Vaccines and Related Biological Products Advisory Committee October 14-15, 2021 Meeting Presentation

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Safety and Immunogenicity of a 50 µg Booster Dose of mRNA-1273 (Moderna COVID-19 Vaccine)

ModernaTX, Inc.

Vaccines and Related Biological Products Advisory Committee

October 14, 2021

Safety and Immunogenicity of a 50 µg Booster Dose of mRNA-1273 (Moderna COVID-19 Vaccine)

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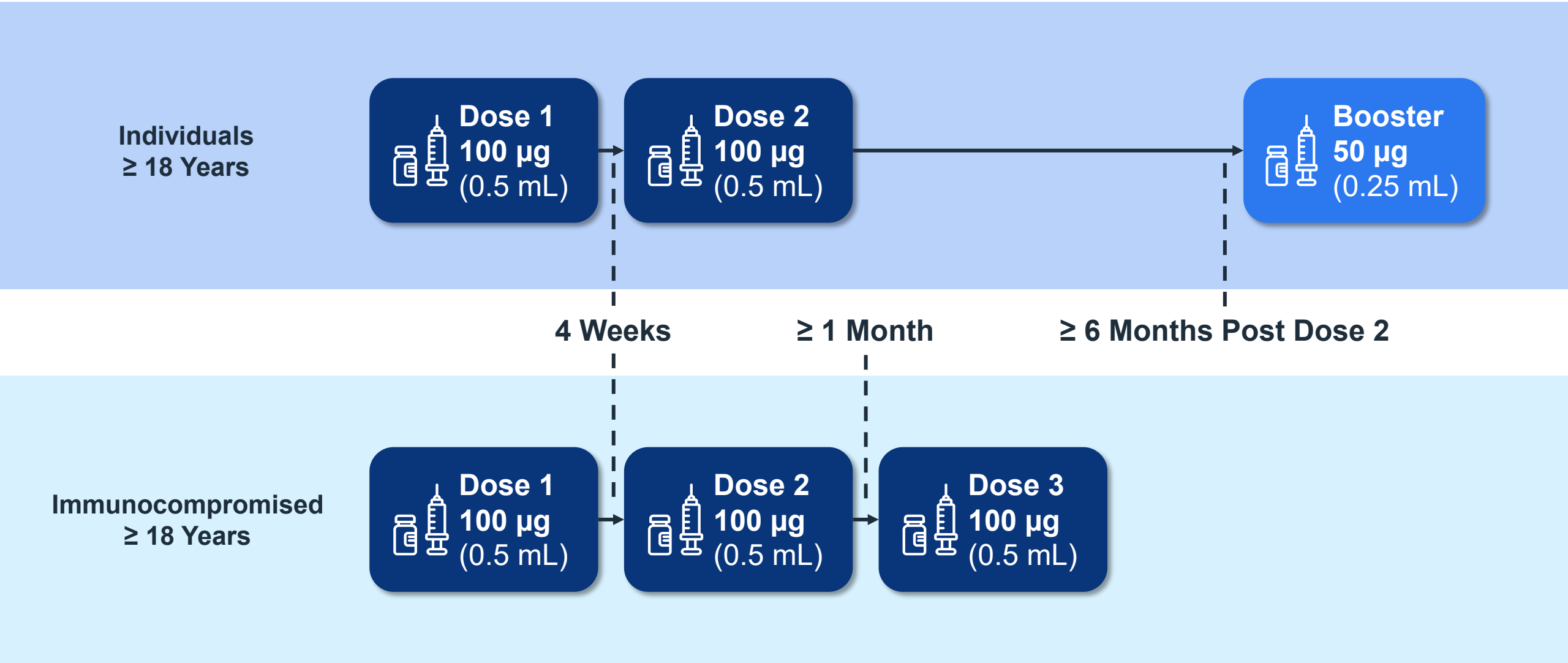
ModernaTX, Inc.

Proposed Use of Moderna Vaccine as a Booster

- Administration of a single 50 µg (0.25 ml) booster dose at least 6 months after completion of a primary series in:
  - Individuals 65 years of age and older;
  - Individuals 18 - 64 years of age at high risk of severe COVID-19; and
  - Individuals 18 - 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19

Proposed mRNA Vaccination Schedules



Outline of Presentation

- Background
- Update on vaccine efficacy (Study 301)
- Antibody persistence 6-8 months after vaccination
- Breakthrough disease in vaccinated individuals from July – August, 2021
- 50 µg booster dose (Study 201B)
  - Rationale for dose selection
  - Study design
  - Safety data
  - Immunogenicity of 50 µg booster dose vs the original virus (D614G) and Delta variant
- Summary

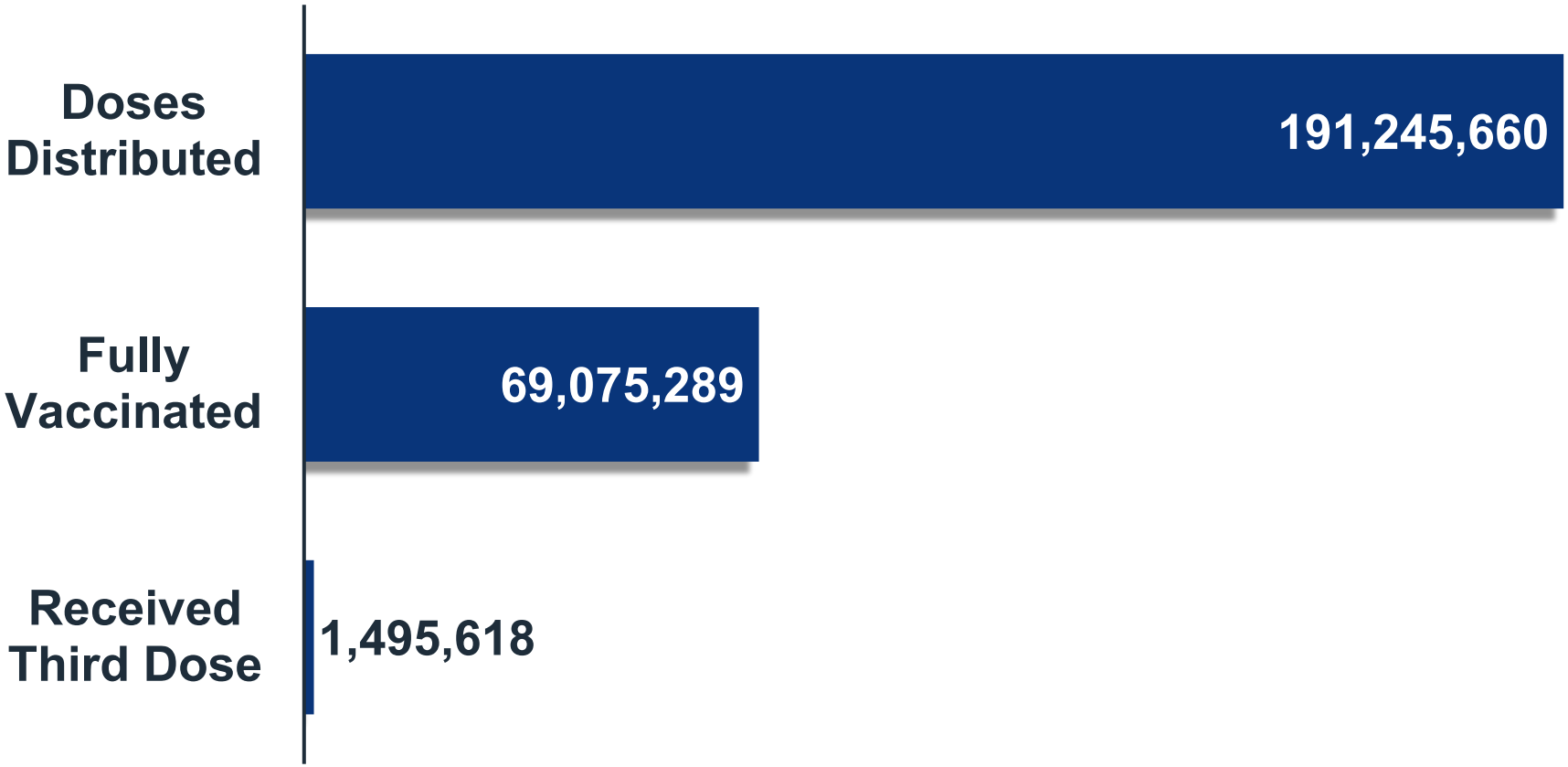
Background

Review of Safety and Efficacy from Phase 3 Study 301

- 30,375 subjects who received at least one dose
  - 15,180 mRNA-1273 recipients
  - 15,166 placebo recipients
- 94.1% vaccine efficacy in per protocol cohort[1]
  - Based on 9-week median follow-up post-dose 2
- Observed to have acceptable safety profile[1]
- 100 µg 2-dose regimen authorized for emergency use for individuals ≥ 18 years old

1. Baden et al NEJM, 2020

Use of Moderna COVID-19 Vaccine in US Since December 2020 EUA



Adapted from CDC COVID Data Tracker (as of October 11, 2021)

Update on mRNA-1273 Efficacy through End of Blinded Phase

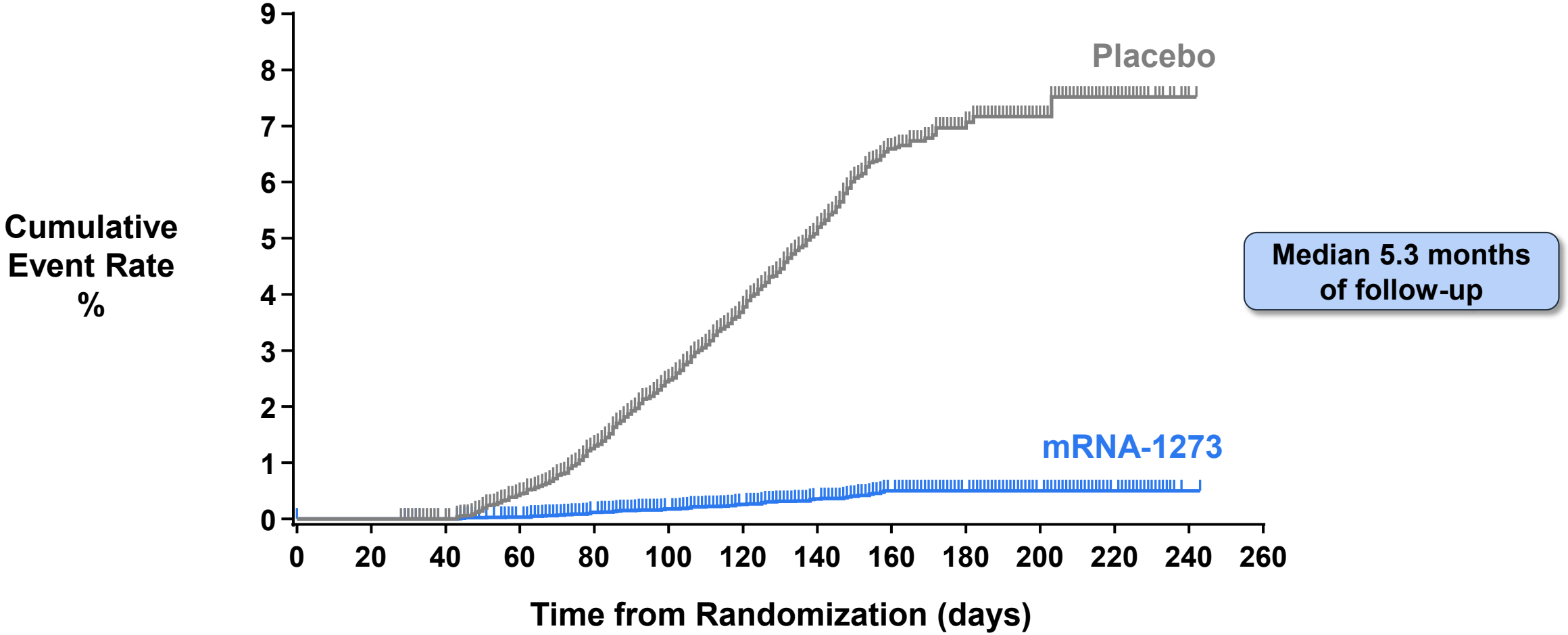
Phase 3 Study 301

Ongoing Phase 3 Study 301 - Efficacy

- Participants unblinded and placebo recipients offered vaccine shortly after EUA
- Subjects followed for any signs of COVID-19 through
  - Weekly e-diary contact
  - Monthly phone calls
- If subject had symptoms of COVID-19, examination and PCR testing conducted by site
- Efficacy results updated through end of blinded phase (March 2021)
- Primary data to support BLA (rolling submission completed August 25, 2021)

mRNA-1273 Vaccine Efficacy to Prevent COVID-19 Disease was 93.2% through 5.3 Months of Follow-up

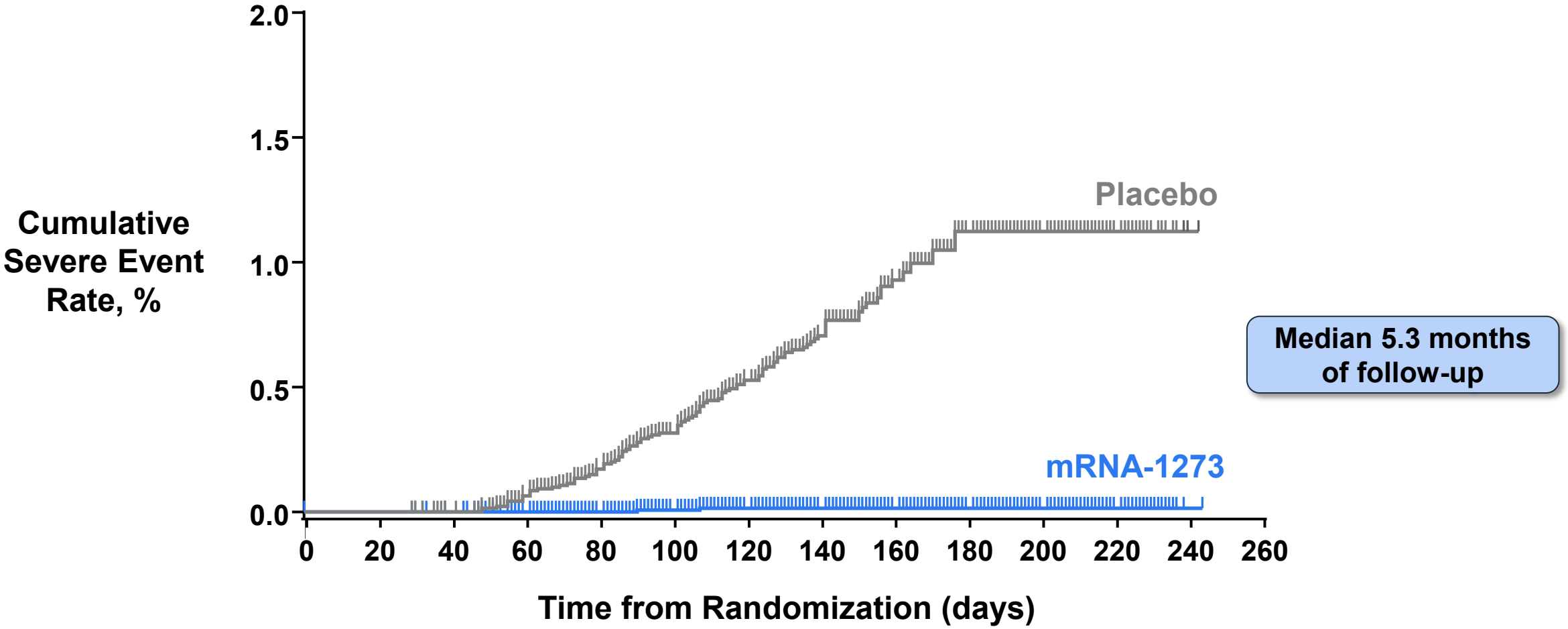
Per Protocol Set



El Sahly, *NEJM,* 2021

mRNA-1273 Vaccine Efficacy to Prevent Severe COVID-19 Disease was 98.2% through 5.3 Months of Follow-up

Per Protocol Set



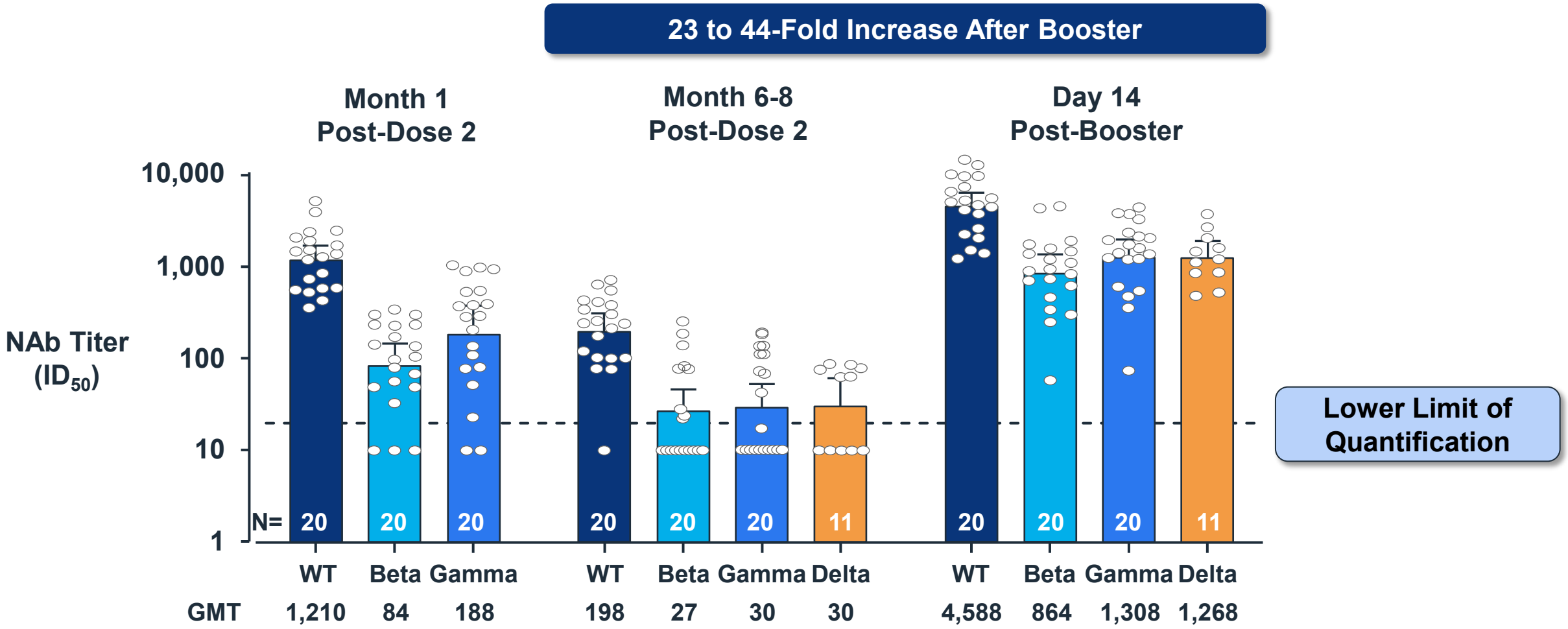
El Sahly, *NEJM,* 2021

Exploratory Analysis of Antibody Persistence and Boosting

Study 201B

Exploratory Analysis Against Variants of Concern

Study 201B 50 µg Booster after 100 µg Primary Series



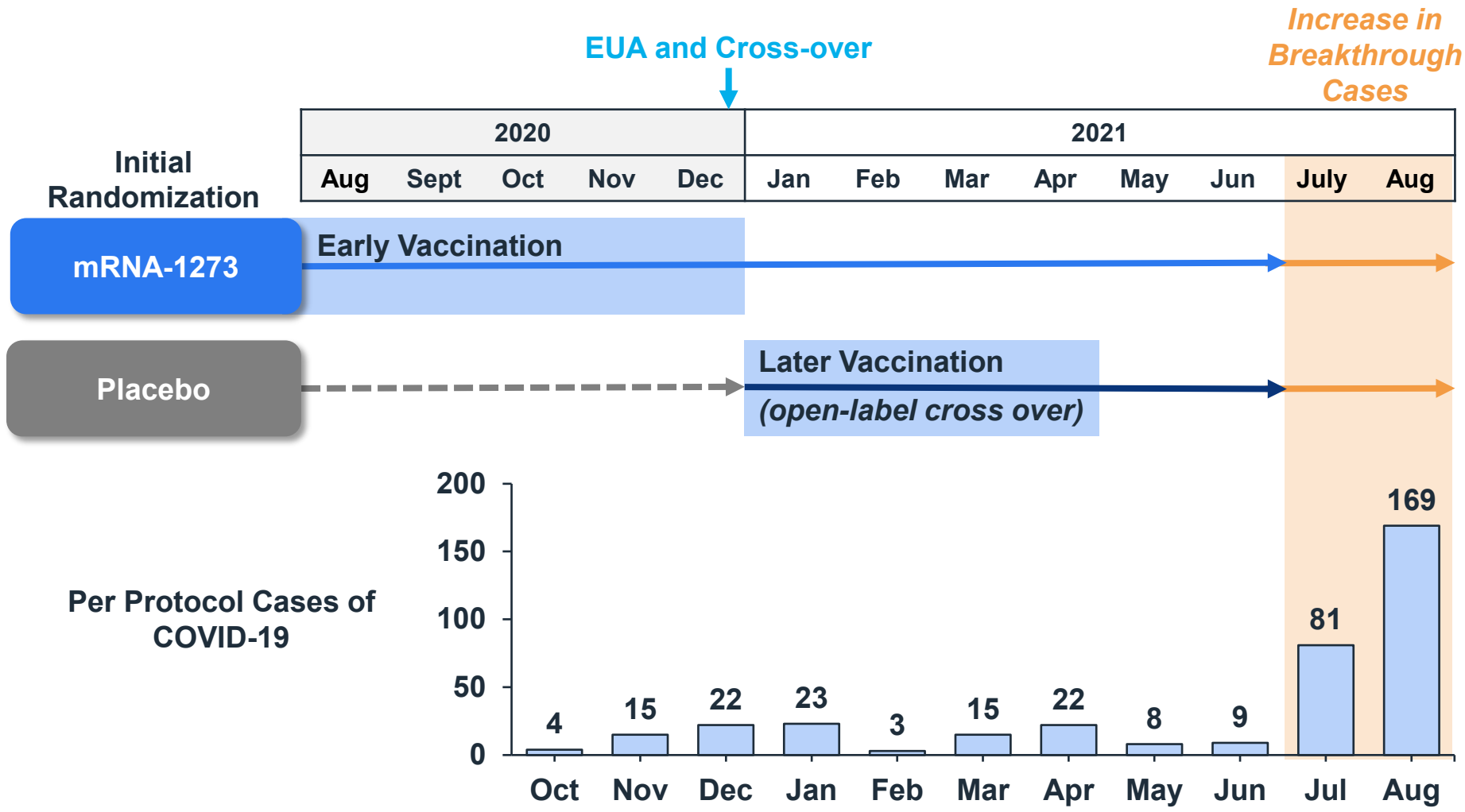
WT: original strain (D614G)
Research VSV pseudoneutralization assay used
Adapted from Choi et al., Nature Medicine 2021

Breakthrough Disease in Vaccinated Individuals from July – August, 2021

Phase 3 Study 301

Breakthrough COVID-19 Cases by Month

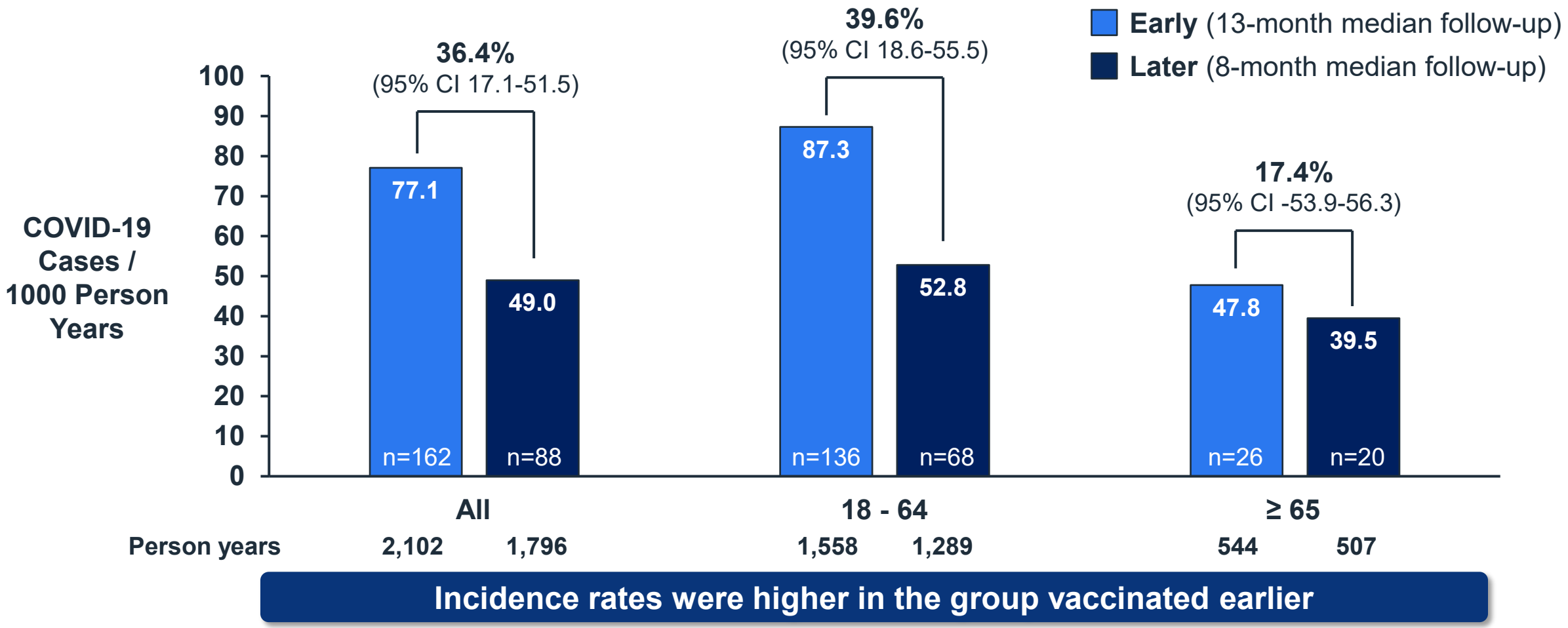
Study 301



mITT Population

Incidence Rates of Breakthrough COVID-19 in Early and Later Vaccinated Groups, July – August 2021

Study 301



Incidence rates were higher in the group vaccinated earlier

Median follow-up from 1st dose
Analysis of breakthrough cases observed from July 1 to August 27, 2021, mITT population
Baden et al., MedRxiv, 2021

50 µg Booster of mRNA-1273 in Previously Vaccinated Individuals

Study 201B

Rationale for Booster Dose Selection

- Goal was to use optimal effective dose for boosting
- Lower booster doses than those used for primary series of other vaccines shown to reactivate immune memory
- Lower booster dose increases worldwide vaccine supply of mRNA-1273

Design of Booster Dose Study 201B

	N	Previous Dose of mRNA-1273 Doses 1 & 2	Booster Dose	Interval Between Dose 2 & Booster Dose
Study 201B (boost with mRNA-1273)	**173**	**50 µg**	**50 µg**	**≥ 6 months**
	171	**100 µg**	**50 µg**	

Safety Set

Demographic Characteristics

Study 201B Safety Set

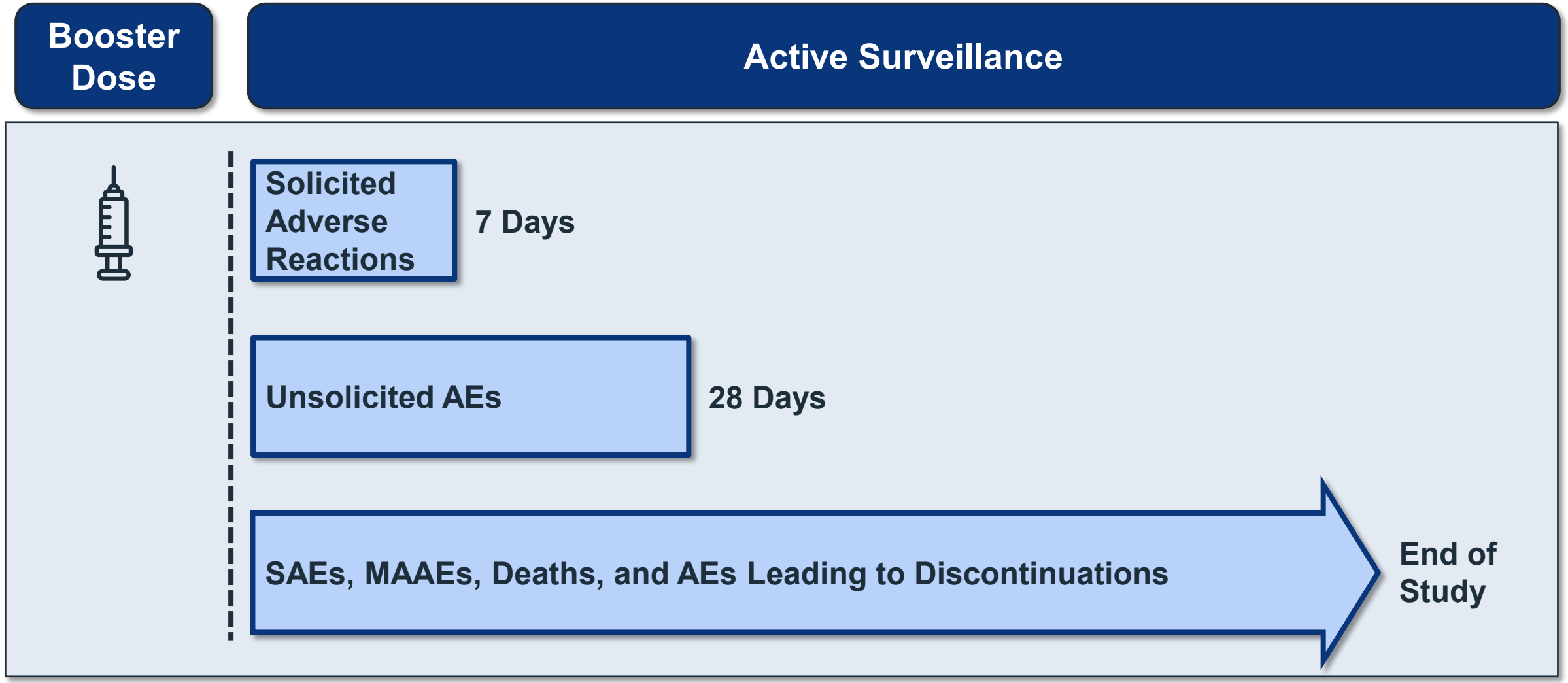
		50 µg Booster After 100 µg Primary Series N = 171	50 µg Booster Pooled N = 344
Age	Mean (years)	52	52
	18-64	78%	76%
	≥ 65	22%	24%
Sex	Female	61%	66%
Race	White	96%	95%
	Black or African American	3%	2%
	Asian	< 1%	< 1%
	American Indian or Alaska Native	< 1%	< 1%
Ethnicity	Hispanic or Latino	6%	6%
	Not Hispanic or Latino	94%	94%

Safety Data for 50 µg Booster After 100 µg Primary Series

Study 201B

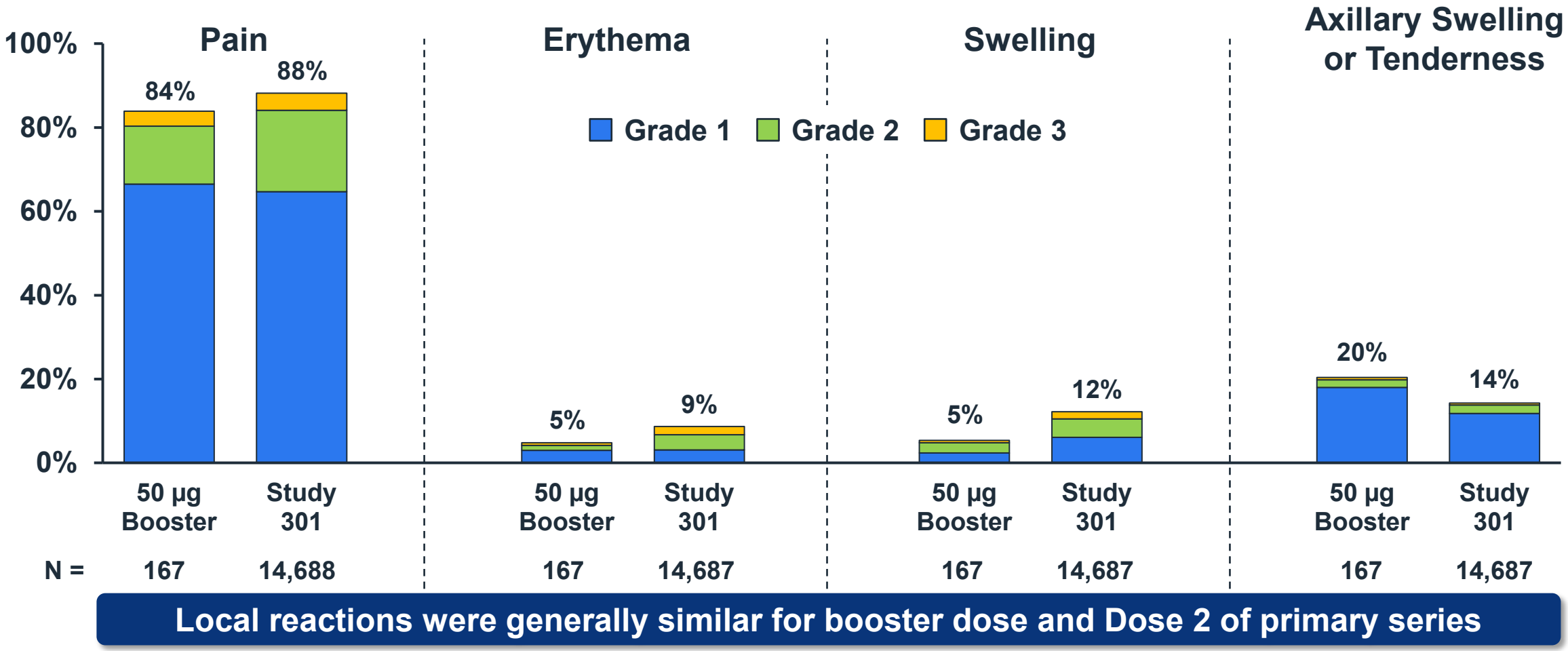
Follow-up Period for Safety Data Collection

Median 5.7 Months Safety Follow-up



Solicited Local Adverse Reactions within 7 Days

Study 201B 50 µg Booster Dose After 100 µg Primary Series vs Study 301

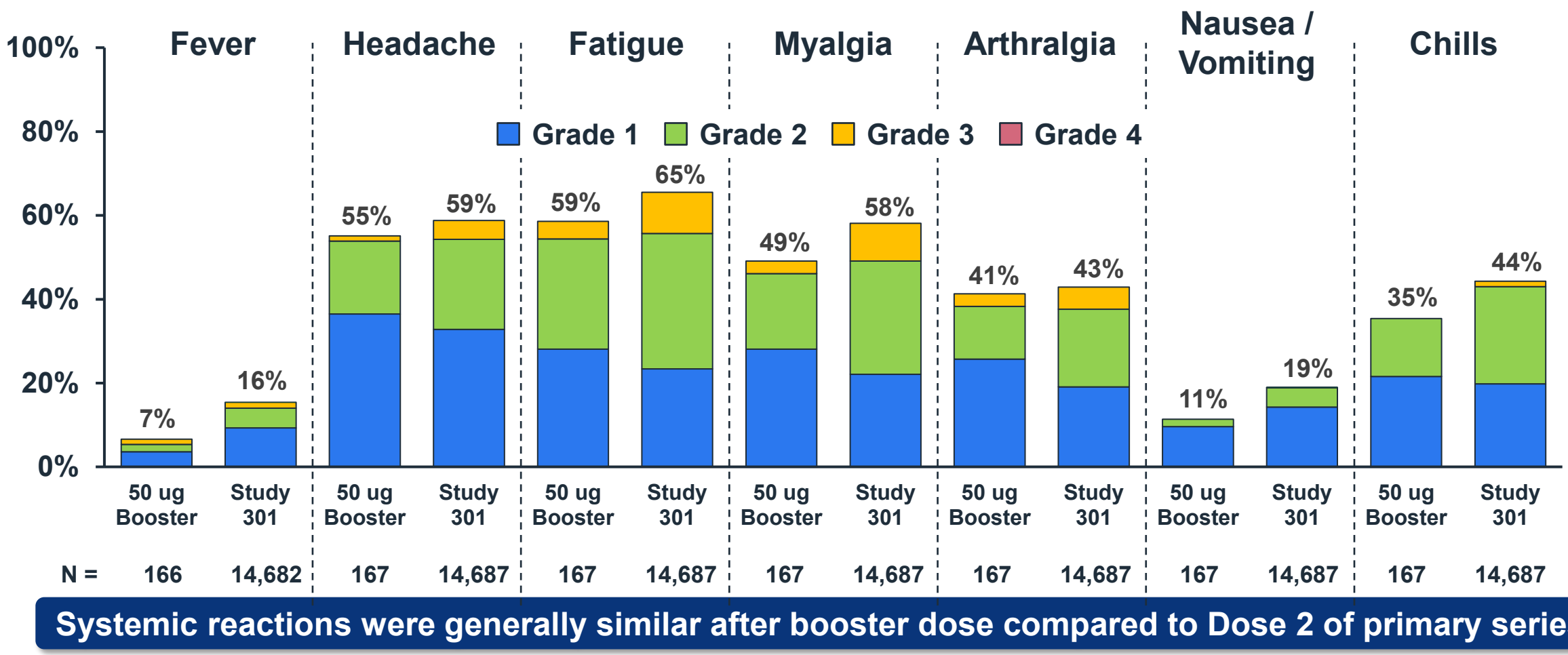


Local reactions were generally similar for booster dose and Dose 2 of primary series

No Grade 4 solicited local adverse reactions were reported
Solicited safety set

Solicited Systemic Adverse Reactions within 7 Days

Study 201B 50 µg Booster Dose After 100 µg Primary Series vs Study 301

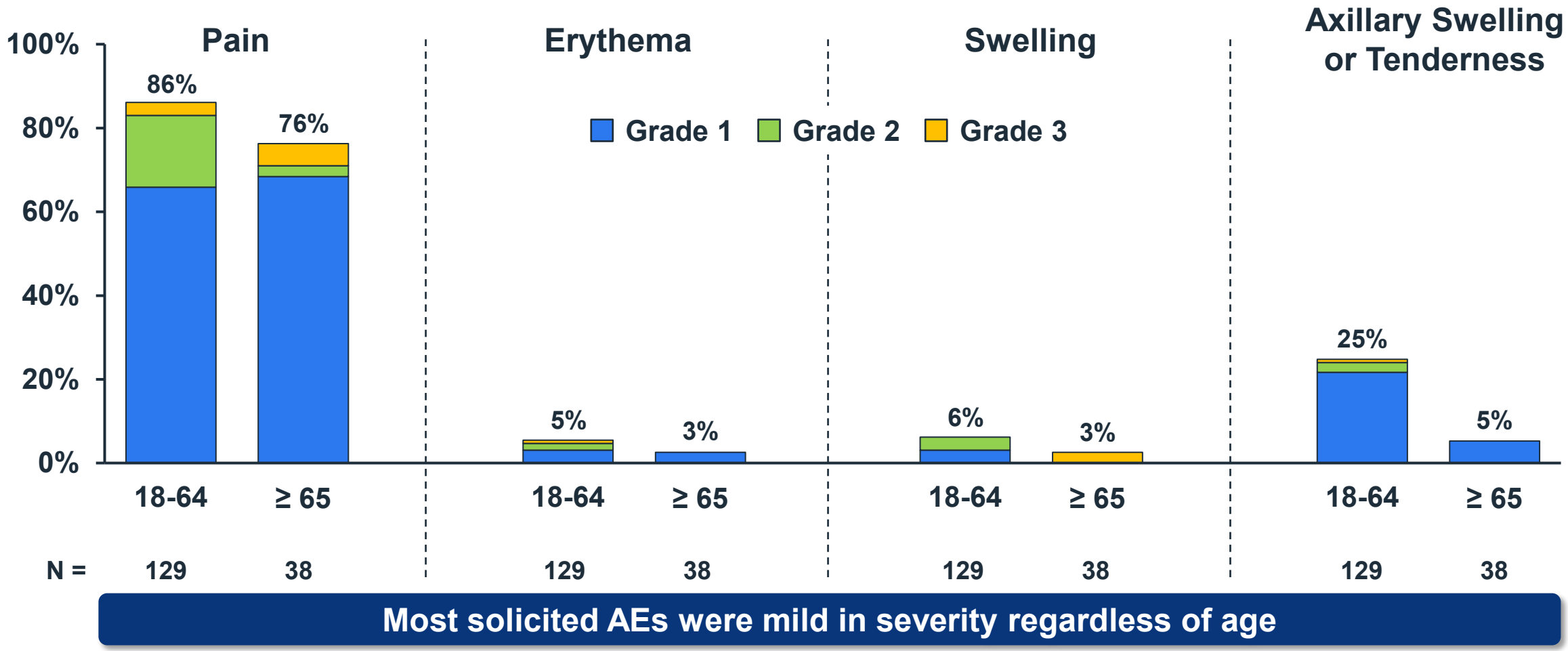


Systemic reactions were generally similar after booster dose compared to Dose 2 of primary series

Grade 4 fever & nausea/vomiting occurred in < 0.1% of subjects in Study 301. No Grade 4 solicited systemic adverse reactions reported in Study 201B.
Solicited safety set

Solicited Local Adverse Reactions by Age

Study 201B 50 µg Booster Dose After 100 µg Primary Series

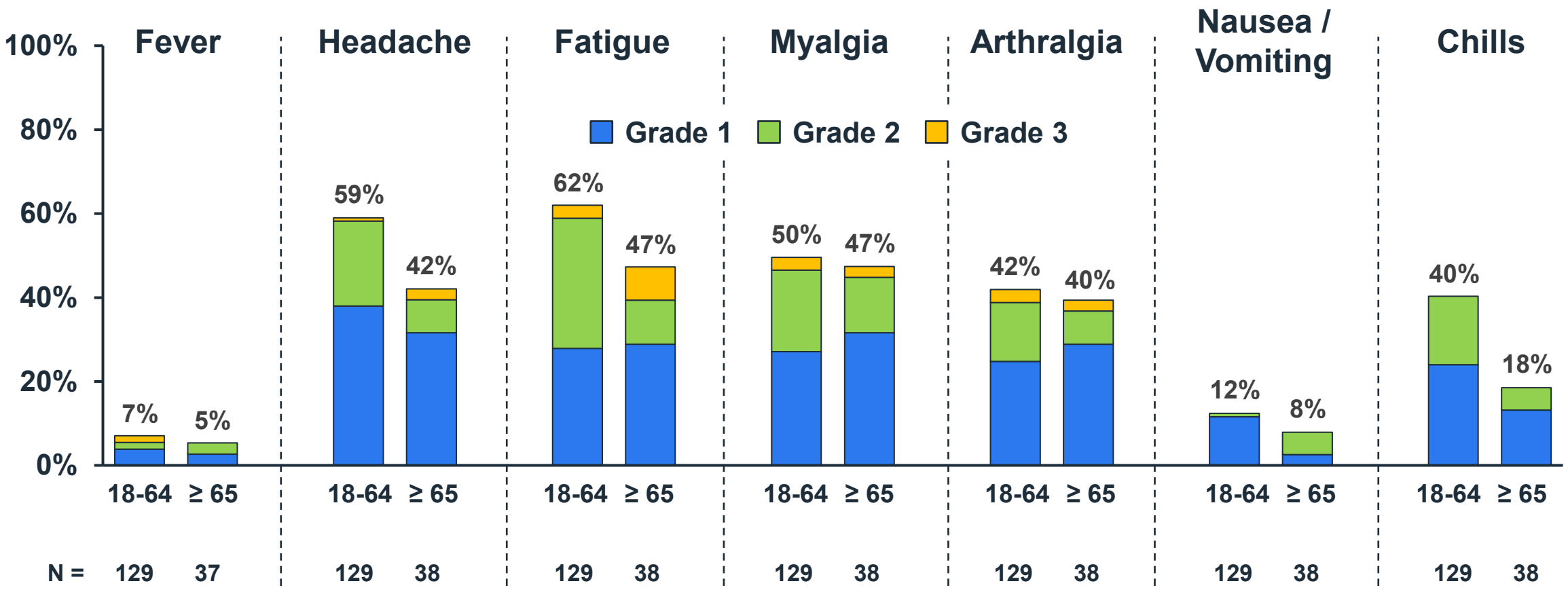


Most solicited AEs were mild in severity regardless of age

No Grade 4 solicited local adverse reactions were reported
Solicited safety set

Solicited Systemic Adverse Reactions by Age

Study 201B 50 µg Booster Dose After 100 µg Primary Series



Systemic reactions were generally less frequent after a booster dose among older adults

No Grade 4 solicited systemic adverse reactions were reported
Solicited safety set

Unsolicited Adverse Events

Study 201B 50 µg Booster Dose vs Study 301

	Participants Reporting at Least One Event, n (%)		
	50 µg Booster After 100 µg Primary Series N = 171	50 µg Booster Pooled N = 344	Study 301 N = 15,184
Medically attended AEs (MAAE)	41 (24%)	78 (23%)	3,468 (23%)
Vaccine-related MAAE	2 (1%)	2 (< 1%)	213 (1%)
Serious adverse events	2 (1%)	4 (1%)	268 (2%)
Vaccine-related SAE	0	0	12 (< 0.1%)
Deaths	0	0	17 (0.1%)
Adverse event leading to study discontinuation	0	0	26 (0.2%)

No vaccine-related SAEs or deaths in Study 201B to date

As of August 16, 2021 (median 5.7 months safety follow-up)

Immunogenicity of 50 µg Booster Dose vs Original Virus (D614G)

Study 201B

Co-primary Endpoints to Demonstrate Noninferiority of Immune Response

Study 201B vs Study 301

- Pre-specified immunogenicity endpoints based on pooled primary series groups
- Immunogenicity was compared 1-month post-booster (Study 201B) to 1-month post-dose 2 (Study 301) using neutralization assays against original virus (D614G) and Delta variant
- 2 co-primary endpoints
  - Geometric mean ratio (GMR)
    - Lower bound of the corresponding 95% CI ≥ 0.67 (non-inferiority margin of 1.5)
    - Point estimate ≥ 1
  - Difference of seroresponse rates (SRR)
    - Lower bound of the 95% CI ≥ -10%
  - Consistent with relevant FDA guidance[1]

1. Food and Drug Administration (FDA) Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19

Vaccine Effectiveness of 50 µg Booster Dose Inferred by Immunobridging to Study 301

Study	N	Previous Dose of mRNA-1273 Doses 1 & 2	Booster Dose	Interval between Dose 2 & Booster Dose
201B (boost with mRNA-1273)	**146**	**50 µg**	**50 µg**	**≥ 6 months**
	149	**100 µg**	**50 µg**	
301 Immunogenicity Subset	**1,055**	**100 µg (primary series only)**	**None**	**-**

Per protocol set

Geometric Mean Ratio (GMR) of Neutralization Titers

Study 201B (Pooled) vs Study 301

Geometric Mean Titer (95% CI)		
28 days Post Booster Study 201B Pooled N = 295	**28 days Post Dose 2 Study 301** N = 1,053	**Post Booster / Post Dose 2 GMR (95% CI)**
1,768 (1,586, 1,970)	**1,033** (974, 1,095)	**1.7** (1.5, 1.9)

First co-primary endpoint of GMR non-inferiority margin of 1.5 and point estimate of ≥ 1.0 met

Per protocol set

Geometric Mean Ratio (GMR) of Neutralization Titers

Study 201B 50 µg Booster Dose After 100 µg Primary Series vs Study 301

Geometric Mean Titer (95% CI)		
28 days Post 50 µg Booster after 100 µg Primary Series Study 201B N = 149	**28 days Post Dose 2 Study 301** N = 1,053	**Post Booster / Post Dose 2 GMR (95% CI)**
1,802 (1,548, 2,099)	**1,027** (968, 1,089)	**1.8** (1.5, 2.1)

Co-primary endpoint of GMR non-inferiority margin of 1.5 and point estimate of ≥ 1.0 also met for 100 µg Primary Series followed by 50 µg Booster

Per protocol set
Measured as pseudovirus neutralization ID_{50}

Seroresponse Rates based on 3.3-Fold Definition (Prespecified Hypothesis)

Study 201B (Pooled) vs Study 301

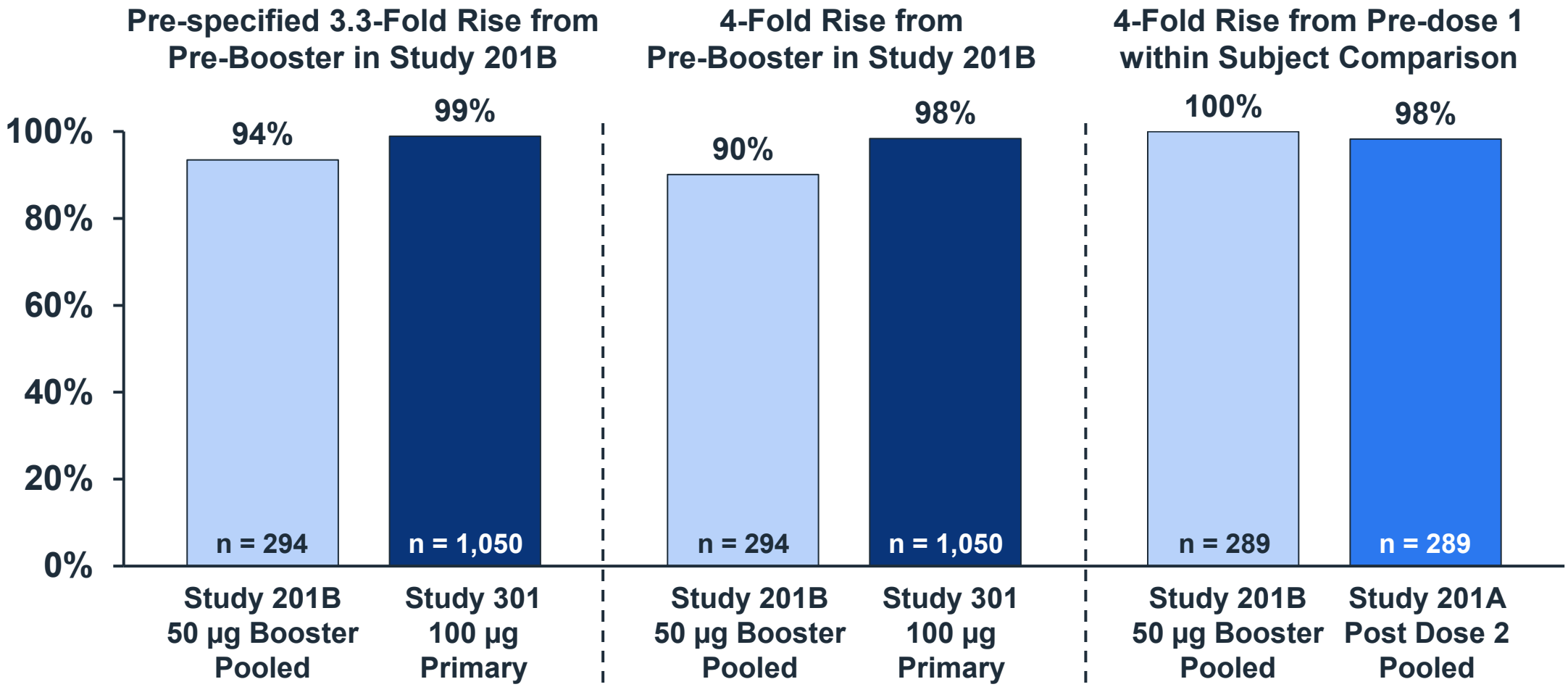
	Study 201B 50 µg Booster Pooled N = 294	Study 301 100 µg Primary Series N = 1,050
Baseline Geometric Mean Titer (GMT)	126	10
GMT 28 days post dose	1,893	1,081
Participants achieving seroresponse, n (%)	275 (94%)	1,038 (99%)
95% CI	90.1, 96.1	98.0, 99.4
Difference in seroresponse rate (SRR)	-5.3	
95% CI	-8.8, -2.9	

Co-primary endpoint of SRR met (lower bound of 95% CI ≥ -10%)

Per protocol set

Observed Seroresponse Rates Using Three Definitions

Study 201B (Pooled) vs Study 301/Study 201A (Pooled)



Regardless of definition, a ≥ 90% seroresponse rate was achieved after 50 µg booster dose in the pooled group

Per protocol set

Seroresponse Rates Based on 4-Fold Rise from Pre-Booster Titers

Study 201B 50 µg Booster after 100 µg Primary Series vs Study 301

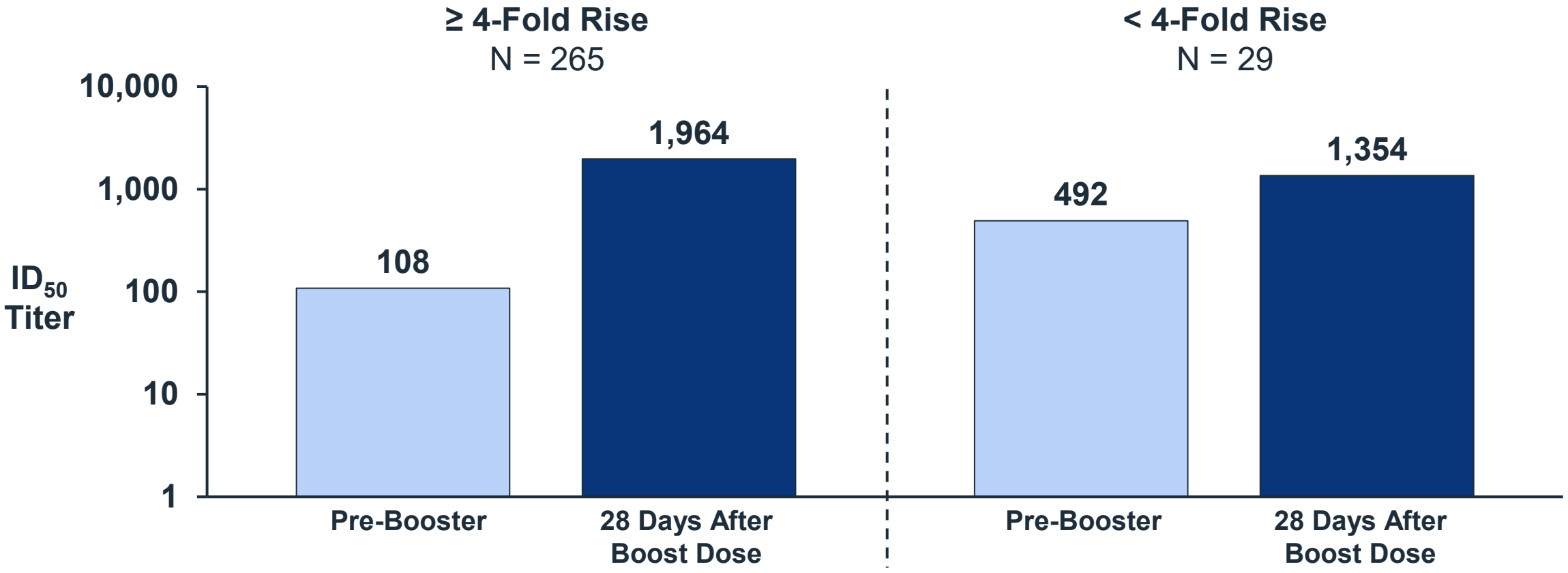
	50 µg Booster After 100 µg Primary Series N = 149	Study 301 100 µg Primary Series N = 1,050
Baseline Geometric Mean Titer (GMT)	150	10
GMT 28 days post dose	1,952	1,081
Participants achieving seroresponse, n (%)	131 (88%)	1,033 (98%)
95% CI	81.6, 92.7	97.4, 99.1
Difference in seroresponse rate (SRR)	-10.5	
95% CI	-16.7, -6.1	

SRR success criteria not met (lower bound of 95% CI ≥ -10%)

Per protocol set

Titer Comparison for Subjects Who Had ≥ 4-Fold Rise vs < 4-Fold Rise after Booster Dose

Study 201B (Pooled)

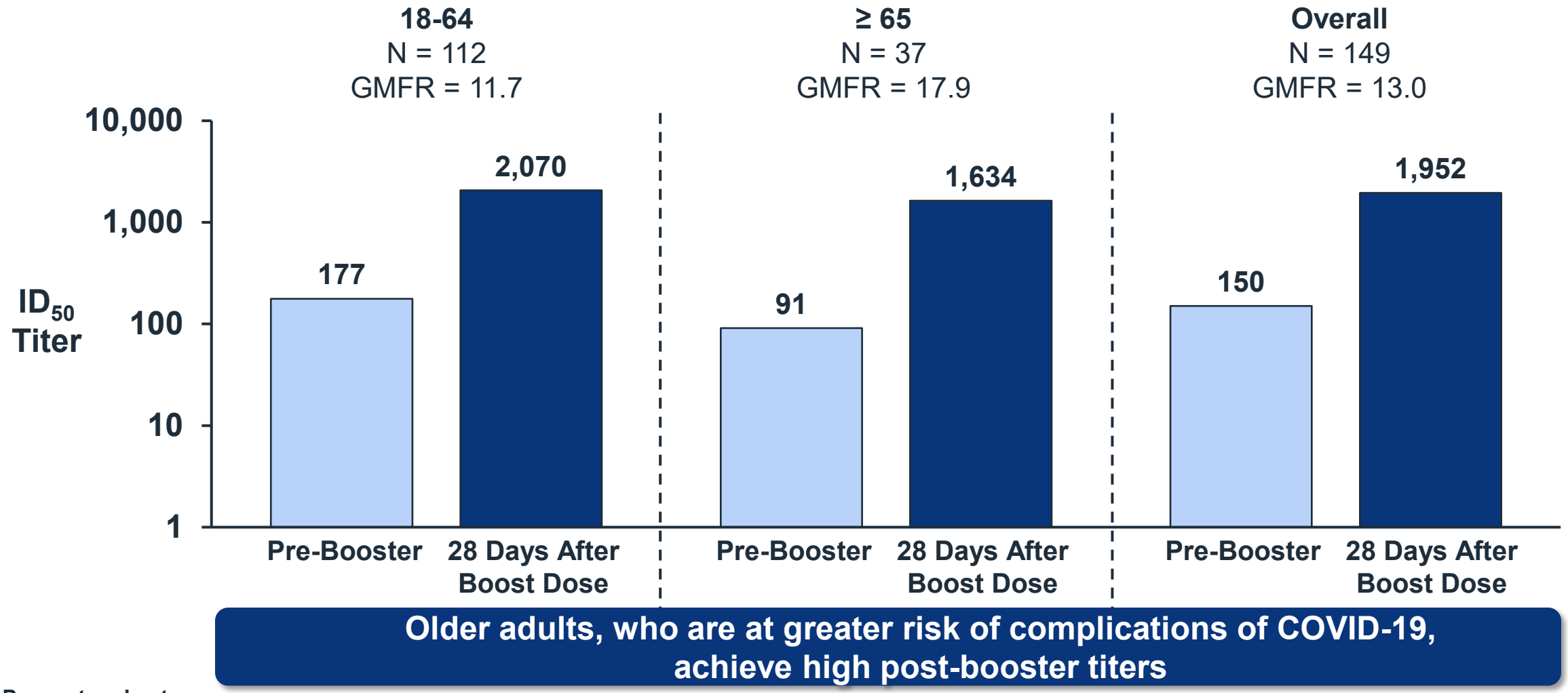


Subjects who did not meet 4-fold rise had 4 times higher pre-booster titers compared to those who did meet 4-fold rise

Per protocol set

Geometric Mean Ratio of Neutralization Titers by Age

Study 201B 50 µg Booster after 100 µg Primary Series vs Study 301

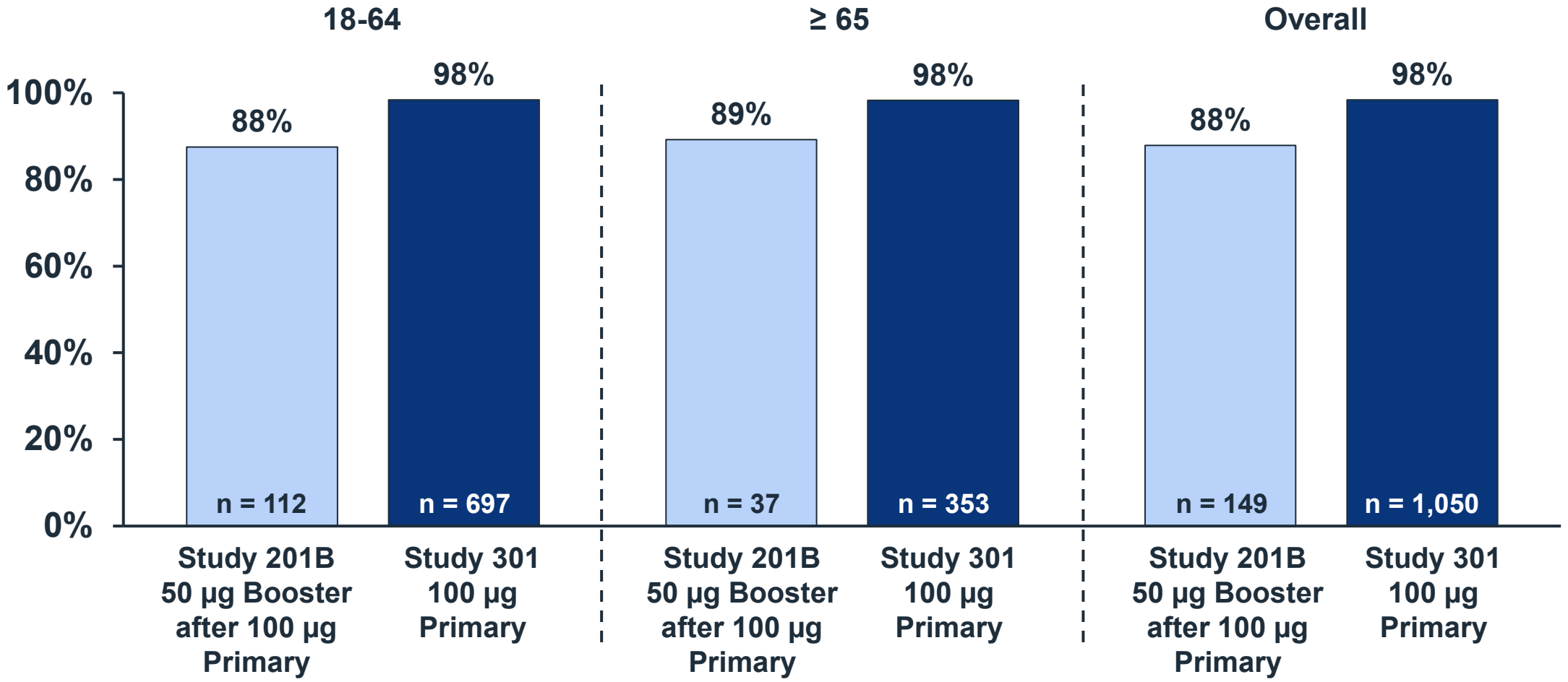


Older adults, who are at greater risk of complications of COVID-19, achieve high post-booster titers

Per protocol set
GMFR = Geometric Mean Fold Rise

Seroresponse Rate Based on 4-Fold Rise from Pre-Booster by Age

Study 201B 50 µg Booster after 100 µg Primary Series vs Study 301



Consistently high seroresponse rate in participants 18-64 and those ≥ 65 years of age

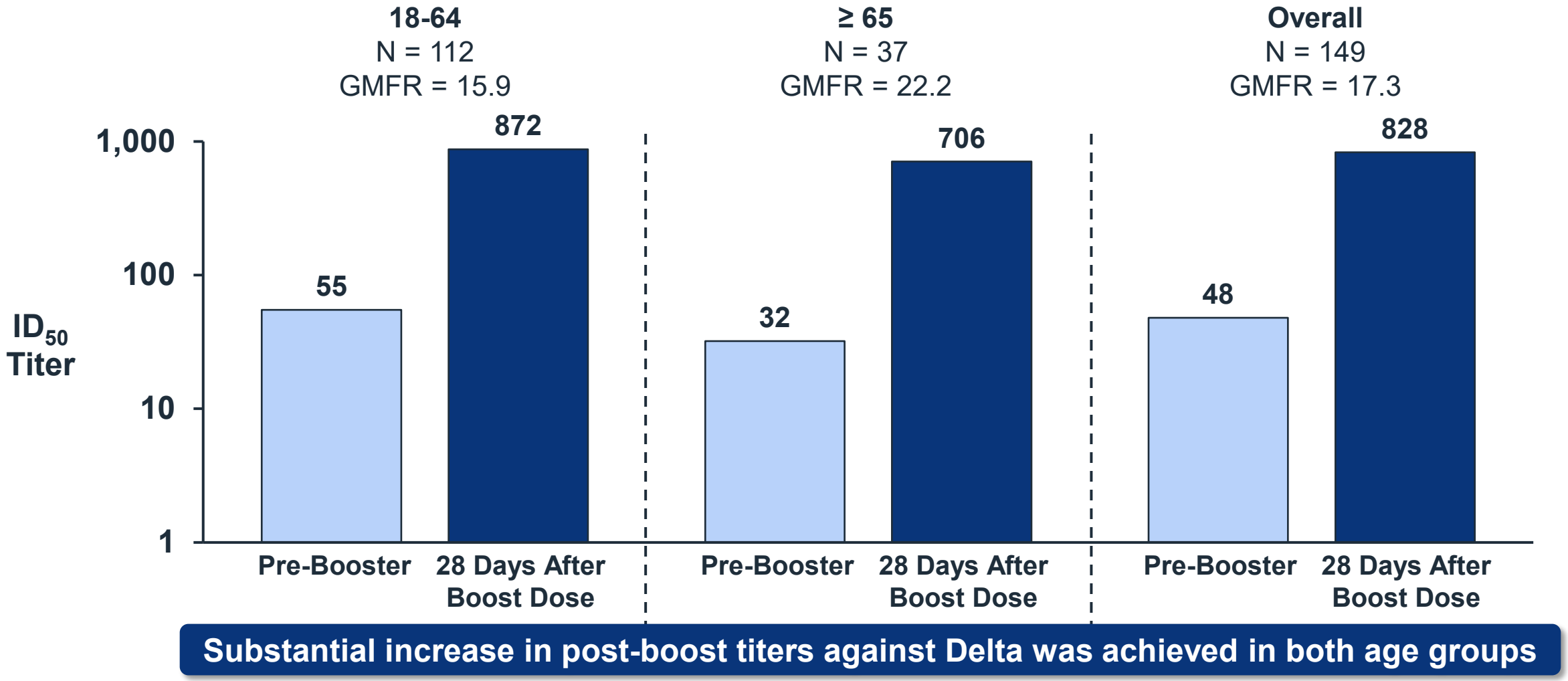
Per protocol set

Immune Response to Delta Variant

Study 201B

Geometric Mean Titers of Neutralization Titers Against Delta Variant

Study 201B 50 µg Booster after 100 µg Primary Series

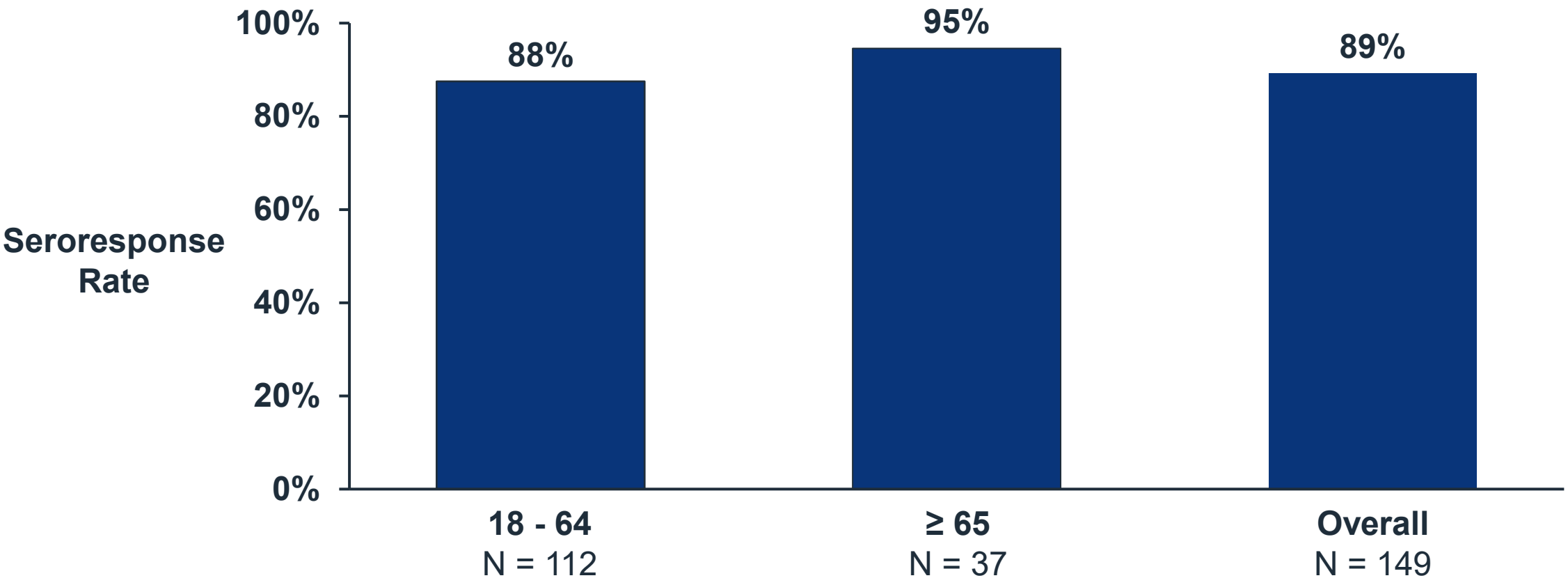


Substantial increase in post-boost titers against Delta was achieved in both age groups

GMFR = Geometric Mean Fold Rise

Seroresponse Rates to Delta Variant Based on 4-Fold Rise from Pre-Booster

Study 201B 50 µg Booster after 100 µg Primary Series



4 weeks post booster

Summary

Safety Summary of 50 µg Booster Dose

- Rates of adverse reactions (ARs) with 50 µg booster dose comparable to those observed after Dose 2 of primary series
  - Pain at injection site most common solicited local AR in both groups
  - Headache, fatigue and myalgia most common systemic ARs in both groups
  - Majority of ARs were mild-to-moderate in severity
  - Axillary swelling or tenderness was the only AR more frequently reported after booster dose
- No vaccine-related SAEs or deaths in Study 201B

Immunogenicity Summary of 50 µg Booster Dose

- Pre-specified co-primary hypotheses (GMR & SRR difference) were met on pooled dataset
- 50 µg booster dose following 100 µg primary series results in
  - Higher antibody responses to original virus (D614G) than post-Dose 2 in Phase 3 Study 301 (GMR = 1.8)
  - 13-fold rise from pre-booster titers for original virus
  - 17-fold rise from pre-booster titers for Delta variant
- Consistently high antibody titers in both age groups (18-64 and ≥ 65)

GMR = geometric mean ratio
SRR = seroresponse rate

Proposed Use of Moderna Vaccine as a Booster

- Administration of a single 50 µg (0.25 ml) booster dose at least 6 months after completion of a primary series in:
  - Individuals 65 years of age and older;
  - Individuals 18 - 64 years of age at high risk of severe COVID-19; and
  - Individuals 18 - 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19

THANK YOU

NIH/COVPN

Investigators and study site personnel

BARDA

Montefiori laboratory at Duke University

Most importantly, the many individuals who participated in these trials

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