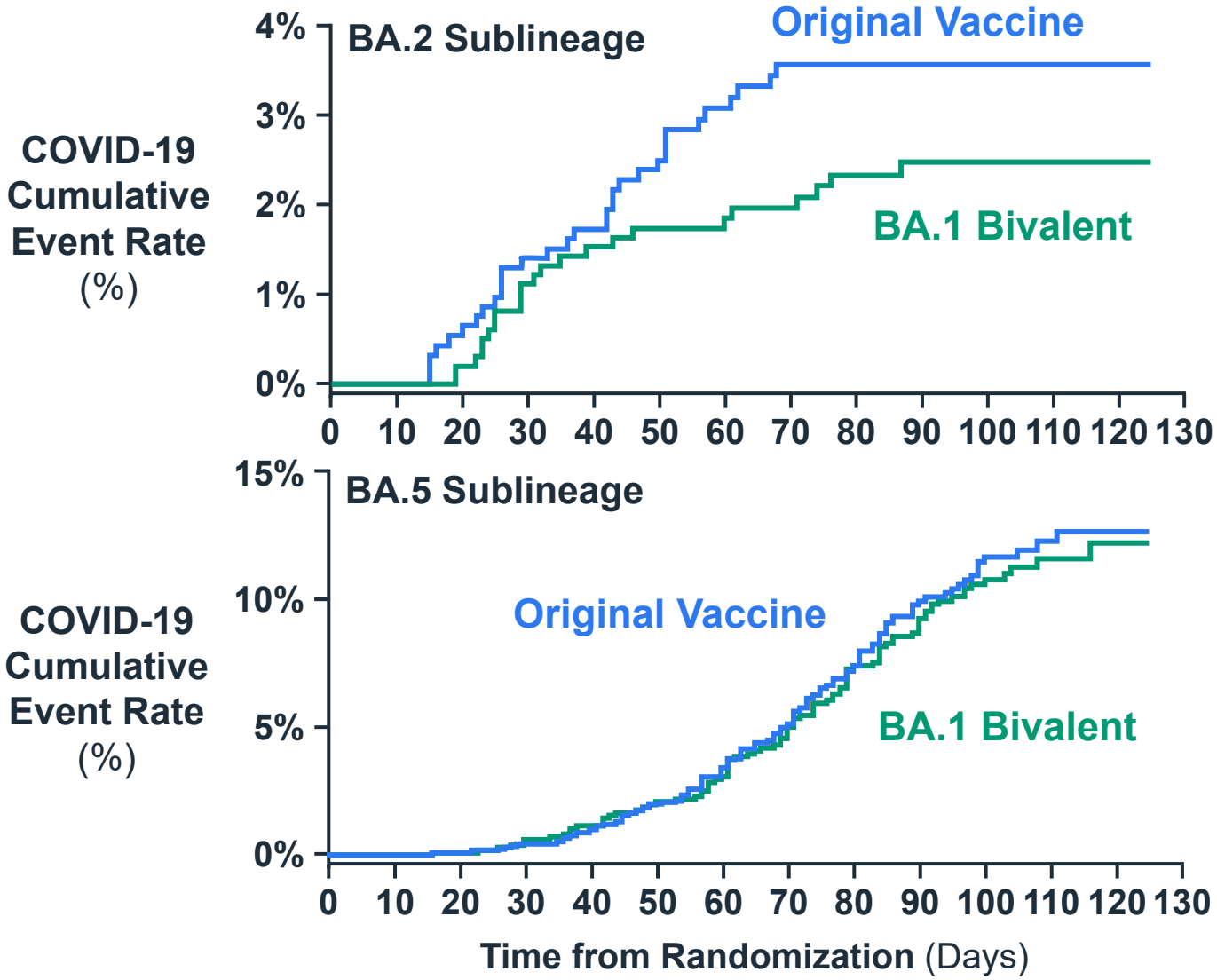
Study 305, Part 2: Primary Case Definition – Per Protocol Set for Efficacy

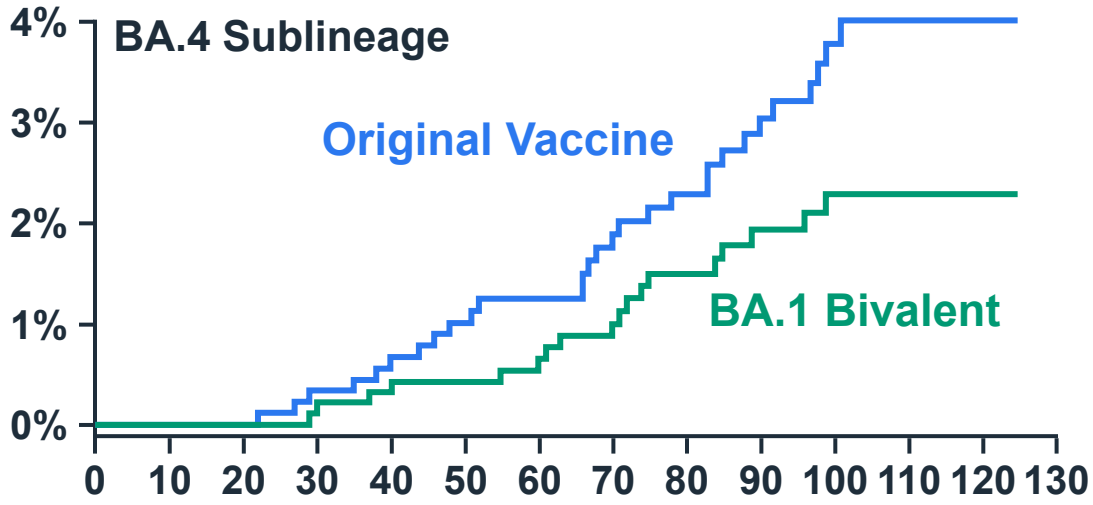
COVID-19 (protocol-defined)	Original Vaccine (mRNA-1273)	BA.1 Bivalent (mRNA-1273.214)
Number of Cases, (%)	**166** (17.7%)	**158** (15.8%)
Incidence Rate Per 1,000/PYs (95% CI)	**711.6** (607.5, 828.5)	**633** (538.1, 739.7)
Relative Vaccine Efficacy (95% CI)	**10%** (-11%, 29%)	



Cumulative Incidence Curve of COVID-19 by Omicron Sublineage Following Receipt of Omicron BA.1 Bivalent or Original Booster

Study 305, Part 2: Primary Case Definition – Per Protocol Set for Efficacy – Exploratory Analysis





	Relative Vaccine Efficacy (95% CI)
Non-BA.5 Sublineage	**37.3%** (6.9, 57.8)
BA.5 Sublineage	**4.4%** (-27.2, 28.2)

Clinical Study of Primary Series of Moderna Omicron Containing BA.1 Bivalent Vaccine in US

6 Months - 5 Years

(Study 306, Part 1)

Ongoing Study of BA.1 Omicron Bivalent Vaccine Primary Series

Study 306, Part 1: Infants, Toddlers & Children, 6 Months - 5 Years

	Study 204 (Historical Control)	**Study 306** (Part 1)
	Original Vaccine (mRNA-1273)	**BA.1 Bivalent** (mRNA-1273.214)
Vaccine Composition	**25 µg** Original Strain	**12.5 µg** Original Strain + **12.5 µg** Omicron BA.1
Enrollment	**October 18, 2021 – June 15, 2022**	**June 21, 2022 – ongoing**
Dose	**Primary Series** (1st and 2nd Dose)	**Primary Series** (1st and 2nd Dose)
Participants	**N = 4,792**	**N = 179**
Median Follow-up	**102 days after Dose 1**	**85 days after Dose 1**
Eligibility	**Vaccine-naive**	**Vaccine-naive**
Data Cutoff	**February 21, 2022**	**December 5, 2022**

Interim analysis
https://clinicaltrials.gov/ct2/show/NCT05436834

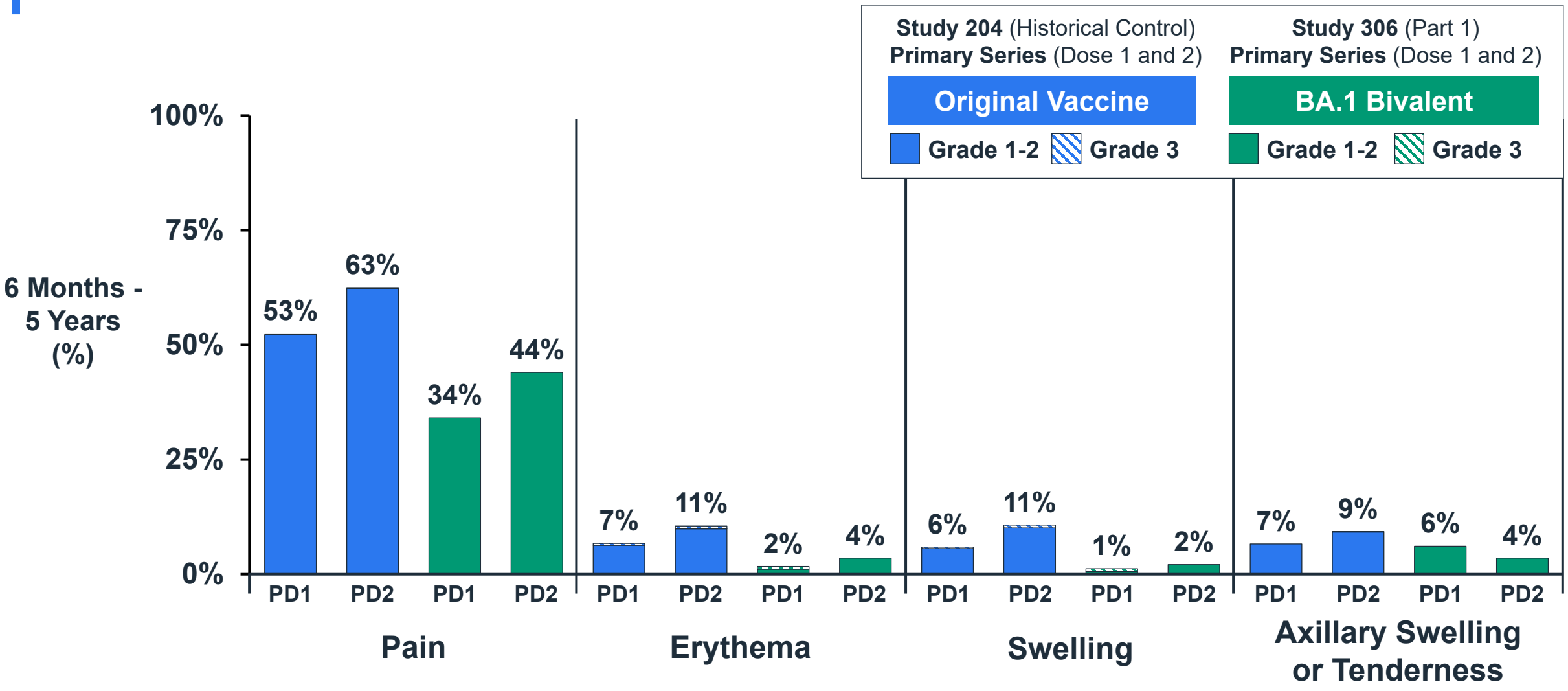
Demographics and Baseline Characteristics

Study 306, Part 1 (Safety Set)

Characteristic	**Study 204** (Historical Control) **Primary Series** (Dose 1 and 2) **Original Vaccine** (mRNA-1273) N = 4,792 Study 204	**Study 306** (Part 1) **Primary Series** (Dose 1 and 2) **BA.1 Bivalent** (mRNA-1273.214) N = 179 Study 306, Part 1
Mean Age – Years	**2**	**3**
Median Age – Years (range)	**2** (0.5, 5)	**3** (0.5, 5)
Non-White Race	**23%**	**35%**
Hispanic / Latino Ethnicity	**14%**	**12%**
Prior SARS-CoV-2 Infection	**8%**	**63%**

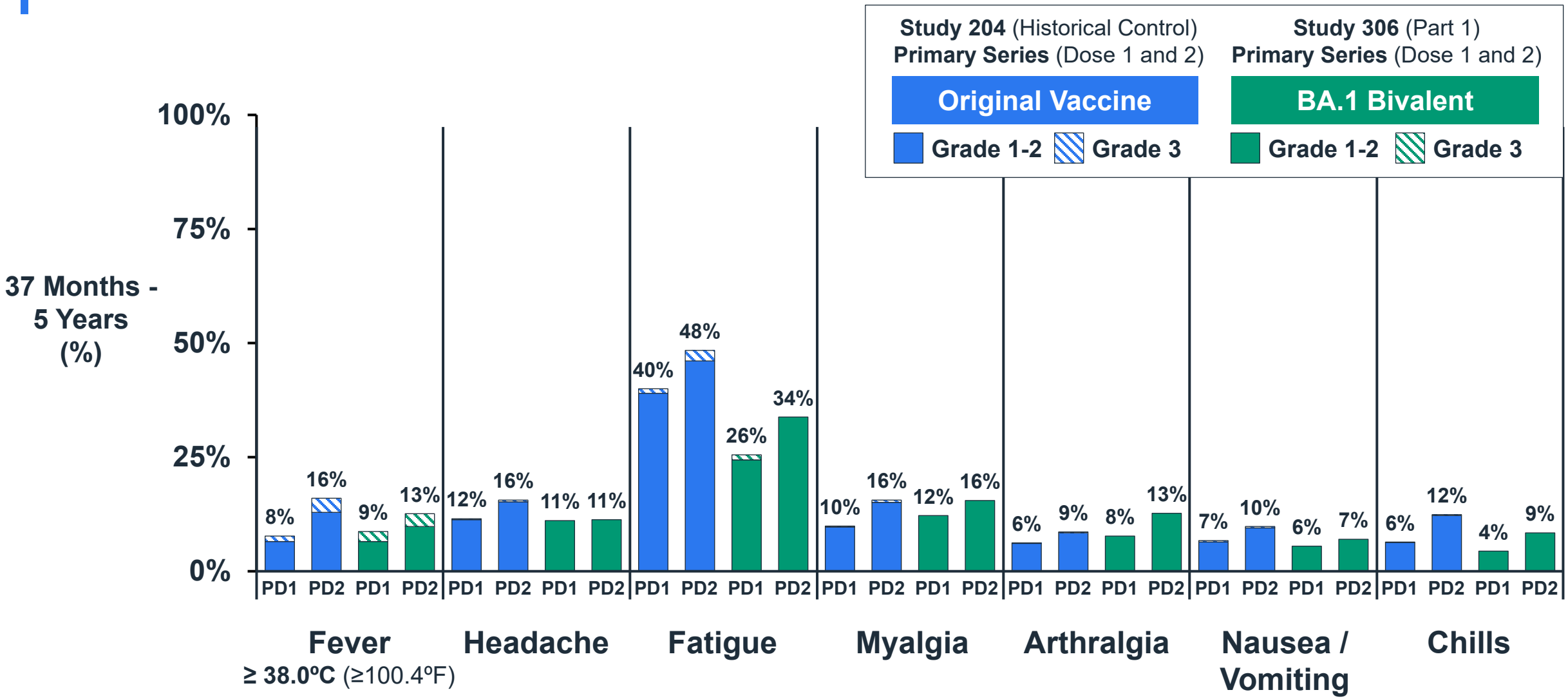
Local Reactions Following BA.1 Omicron Bivalent Primary Series

Study 306, Part 1: 6 Months - 5 Years (Solicited Safety Set)



Systemic Reactions Following BA.1 Omicron Bivalent Primary Series

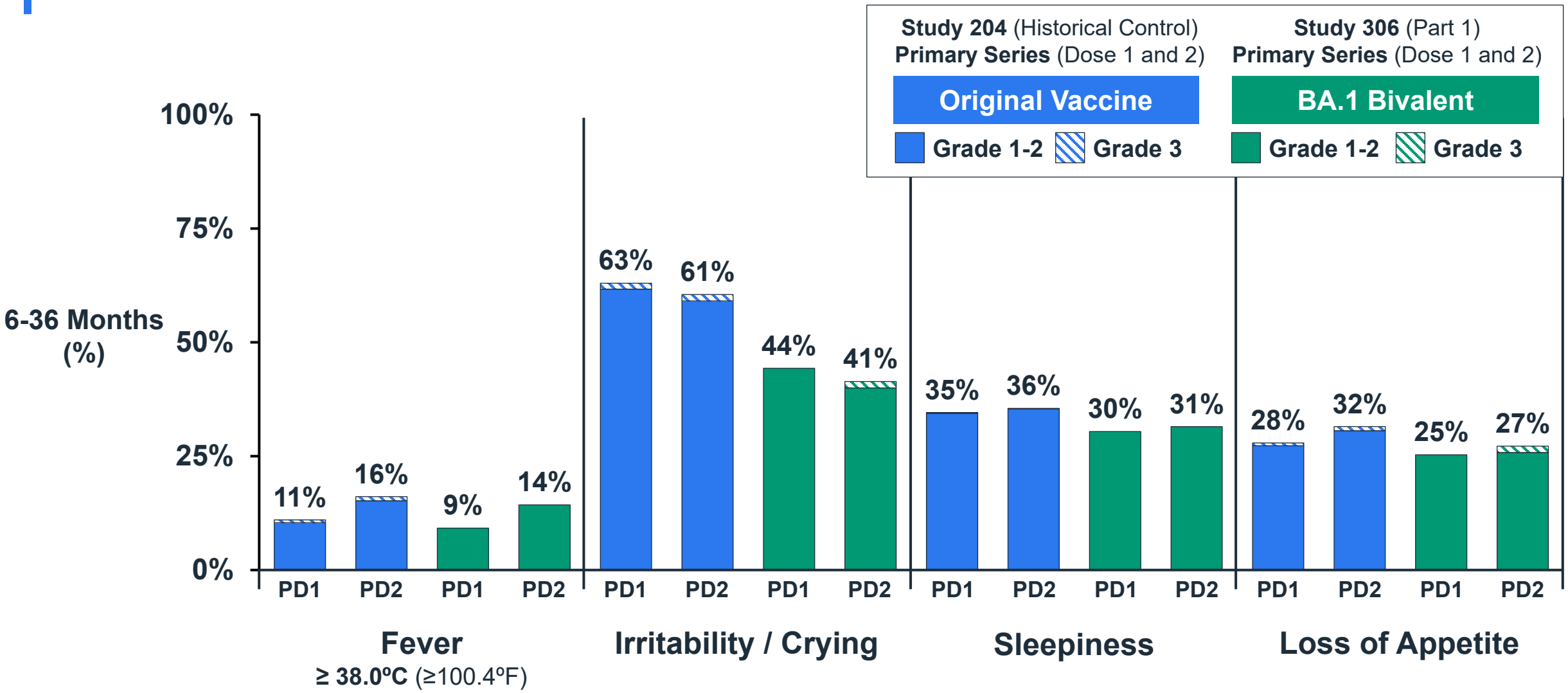
Study 306, Part 1: 37 Months - 5 Years (Solicited Safety Set)



No Grade 4 events reported among participants receiving BA.1 Bivalent
5 events of Grade 4 fever reported with Original Vaccine– 1 post dose 1, 4 post dose 2

Systemic Reactions Following BA.1 Omicron Bivalent Primary Series

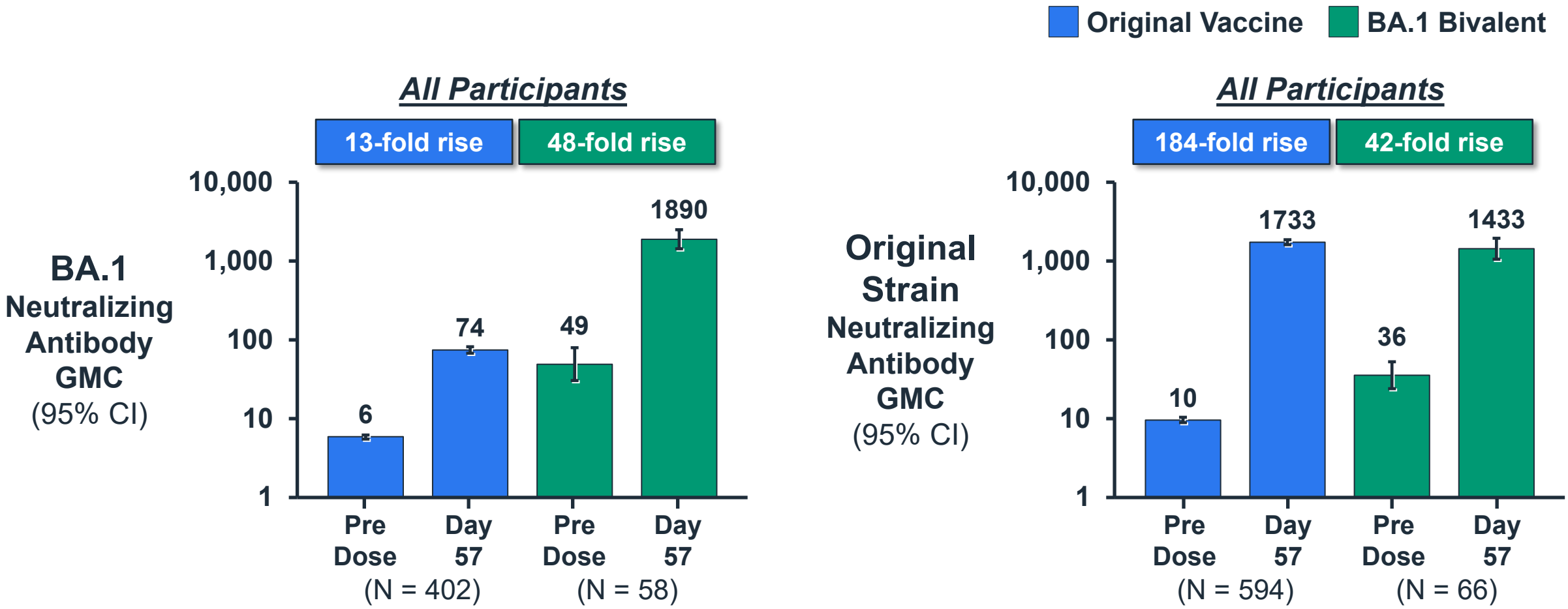
Study 306, Part 1: 6 - 36 Months (Solicited Safety Set)



No Grade 4 events reported among participants receiving BA.1 Bivalent
10 events of Grade 4 fever reported with Original Vaccine– 4 postdose 1, 6 postdose 2

Neutralizing Antibodies After Primary Series of BA.1 Omicron Bivalent Vaccine and Original Vaccine

Study 306, Part 1 (Per-Protocol Immunogenicity Set, including baseline SARS-CoV-2 negative and positive)
6 Months – 5 Years



Geometric Mean Ratio (95% CI) vs Original Vaccine from Study 204	**25.4** (20.1,32.1)	**0.83** (0.67, 1.02)

PPD–pseudovirus neut assay; Study 204 data cutoff 07Sep2022, Immunogenicity Subset enrolled 18Oct2021- 03Nov2021; Study 306 Part 1 enrolled 21Jun2022 - ongoing

Real World Effectiveness of Omicron Containing Bivalent Booster Vaccines

Effectiveness of Moderna BA.4/BA.5 Bivalent mRNA Vaccine in Immunocompetent Individuals, Kaiser Permanente

Aug 31-Dec 31, 2022, Interim Analysis

- 157,435 BA.4/BA.5 boosted individuals and 314,837 controls

COVID-19 Outcomes	Relative VE (compared with individuals who had ≥2 original vaccine doses)	Absolute VE (compared with individuals not vaccinated with any COVID-19 vaccine)
Hospitalization (Chart confirmed)*	**73%** (64% - 80%)	**83%** (75% - 88%)
ED and urgent care	**56%** (50% - 62%)	**57%** (47% - 65%)

- **Bivalent BA.4/BA.5 booster provides additional protection against hospitalizations, ED and urgent care visits**

Unpublished data

- **Chart confirmed hospitalization for COVID-19.**
- **COVID-19 in-hospital deaths occurred in 2 persons in bivalent cohort and 6 in non-bivalent cohorts**

Data Collection Ongoing/Planned

- Additional durability assessment of immune response with bivalent primary series and booster
- Continued safety follow-up of vaccine recipients (primary series and booster)
- Assessment of immunogenicity and safety of 2 different bivalent vaccines administered 1 year apart
- Primary series (bivalent) evaluation:
  - Infants <6 months
  - Single dose primary series in unvaccinated adolescents
    - “Boost-only” strategy for high seroprevalence groups

Preclinical Results from Authorized and Investigational Bivalent Vaccines

Darin Edwards, PhD

Senior Director of Immunology, Infectious Disease Group

Moderna, Inc.

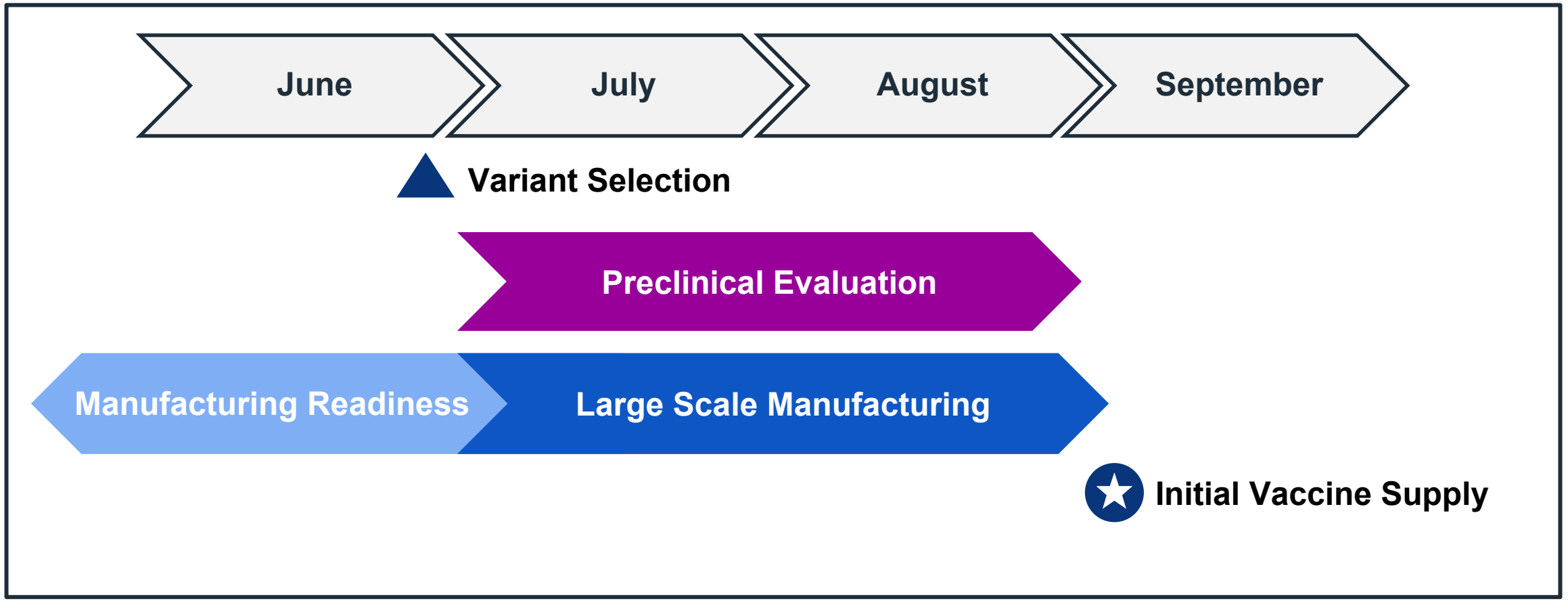
Moderna Continues to Prepare New Candidate Vaccines Against Emerging Variants

- Moderna performs continuous epidemiological monitoring and risk assessment of variants
  - Variants identified that contain immune evading mutations versus authorized vaccines & increased growth dynamics
  - These assessments used to determine which future candidate vaccines to pursue at risk
    - *Example*: BQ.1.1, BN.1, and XBB.1 identified as possible vaccine candidates early October 2022

- At-risk candidate vaccine preparation and preclinical evaluations begin in parallel
  - Preclinical materials prepared at small scale and animal studies are performed
  - Key manufacturing steps taken to prepare for large scale manufacturing, if needed

- Early activities allow for expedited delivery of new vaccines should regulatory agencies request specific vaccine composition updates

Timeline of 2022 Development of Omicron-Containing BA.4 / BA.5 Bivalent Vaccine

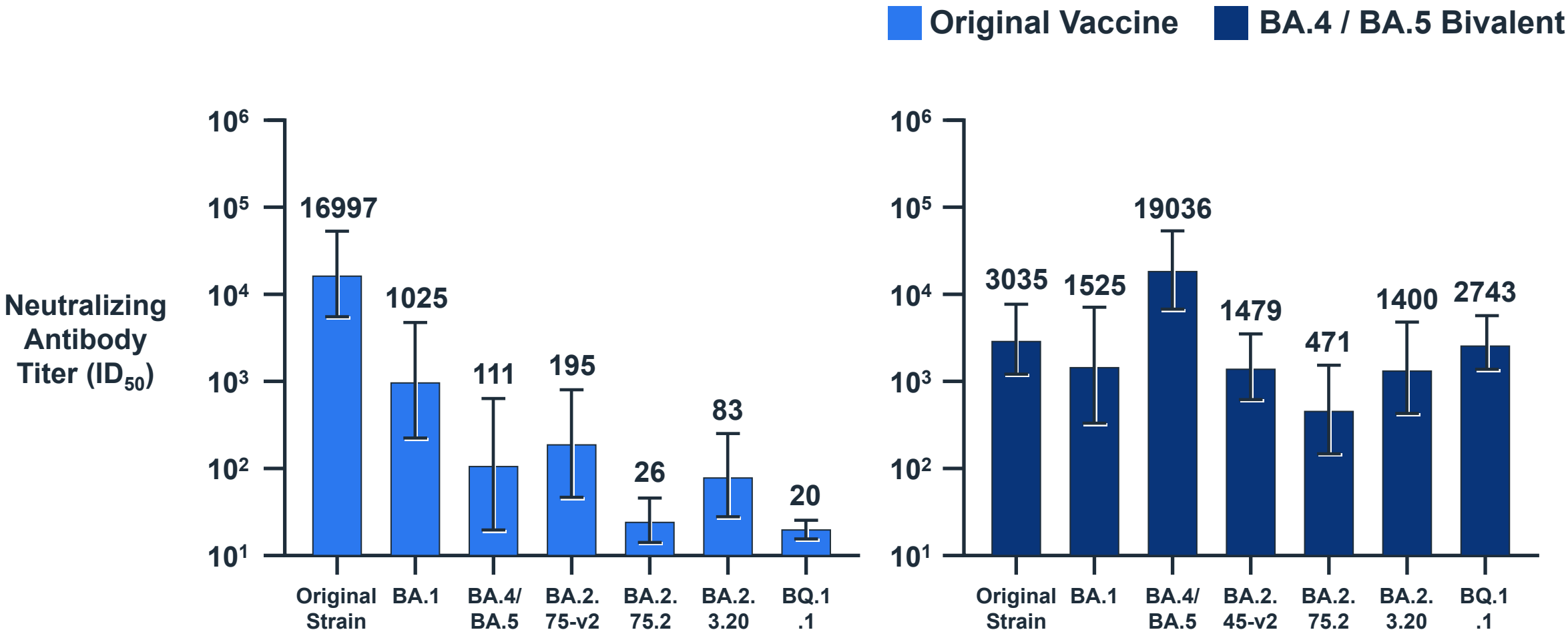


19 Moderna COVID-19 Vaccines Evaluated in Preclinical and/or Clinical Studies

Monovalent Vaccines	Preclinical Data	Clinical Data
Original (D614G)	☑	☑
Delta	☑	☑
Beta	☑	☑
BA.1	☑	☑
BA.4/BA.5	☑	☑
XBB.1	☑	
BQ.1.1	☑	
BN.1	☑	

Bivalent Vaccines	Preclinical Data	Clinical Data
Original + Beta	☑	☑
Original + BA.1	☑	☑
Original + BA.4/BA.5	☑	☑
Original + XBB.1	☑	
Original + BQ.1.1	☑	
Original + BN.1	☑	
Beta + Delta	☑	☑
BA.4/BA.5 + XBB.1	☑	
BA.4/BA.5 + BQ.1.1	☑	
BA.4/BA.5 + BN.1	☑	
XBB.1 + BQ.1.1	☑	

BA.4 / BA.5 Bivalent Vaccine Drives Significant Neutralization Compared to Monovalent Vaccine Across Variants in Preclinical Studies in Mice



N = 8 mice/group
Moderna research grade neutralization assay
https://doi.org/10.1101/2022.09.12.507614

Conclusions

Rituparna Das, MD, PhD

Vice President, Clinical Development, COVID-19 Vaccines

Moderna, Inc.

Omicron-Containing mRNA-1273 Bivalent Vaccines

- BA.4 / BA.5 bivalent vaccine met all immunogenicity endpoints; results consistent for 18-64 and ≥65 years
- Randomized active-controlled study in UK with BA.1 bivalent vaccine confirmed immunogenicity endpoints
  - Not powered for difference in COVID-19 rates; non-significant trend to lower rates in BA.1 bivalent group compared to original vaccine
  - Sequencing shows trend of reduced COVID-19 rates driven by BA.2 and BA.4 sublineages, but not BA.5 sublineages
- Cross neutralization observed for emerging Omicron subvariants
- Primary series with BA.1 bivalent vaccine met immunogenicity endpoints and was well tolerated in children
- Real world effectiveness data from Kaiser-Permanente confirms additional protection from hospitalizations and ED/urgent care visits with BA.4 / BA.5 bivalent booster

Moderna Continues to Prepare as SARS-CoV-2 Variants Continue to Emerge

- As SARS-CoV-2 continues to evolve, boosters with bivalent vaccines can protect against infections when the variant is more closely-related, but continue to protect against severe disease even as the variants diverge
- Moderna will continue epidemiological monitoring and risk assessment of emerging variants/subvariants
  - Candidate vaccines generated for preclinical evaluation as needed
- Moderna is committed to providing data and manufacturing readiness to support timing and composition decisions for harmonized updates to boosters and primary series

THANK YOU to Our Study Collaborators, Investigators, and Participants

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

ADDITIONAL DATA FOR VRBPAC MEMBERS

SLIDES NOT PRESENTED

Clinical Study of Booster of Moderna Omicron Containing BA.1 Bivalent Vaccine in US

6 Months - 5 Years

(Study 306 Part 2)

Open-label, Phase 3 Study of BA.1 Omicron Bivalent Vaccine Booster in Infants & Children, 6 Months - 5 Years

Study 306 Part 2

	Study 204 (Historical Control)	**Study 306** (Part 2)
	Original Vaccine (mRNA-1273)	**BA.1 Bivalent** (mRNA-1273.214)
Vaccine Composition	**25 µg** Original Strain	**5 µg** Original Strain + **5 µg** Omicron BA.1
Enrollment	**October 18, 2021 – June 15, 2022**	**June 22 – September 20, 2022**
Dose	**Primary Series** (1st and 2nd Dose)	**3rd Dose** (1st Booster)
Participants	**N = 4,792**	**N = 539**
Median Follow-up	**102 days after Dose 1**	**117 Days after Booster**
Eligibility	**Vaccine-naive**	**Previously received 25 µg mRNA-1273 Primary Series**
Data Cutoff	**February 21, 2022**	**December 5, 2022**

Interim analysis

https://clinicaltrials.gov/ct2/show/NCT05436834

Demographics and Baseline Characteristics

Study 306 Part 2 (Safety Set)

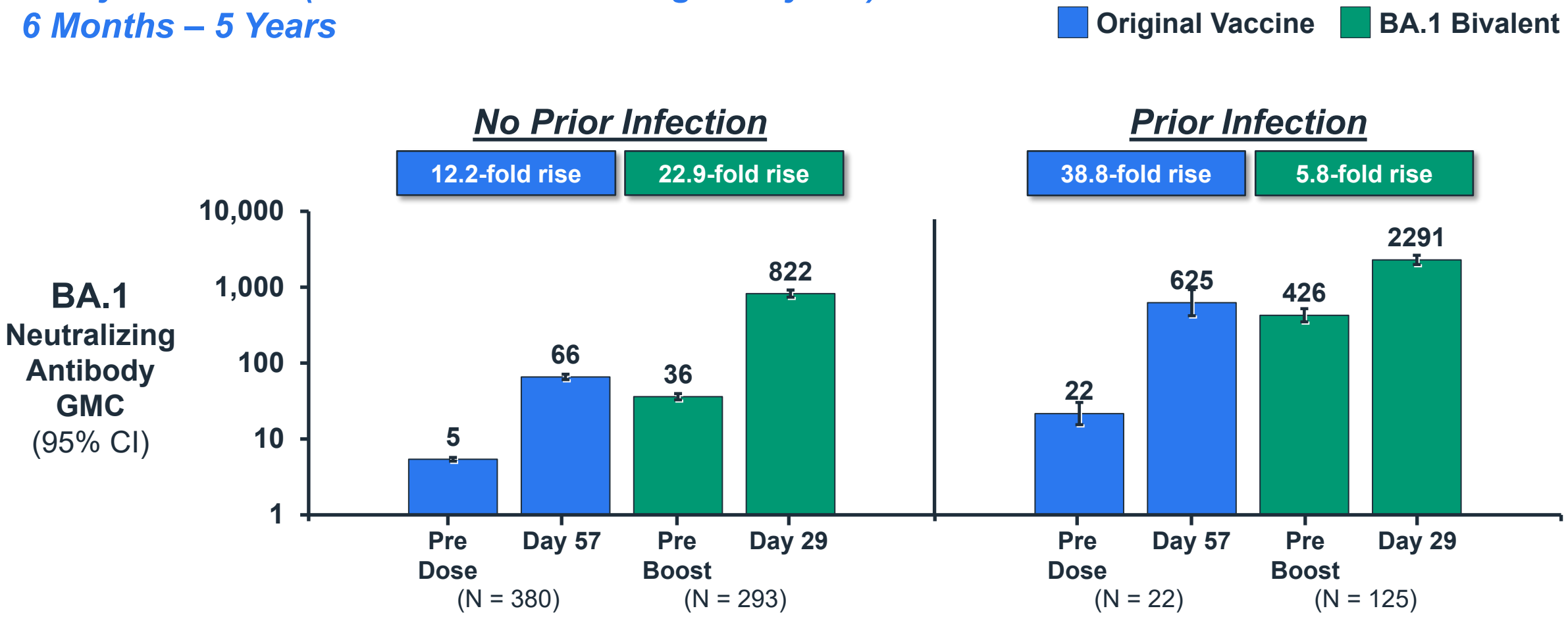
Characteristic	**Study 204** (Historical Control) **2nd Dose** (Primary Series) **Original Vaccine** (mRNA-1273) N = 4,792 Study 204	**Study 306** (Part 2) **3rd Dose** (1st Booster) **BA.1 Bivalent** (mRNA-1273.214) N = 539 Study 306 Part 2
Mean Age – Years	**2**	**3**
Median Age – Years (range)	**2** (0.5, 5)	**3** (0.9, 5)
Non-White Race	**23%**	**19%**
Hispanic / Latino Ethnicity	**14%**	**11%**
Prior SARS-CoV-2 Infection	**8%**	**28%**

Study 204 data cutoff of 21 Feb 2022

Omicron BA.1 Neutralizing Antibodies After Omicron BA.1 Bivalent Booster Compared to Primary Series of Original Vaccine

Study 306 Part 2 (Per-Protocol Immunogenicity Set)

6 Months – 5 Years



	No Prior Infection	Prior Infection
Geometric Mean Ratio (95% CI) vs Original Vaccine from Study 204	**12.5** (11.0, 14.3)	**3.7** (2.5, 5.3)

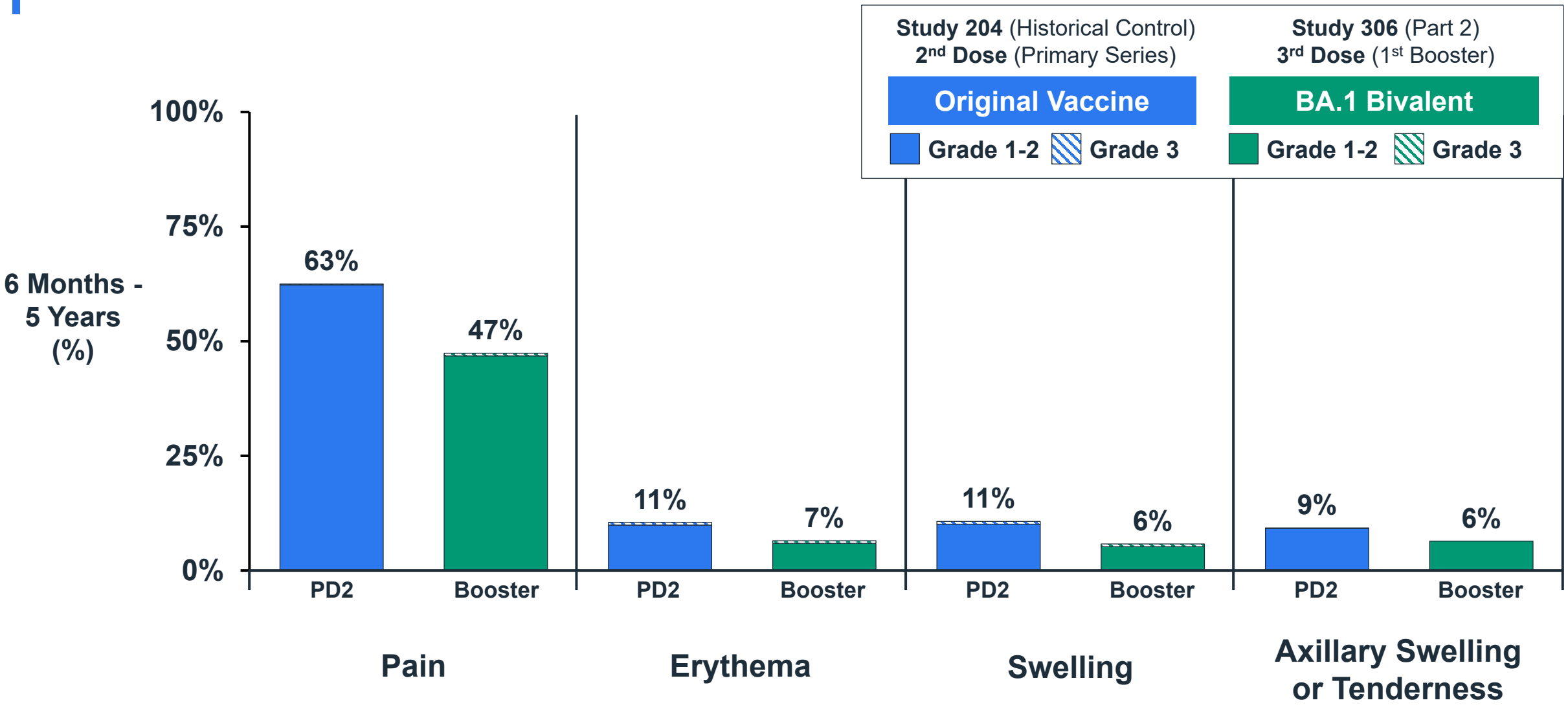
Co-primary objectives based on GMR against original strain and Seroresponse Rate against both BA.1 subvariant and original strain were also met

P204, Part 2 participants received 25 μg primary series of original vaccine; P306, Part 2 participants received 25 ug primary series of original vaccine & 10 μg booster of BA.1 Omicron

PPD–pseudovirus neut assay; Study 204 data cutoff 07Sep2022, Immunogenicity Subset enrolled 18Oct2021- 03Nov2021.

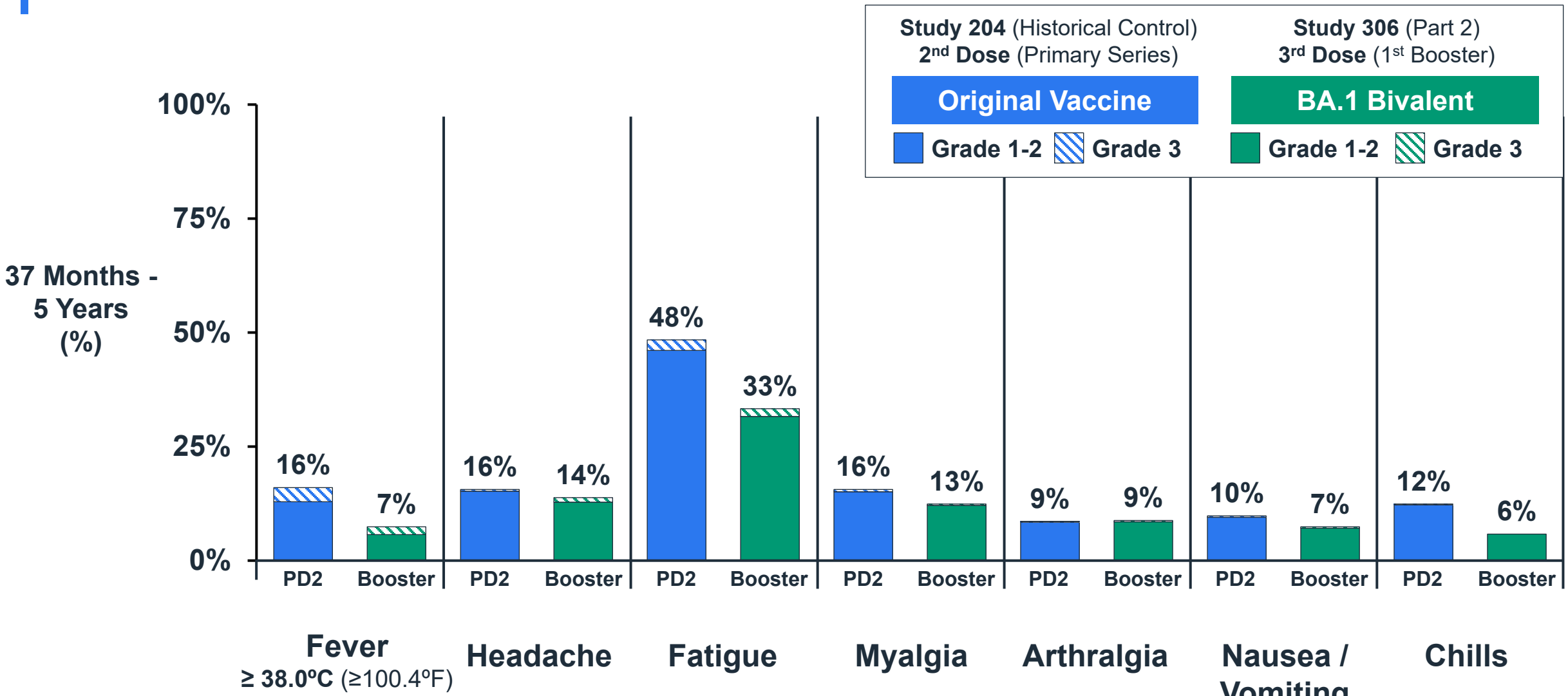
Local Reactions Following BA.1 Omicron Bivalent Booster

Study 306 Part 2: 6 Months - 5 Years (Solicited Safety Set)



Systemic Reactions Following BA.1 Omicron Bivalent Booster

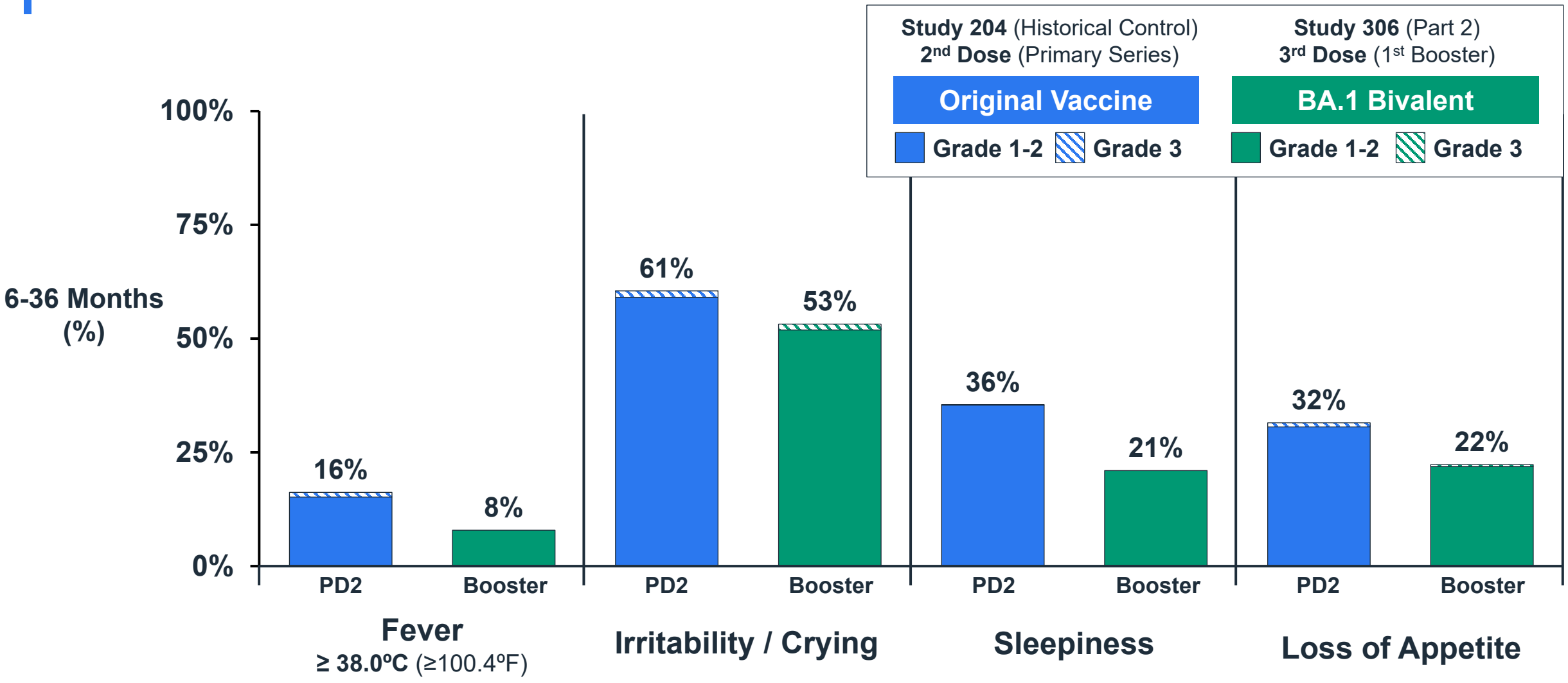
Study 306 Part 2: 37 Months - 5 Years (Solicited Safety Set)



No Grade 4 events reported among participants receiving BA.1 Bivalent Booster
4 Events of Grade 4 fever reported with Original Vaccine post dose 2

Systemic Reactions Following BA.1 Omicron Bivalent Booster

Study 306 Part 2: 6 - 36 Months (Solicited Safety Set)



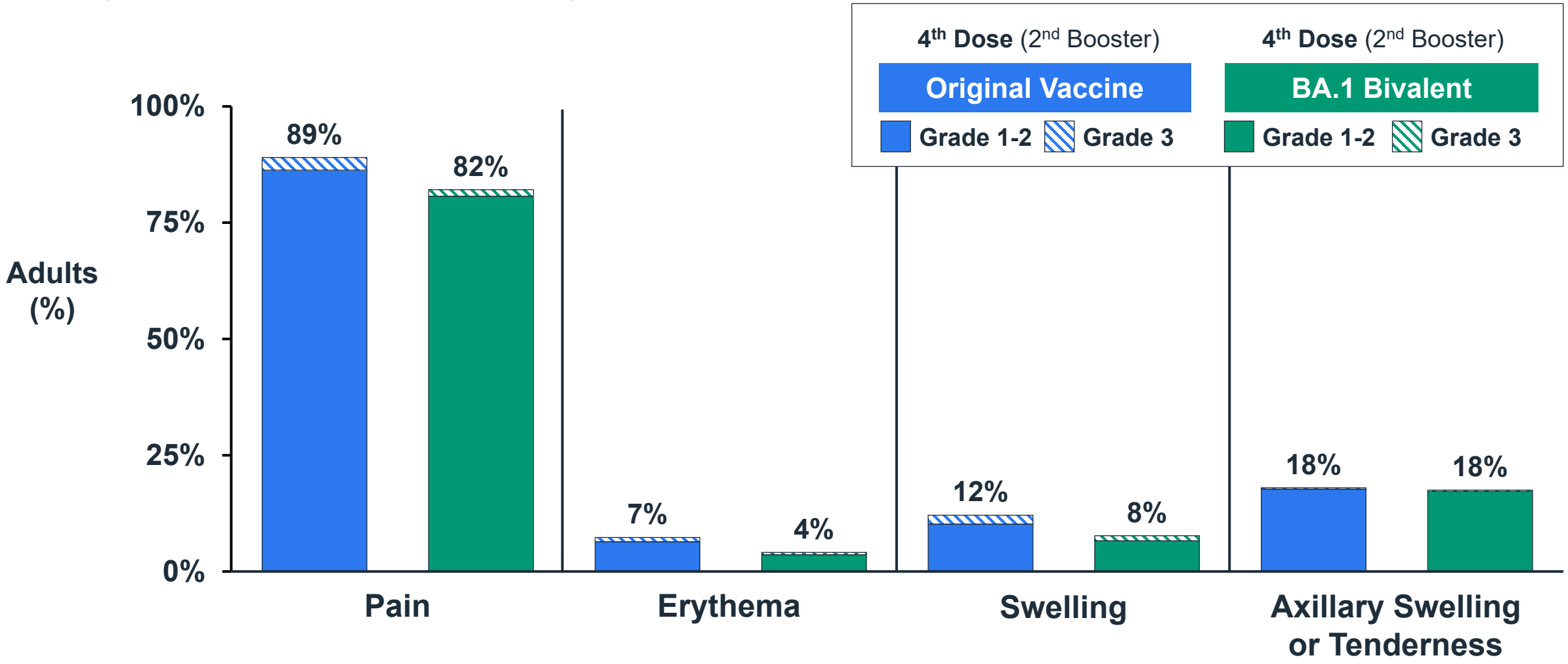
No Grade 4 events reported among participants receiving BA.1 Bivalent Booster
6 Events of Grade 4 fever reported with Original Vaccine post dose 2

Randomized, Active-Controlled Study Moderna Omicron Containing BA.1 Bivalent Vaccine vs Original Vaccine Boosters

Adults in United Kingdom (Study 305)

Local Reactions Following BA.1 Bivalent Booster Similar to Booster of Original Vaccine in ≥16 Year Olds

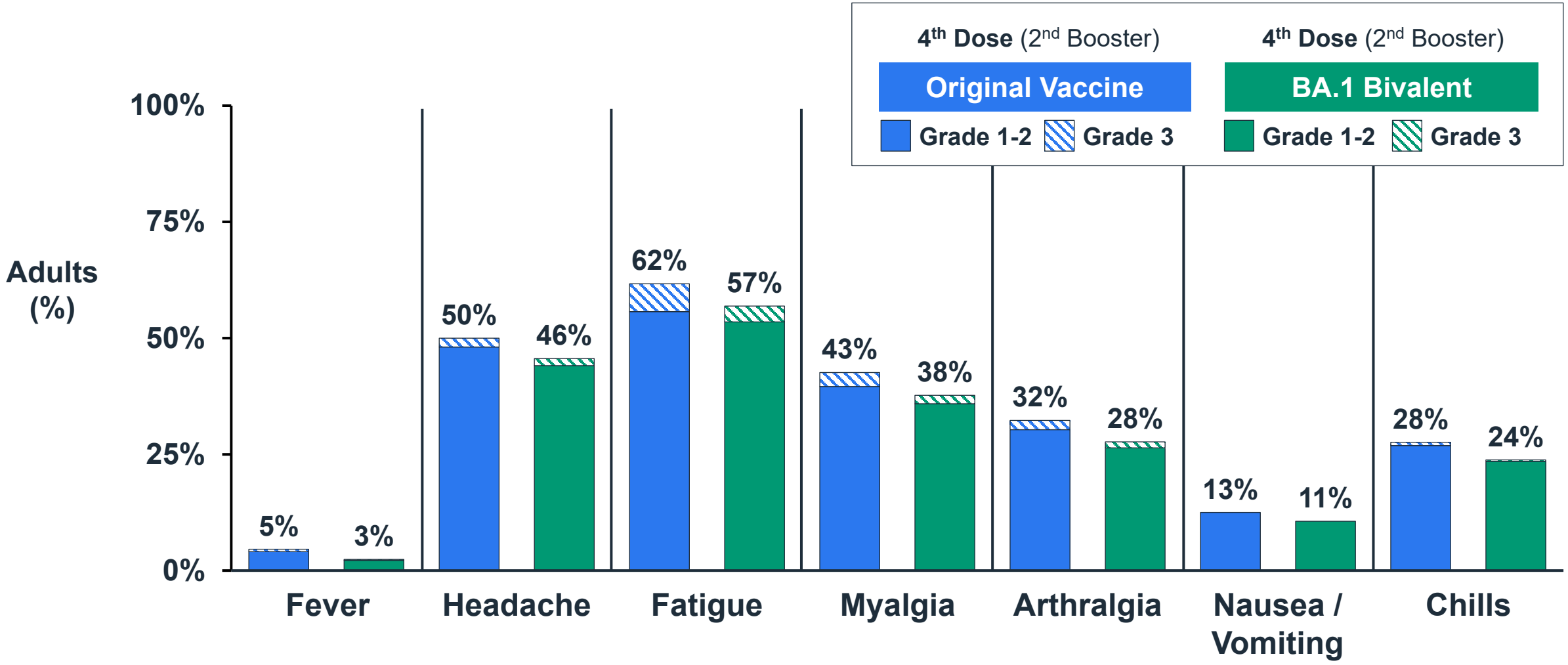
Study 305, Part 2, Solicited Safety Set



Includes local reactions after dose 3 or dose 4 (99% after dose 4)
Solicited local adverse reactions within 7 days after injection

Systemic Reactions Following BA.1 Bivalent Booster Similar to Booster of Original Vaccine in ≥16 Year Olds

Study 305, Part 2, Solicited Safety Set



Includes systemic reactions after dose 3 or dose 4 (99% after dose 4)
No Grade 4 events reported