RSV vaccine (mRNA-1345)

Last updated: 5/31/24

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial
Adults	**COVID-19 vaccine**	Spikevax®					
	COVID-19 vaccine Next gen	mRNA-1283					
	Flu vaccines	mRNA-1010					
		mRNA-1020					
		mRNA-1030					
		mRNA-1011					
		mRNA-1012					
Infectious disease vaccines	**RSV vaccine** older adults	mRNA-1345					
	Flu + COVID vaccine	mRNA-1083					
	Flu + COVID + RSV vaccine	mRNA-1230					
	Flu + RSV vaccine	mRNA-1045					
	Endemic HCoV vaccine	mRNA-1287					
	Pandemic Flu	mRNA-1018					
	RSV + hMPV vaccine	mRNA-1365					
Adolescents & Pediatrics	**COVID-19 vaccine** adolescents	mRNA-1273.815					
	COVID-19 vaccine pediatrics	mRNA-1273.815					
	RSV vaccine pediatrics	mRNA-1345					

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RSV (mRNA-1345) development program in adults >50 years old

Adults
(Ages: 60+)

Phase 3
P301 Part A

- Pivotal Phase 3 efficacy and safety
- Received U.S. FDA regulatory approval May 31, 2024; preparing for 2024 U.S. launch

Adults
(Ages: 60+)

Phase 3
P301 Part B

- 24-month revaccination
- Trial ongoing

Adults
(Ages: 50+)

Phase 3
P302 Part A

- Standard dose influenza vaccine co-administration

Adults
(Ages: 50+)

Phase 3
P302 Part B

- COVID-19 vaccine co-administration

Adults
(Ages: 50+)

Phase 3
P302 Part C

- 12-month revaccination

Adults
(Ages: 65+)

Phase 3
P304

- High dose influenza vaccine co-administration;
- Trial fully enrolled

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RSV (mRNA-1345) P301 Part A older adult pivotal safety and efficacy

Phase 2/3 pivotal vaccine efficacy and safety trial designed to evaluate the safety, tolerability, and efficacy of mRNA-1345 (50 µg) in adults ≥ 60 years of age

Design
Randomized 1:1, observer-blind, placebo-controlled study

Number of participants
~37,000 adults ≥ 60 years of age (Phase 2:~2000; Phase 3: ~35,000)

Vaccination schedule
Single dose of mRNA-1345 (50 µg) or placebo

Duration
Participants followed up for 24 months after study injection

Site location
22 countries

Phase 2/3 pivotal efficacy
≥ 60 years of age
Total N ~ 37,000

mRNA-1345	Placebo
N~18,500	N~18,500

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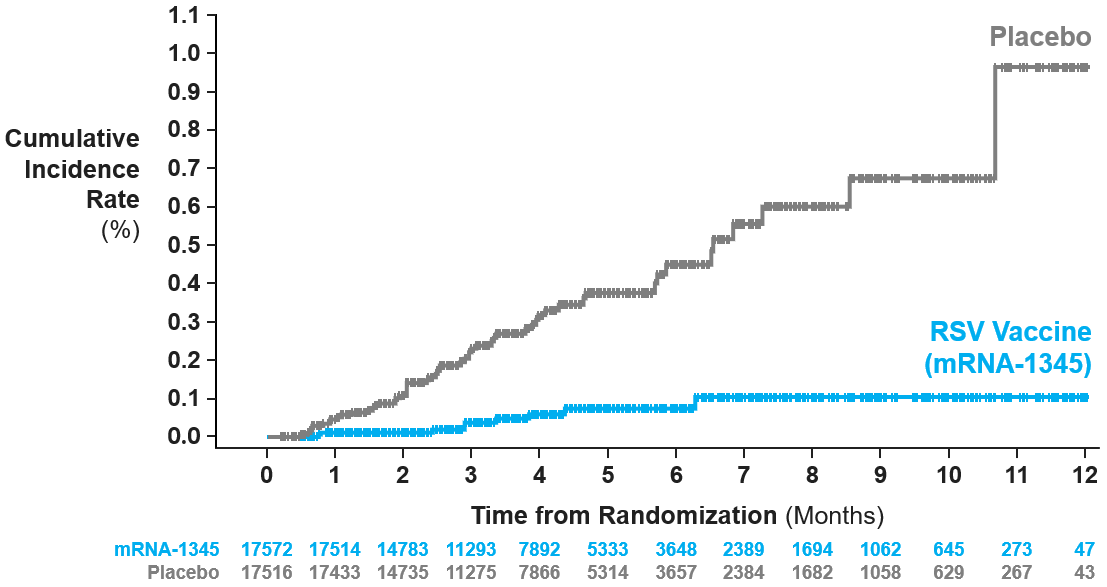
RSV vaccine efficacy met primary and key secondary endpoints in primary analysis

Study 301 per protocol analysis, median follow up of 3.7 months (maximum of 12.6 months) after vaccine/placebo

	Cases, n (%)		
	mRNA-1345 (N = 17,572)	**Placebo** (N = 17,516)	**Vaccine Efficacy (%) Based on Hazard Ratios[1]**
RSV LRTD ≥ 2 symptoms	9 (0.05%)	55 (0.31%)	**83.7%** (66.0%, 92.2%)
RSV LRTD ≥ 3 symptoms	3 (0.02%)	17 (0.10%)	**82.4%** (34.8%, 95.3%)
RSV ARD	26 (0.15%)	82 (0.47%)	**68.4%** (50.9%, 79.7%)

RSV-LRTD ≥ 2 symptoms



The results of the primary efficacy and safety analysis of this Phase 2/3 efficacy study were recently published in the NEJM[1]

1.https://www.nejm.org/doi/full/10.1056/NEJMoa2307079?query=featured_home

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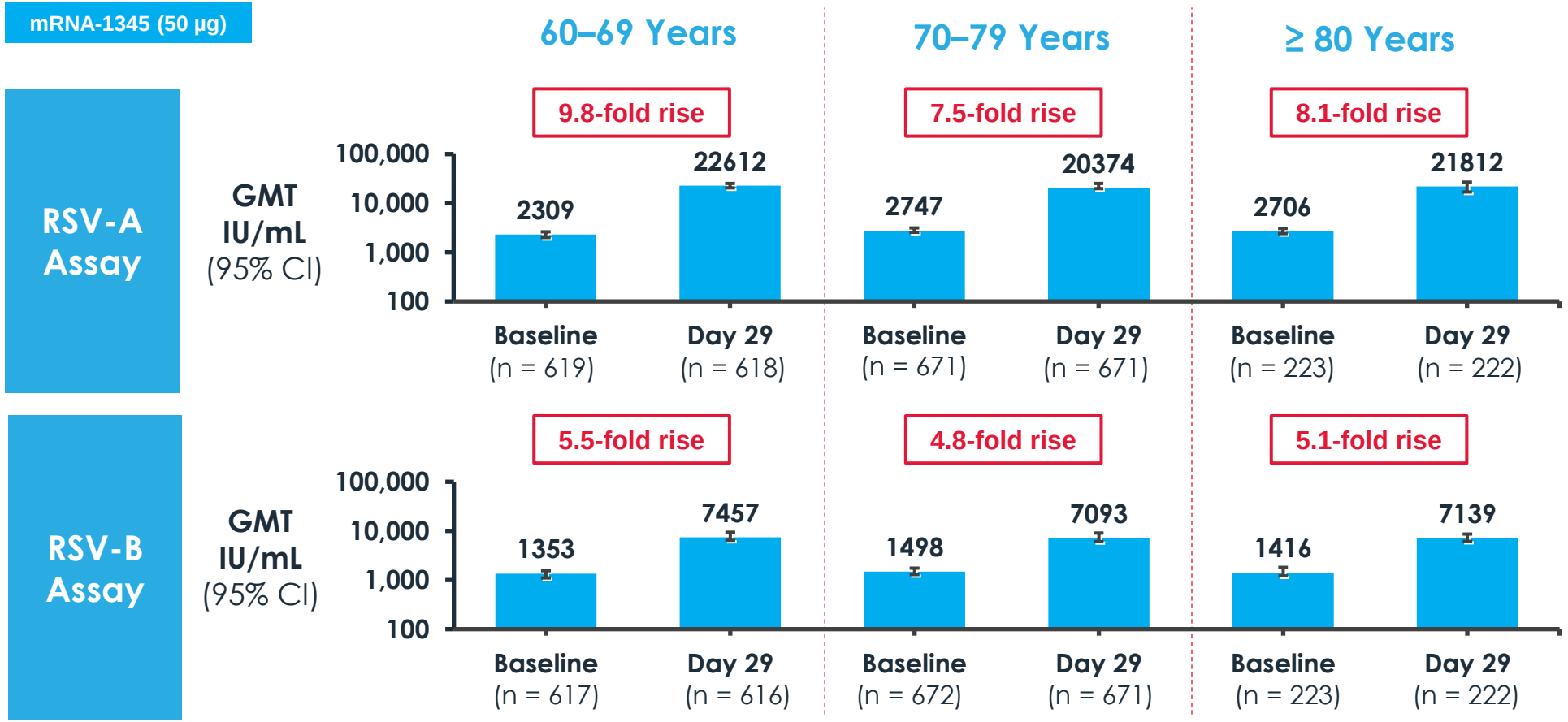
RSV neutralizing antibody responses are similar across age groups, including ≥ 80 years old

Study 301 – RSV neutralizing antibody (IU/mL)

Per Protocol Immunogenicity Set

mRNA-1345 (50 µg)



- Baseline titers similar across age groups
- Day 29 titers and fold rise are similar across age groups

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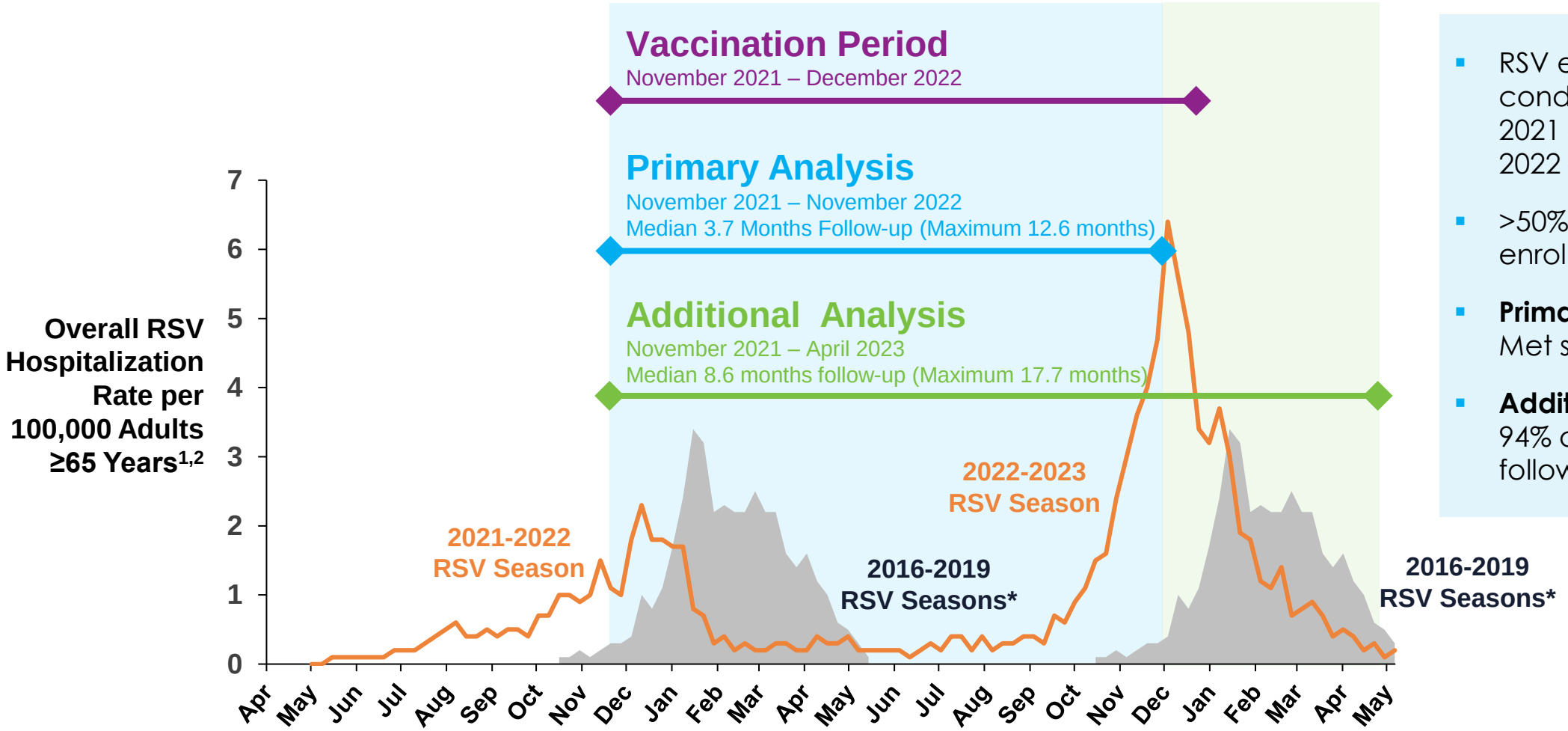
Primary and additional analyses confirm durable protection through full 2022-2023 RSV season for mRNA-1345



- RSV efficacy study conducted across 2021 – 2022 and 2022 – 2023 seasons
- >50% of participants enrolled in US
- **Primary Analysis:** Met success criteria[2]
- **Additional Analysis:** 94% of participants followed for ≥6 months

*Median RSV hospitalization rate for 2016 – 2019. Data only collected from October to April each year.

1. CDC. Respiratory Syncytial Virus Hospitalization Surveillance Network (RSV-NET). https://data.cdc.gov/Public-Health-Surveillance/Weekly-Rates-of-Laboratory-Confirmed-RSV-Hospitali/29hc-w46k/data_preview. 2. Wilson E, et al. NEJM. 2023;389:2233-2244.

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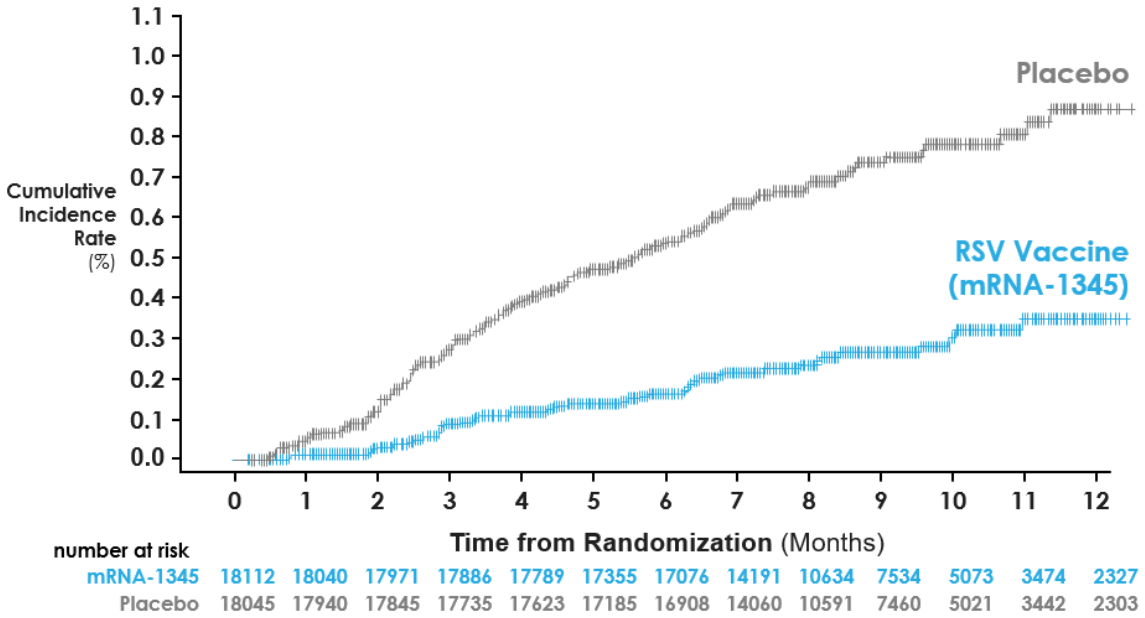
Additional analysis: efficacy of mRNA-1345 against RSV LRTD among adults ≥ 60 Years

Unblinded analysis, median follow-up of 8.6 months (maximum of 17.7 months) after vaccine/placebo

	Cases, n (%)		
	RSV Vaccine (mRNA-1345) (N = 18,112)	**Placebo** (N = 18,045)	**Vaccine Efficacy (%) Based on Hazard Ratios (95% CI)**
RSV LRTD ≥ 2 symptoms	47 (0.26%)	127 (0.70%)	**63.3%** (48.7%, 73.7%)
RSV LRTD ≥ 3 symptoms	19 (0.10%)	51 (0.28%)	**63.0%** (37.3%, 78.2%)
RSV ARD	86 (0.47%)	185 (1.03%)	**53.9%** (40.5%, 64.3%)
RSV-LRTD Associated Shortness of Breath[1]	11/18,101 (0.06%)	43/18,002 (0.24%)	**74.6%** (50.7%, 86.9%)

RSV-LRTD ≥ 2 symptoms



- Vaccine protection continues over a longer period (median 8.6 months) through high-transmission 2022/2023 RSV season
- Lower bound of the confidence interval continued to exceed 20%

1. Shortness of breath was a post hoc analysis

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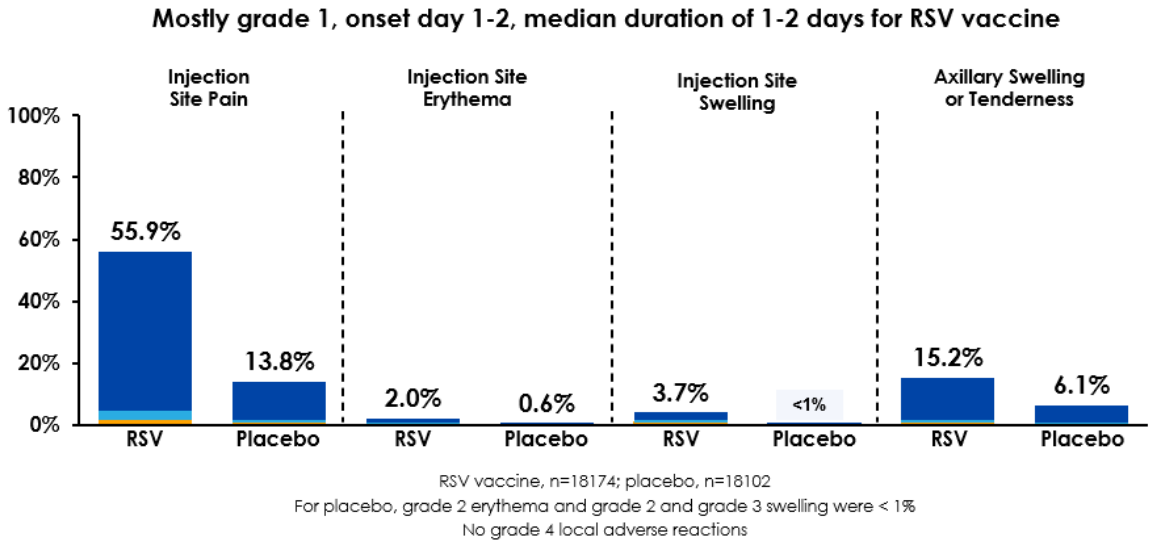
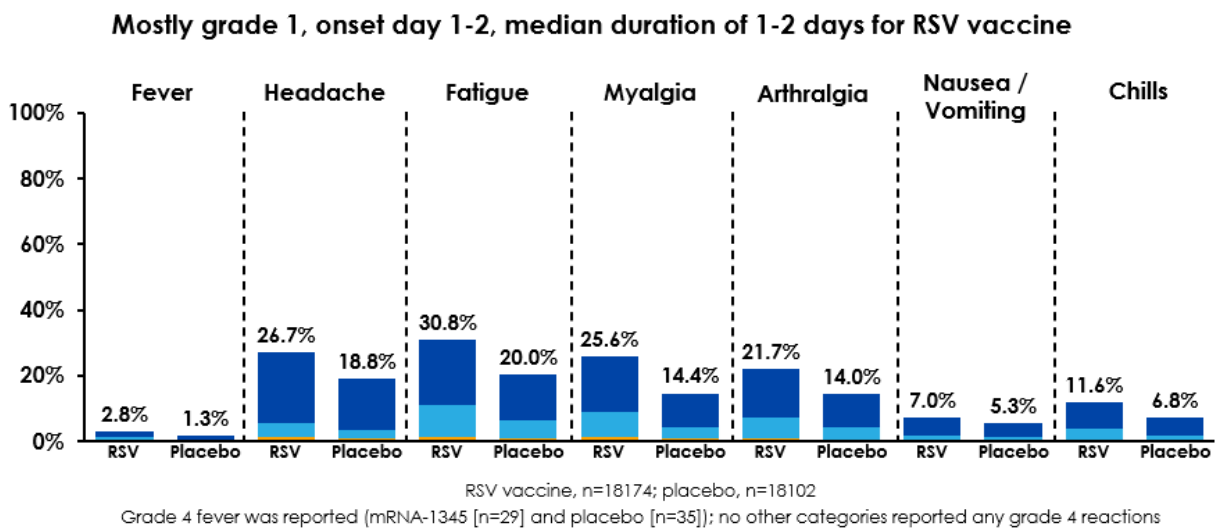
mRNA-1345 reactogenicity

Study 301 - Solicited Safety Set

Solicited Local Reactions within 7 Days After RSV Vaccine vs Placebo



Solicited Systemic Reactions within 7 Days After RSV Vaccine vs Placebo



Grade 1 Grade 2 Grade 3

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RSV P301 summary and next steps

Efficacy	• 83.7% and 82.4% against RSV LRTD with ≥2 and ≥3, respectively, lower respiratory signs/symptoms in primary analysis of adults 60 and over • RSV-A & RSV-B nAb responses similar across age groups, including those ≥80 years old
Safety	• Well tolerated; solicited adverse reactions were mostly grade 1 or 2 • No safety concerns identified
Next steps	• Received U.S. FDA regulatory approval May 31, 2024; anticipating approvals in other countries • Expecting to launch in the U.S. in 2024 after ACIP recommendation

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RSV is the leading cause of respiratory illness in young children and older adults are at high risk for severe RSV infections

Disease burden in pediatrics

- Hospitalization rate in children <5 years old in the U.S.: ~3:1000[1]
- Annually ~2 million medically attended RSV infections in children <5 years old in the U.S., with up to 80,000 hospitalized[2]
- Pediatric RSV results in an estimated ~$2 billion in annual medical costs in the U.S.
- Almost all children will have had an RSV infection by their second birthday[3]

Disease burden in older adults

- There are up to 160,000 hospitalizations in adults 65+ due to RSV in the U.S. each year, and up to 10,000 deaths[4]
- In industrialized countries, it is estimated that there are ~1.5 million episodes of acute respiratory tract infection in older adults annually; globally, it is estimated that there are ~336,000 hospitalizations related to RSV in older adults each year[5]

Long-term RSV infection sequelae

Pediatric populations[6]
- Recurrent wheeze
- Asthma
- Impaired lung function

Older adults[7]
- Exacerbation of chronic obstructive pulmonary disease
- Higher 1 year mortality after severe illness

(1) Rha, Brian, et al., *Pediatrics* (2020), https://doi.org/10.1542/peds.2019-3611
(2) RSV Surveillance & Research, CDC, https://www.cdc.gov/rsv/research/index.html
(3) Respiratory Syncytial Virus Infection (RSV), CDC, https://www.cdc.gov/rsv/about/symptoms.html
(4) RSV in Older Adults and Adults with Chronic Medical Conditions, CDC, https://www.cdc.gov/rsv/high-risk/older-adults.html
(5) Shi, Ting, et al., *J Infect Dis.* (2020), https://doi.org/10.1093/infdis/jiz059.
(6) Shi, Ting et al., *J Infect Dis*. (2020), https://doi.org/10.1093/infdis/jiz311
(7) Ackerson, Bradley et al., *Clin Infect Dis.*(2019), https://doi.org/10.1093/cid/ciy991

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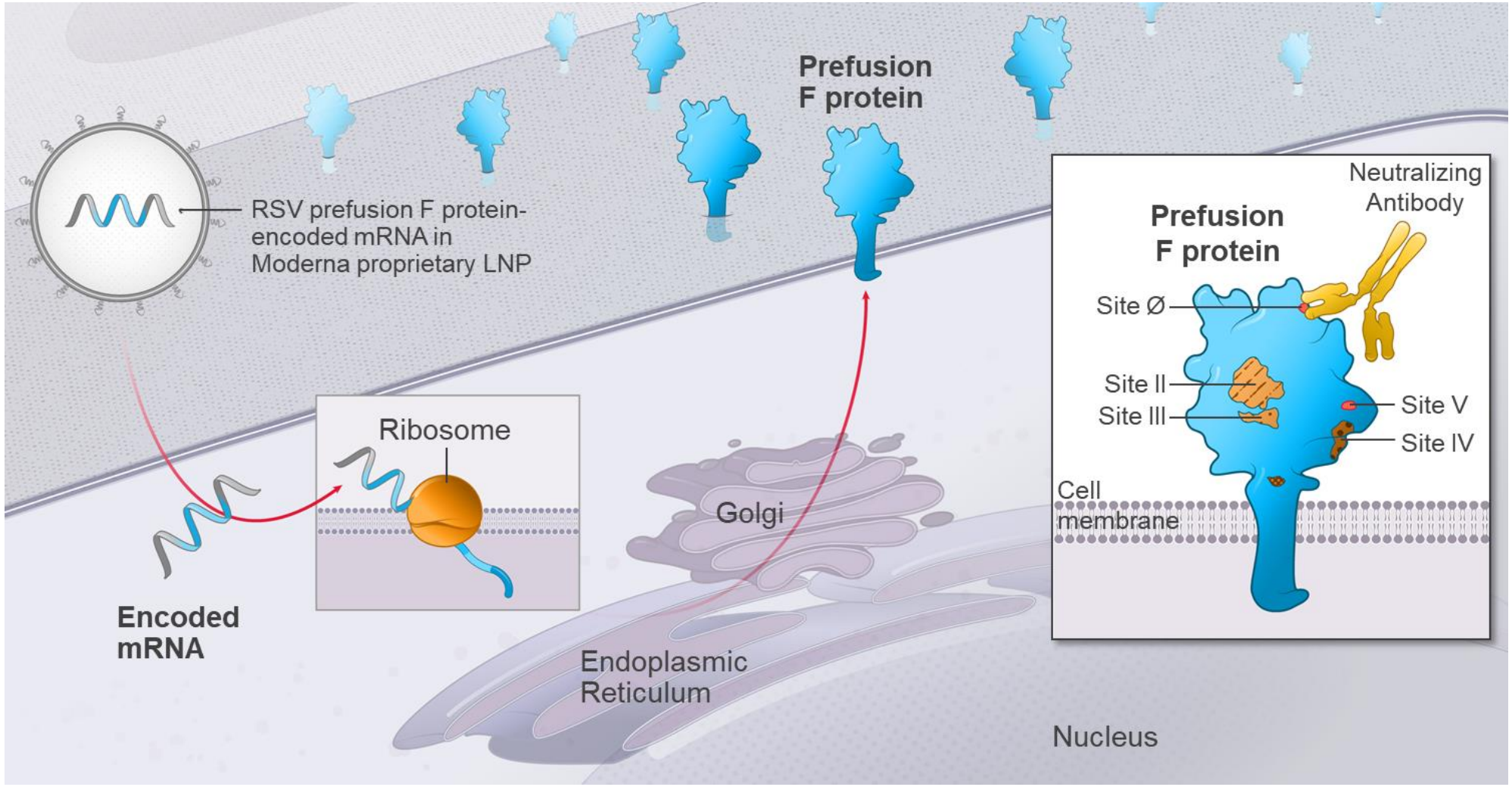
RSV vaccine (mRNA-1345) encodes for a stabilized prefusion F glycoprotein



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mRNA-1345 Phase 3 in older adults – summary of primary analysis and next steps

Efficacy

- 83.7% and 82.4% vaccine efficacy against RSV-LRTD with ≥2 and ≥ 3 signs/symptoms, respectively
- Secondary analysis was performed according to the presence/absence of medical comorbidities for RSV-LRTD with ≥2 symptoms
  - VE for RSV-LRTD with no comorbidity was 81.6%
  - VE for RSV-LRTD with ≥ 1 comorbidity was 88.4%

Safety

- Pain was the most frequently reported local solicited symptom
- Headache, fatigue, myalgia and arthralgia were the most frequently reported systemic solicited symptoms
- Most solicited adverse reactions were grade 1 or grade 2
- No cases of GBS or ADEM have been reported in mRNA-1345 Phase 3 study
- No safety concerns identified

Next steps

- Received U.S. FDA regulatory approval May 31, 2024; anticipating approvals in other countries

RSV-LRTD: Respiratory Syncytial Virus Lower Respiratory Tract Disease
GBS: Guillain-Barré Syndrome
ADEM: Acute demyelinating encephalomyelitis
*Medical comorbidities included COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease

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Safety and Efficacy of mRNA-1345, an mRNA-based Vaccine Against Respiratory Syncytial Virus, in Adults 60 Years and Older

Eleanor Wilson, Jaya Goswami, Sonia K. Stoszek, Runa Mithani, Shraddha Mehta, Archana Kapoor, Wenmei Huang, Lan Lan, Laila El Asmar, Catherine A. Panozzo, Parinaz Ghaswalla, Allison August, Christine A. Shaw, Jacqueline Miller, Grace L. Chen

February 23, 2023
Presented at the 7th ReSViNET Conference (RSVVW 2023)
Lisbon, Portugal

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- EW, JG, SKS, RM, SM, AK, WH, LL, LEA, CAP, PG, AA, CAS, JM, and GLC are employees of Moderna, Inc., and hold stock/stock options in the company
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- This study was funded by Moderna, Inc.

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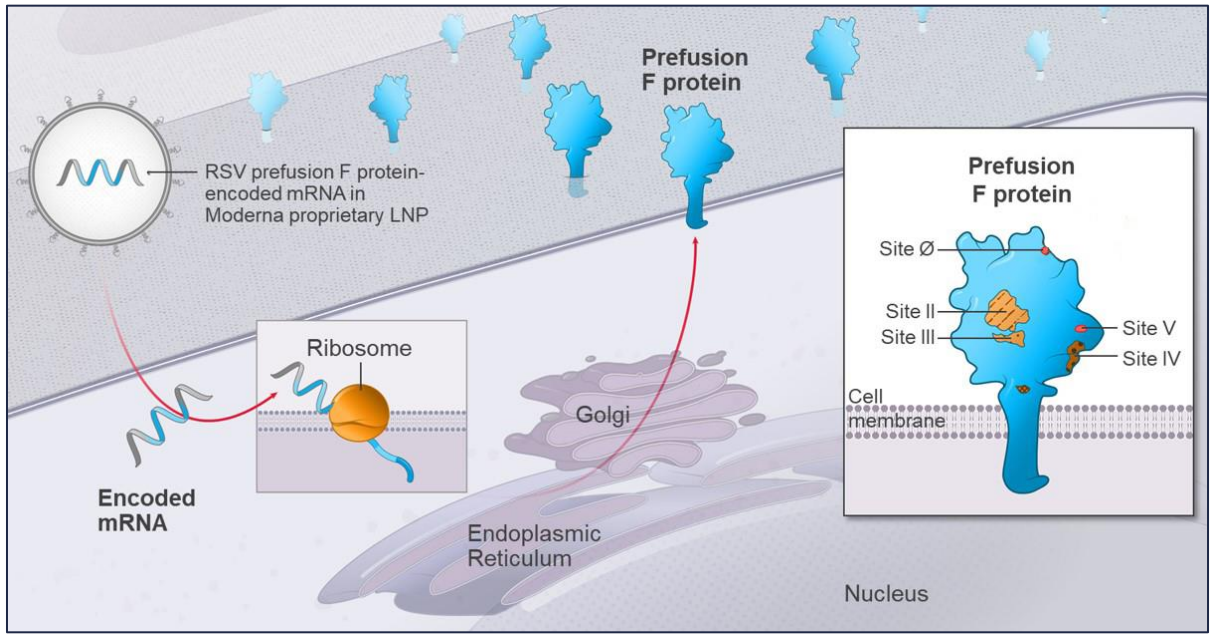
mRNA-1345, an mRNA-based RSV Vaccine, Encodes for a Stabilized Prefusion F Glycoprotein

- **mRNA-1345** is an mRNA-based RSV vaccine candidate consisting of a single mRNA sequence encoding the membrane-anchored RSV F glycoprotein stabilized in the prefusion conformation

Prefusion F elicits superior neutralizing antibody responses compared to post-fusion F[1,2]

F protein antibodies cross-react between RSV-A and RSV-B[3]

Phase 1 data show that mRNA-1345 is well tolerated and boosts antibody levels through 6 months[4]



F, fusion; LNP, lipid nanoparticle; mRNA, messenger ribonucleic acid.

1. Crank MC, et al. *Science*. 2019;365:505-509. 2. McKekkan JS, et al. *Science*. 2013;342(6158):592-598. 3. Aranda SS and Polack FP. *Front Immunol*. 2019;10:1006. 4. Chen GL, et al. *Open Forum Infect Dis*. 2022;9(suppl 2):ofac492.312.

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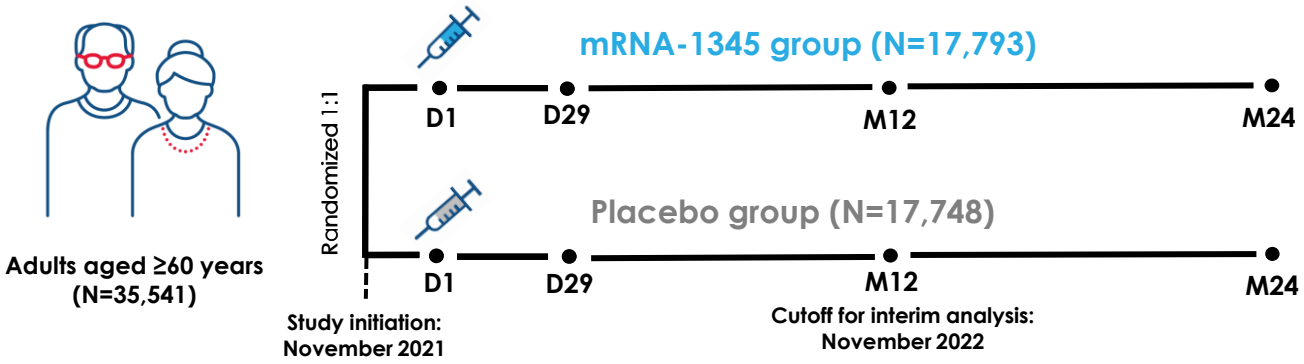
mRNA-1345 Phase 2/3 Clinical Trial

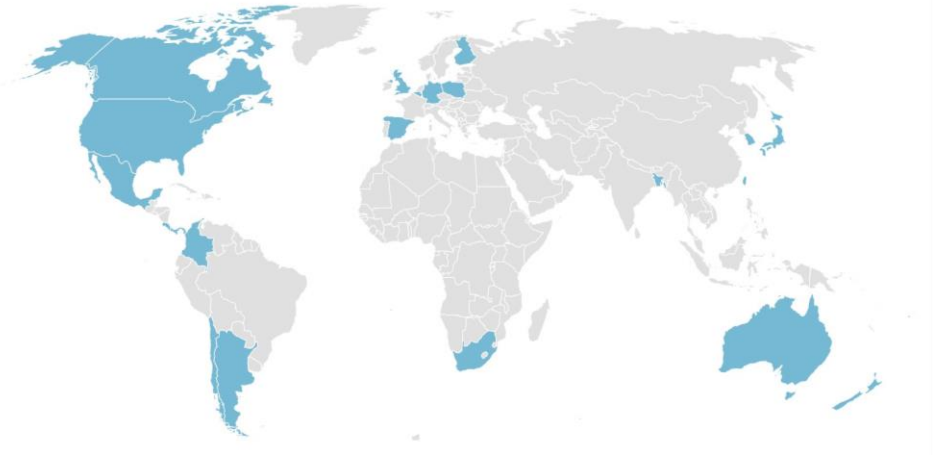
ConquerRSV

- In this ongoing phase 2/3, randomized, double-blind, placebo-controlled, case-driven study in adults aged ≥60 years (NCT05127434)[1], 35,541 participants from 22 countries were randomized 1:1 to receive 1 dose of mRNA-1345 50 µg or placebo
  - Healthy participants were included, as well as medically stable participants with ≥1 chronic medical diagnoses

Study Schedule – Phase 3



Trial Sites



Primary Efficacy Endpoints

- Vaccine efficacy of mRNA-1345 to **prevent a first episode of RSV lower respiratory tract disease (LRTD) with ≥2 or ≥3 symptoms** between 14 days to 12 months following injection

Note: Study schedule data are from the Randomization Set analysis population.
Solicited local and systemic adverse reactions were collected up to 7 days post-injection; unsolicited adverse events were collected up to 28 days post-injection; medically-attended adverse events, adverse events of special interest, serious adverse events, and adverse events leading to withdrawal are collected up to 24 months post-injection.
D, day; LRTD, lower respiratory tract disease; M, month; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus.
[1]ClinicalTrials.gov. NCT05127434. Accessed January 31, 2023. https://clinicaltrials.gov/ct2/show/NCT05127434

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mRNA-1345 Phase 2/3 Clinical Trial: Efficacy Endpoint Definition

Two Primary Endpoint Definitions for RSV Lower Respiratory Tract Disease (LRTD)

RSV LRTD with 2 or more lower respiratory symptoms

- RT-PCR-confirmed RSV *PLUS*
- Radiologic evidence of pneumonia

  OR
- New or worsening of 2 or more of the following symptoms for ≥24 hours:

RSV LRTD with 3 or more lower respiratory symptoms

- RT-PCR-confirmed RSV *PLUS*
- Radiologic evidence of pneumonia

  OR
- New or worsening of 3 or more of the following symptoms for ≥24 hours:

LRTD Symptoms

- Shortness of breath
- Cough and/or fever
- Wheezing/rales/rhonchi
- Sputum production
- Tachypnea
- Hypoxemia
- Pleuritic chest pain

LRTD, lower respiratory tract disease; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction.

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Demographics and Baseline Characteristics

	mRNA-1345 (N=17,793)	Placebo (N=17,748)
Age at Enrollment (Years), Mean (SD)	68.1 (6.19)	68.1 (6.20)
Age Group, n (%)[a]		
60 to 69 Years	11,315 (63.6)	11,270 (63.5)
70 to 79 Years	5493 (30.9)	5478 (30.9)
≥80 Years	985 (5.5)	1000 (5.6)
Sex, n (%)		
Male	9100 (51.1)	9004 (50.7)
Female	8693 (48.9)	8744 (49.3)
Comorbidities of Interest, n (%)[b]		
0	12,535 (70.4)	12,593 (71.0)
≥1	5258 (29.6)	5155 (29.0)

	mRNA-1345 (N=17,793)	Placebo (N=17,748)
Race Groups, n (%)		
White	11,285 (63.4)	11,254 (63.4)
Black	2210 (12.4)	2173 (12.2)
Asian	1541 (8.7)	1535 (8.6)
Other[c]	2688 (15.1)	2680 (15.1)
Unknown/Not Reported	69 (0.4)	106 (0.6)
Ethnicity, n (%)		
Hispanic or Latino	6112 (34.4)	6162 (34.7)
Not Hispanic or Latino	11,495 (64.6)	11,377 (64.1)
Unknown	27 (0.2)	22 (0.1)
Not Reported	159 (0.9)	187 (1.1)

- Demographics and baseline characteristics were well matched across groups

Note: Data are from the Randomization Set analysis population.
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; mRNA, messenger ribonucleic acid; SD, standard deviation.
[a]Derived from age and risk collected on electronic case report forms. [b]Comorbidities of interest include COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease. [c]Other race includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, or Multiple.

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Overview of Solicited Adverse Reactions

	mRNA-1345	Placebo
Solicited local adverse reactions within 7 days		
Solicited local adverse reactions within 7 days, n/N (%)	10,367/17,662 (58.7%)	2845/17,593 (16.2%)
Grade 3 or greater cases, n/N (%)	558/17,662 (3.2%)	305/17,593 (1.7%)
Solicited systemic adverse reactions within 7 days		
Solicited systemic adverse reactions within 7 days, n/N (%)	8432/17,662 (47.7%)	5798/17,597 (32.9%)
Grade 3 or greater cases, n/N (%)	710/17,662 (4.0%)	508/17,597 (2.9%)

- To date, most solicited adverse reactions were mild to moderate
- The most commonly reported solicited adverse reactions in the mRNA-1345 group were injection site pain, fatigue, headache, myalgia, and arthralgia

Note: Data are from the Solicited Safety Set analysis population.
mRNA, messenger ribonucleic acid.

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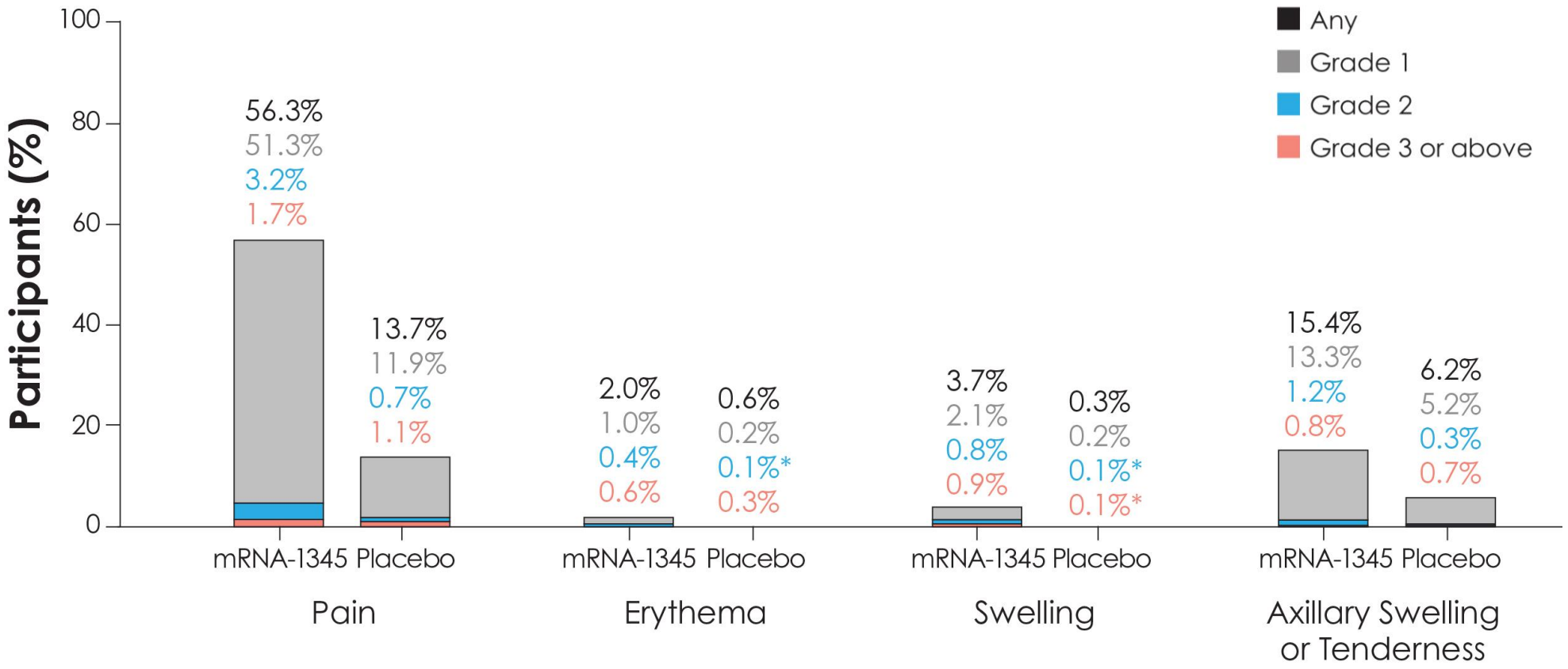
Percentage of Participants With Solicited Local Adverse Reactions Within 7 Days



- Pain at the injection site (mostly grade 1) was the most frequently reported local adverse reaction

Note: Data are from the Solicited Safety Set analysis population.
Summary of participants with solicited adverse reactions within 7 days after injection by grade; placebo (n = 17,598); mRNA-1345 50 µg (n = 17,665).
Note: *For placebo, grade 2 for erythema and grade 2 and grade 3 or above for swelling are <0.1%.
mRNA, messenger ribonucleic acid.

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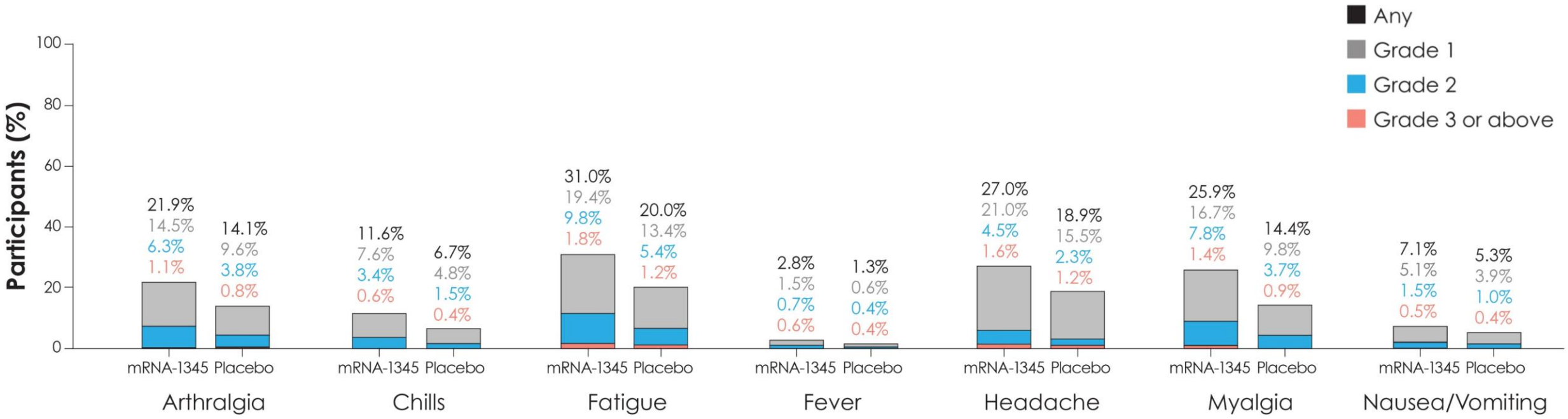
Percentage of Participants With Solicited Systemic Adverse Reactions Within 7 Days



- Arthralgia, fatigue, headache, and myalgia were the most frequently reported systemic adverse reactions

Note: Data are from the Solicited Safety Set analysis population.
Summary of participants with solicited adverse reactions within 7 days after injection by grade; placebo (n = 17,598); mRNA-1345 50 µg (n = 17,665).
mRNA, messenger ribonucleic acid.

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Efficacy of mRNA-1345 Against RSV LRTD

	mRNA-1345 (N=17,572)	Placebo (N=17,516)
RSV LRTD with ≥2 symptoms		
Cases, n/N (%)[a,b]	9/17,572 (0.05%)	55/17,516 (0.31%)
VE (%) based on hazard ratios (alpha adjusted 95.88% CI)[c]	**83.7%** (66.0%, 92.2%)	
RSV LRTD with ≥3 symptoms		
Cases, n/N (%)[a,b]	3/17,572 (0.02%)	17/17,516 (0.10%)
VE (%) based on hazard ratios (alpha adjusted 96.36% CI)[c]	**82.4%** (34.8%, 95.3%)	

Note: Data are from the Per-Protocol Efficacy Set analysis population, 14 days to 12 months post-injection.
CI, confidence interval; LRTD, lower respiratory tract disease; mRNA, messenger ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; VE, vaccine efficacy.
[a]Protocol-defined RSV-LRTD with ≥2 and ≥3 symptoms is based on eligible symptoms onset within a timeframe of +/- 14 days from positive RSV RT-PCR collection date.
[b]The time to first occurrence of protocol-defined RSV-LRTD with ≥2 and ≥3 symptoms will be calculated as date of case — date of randomization + 1.
[c]VE is defined as 100% x (1 — hazard ratio [mRNA-1345 vs. placebo]). The CI for VE is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a fixed effect, adjusting for stratification factors at randomization.

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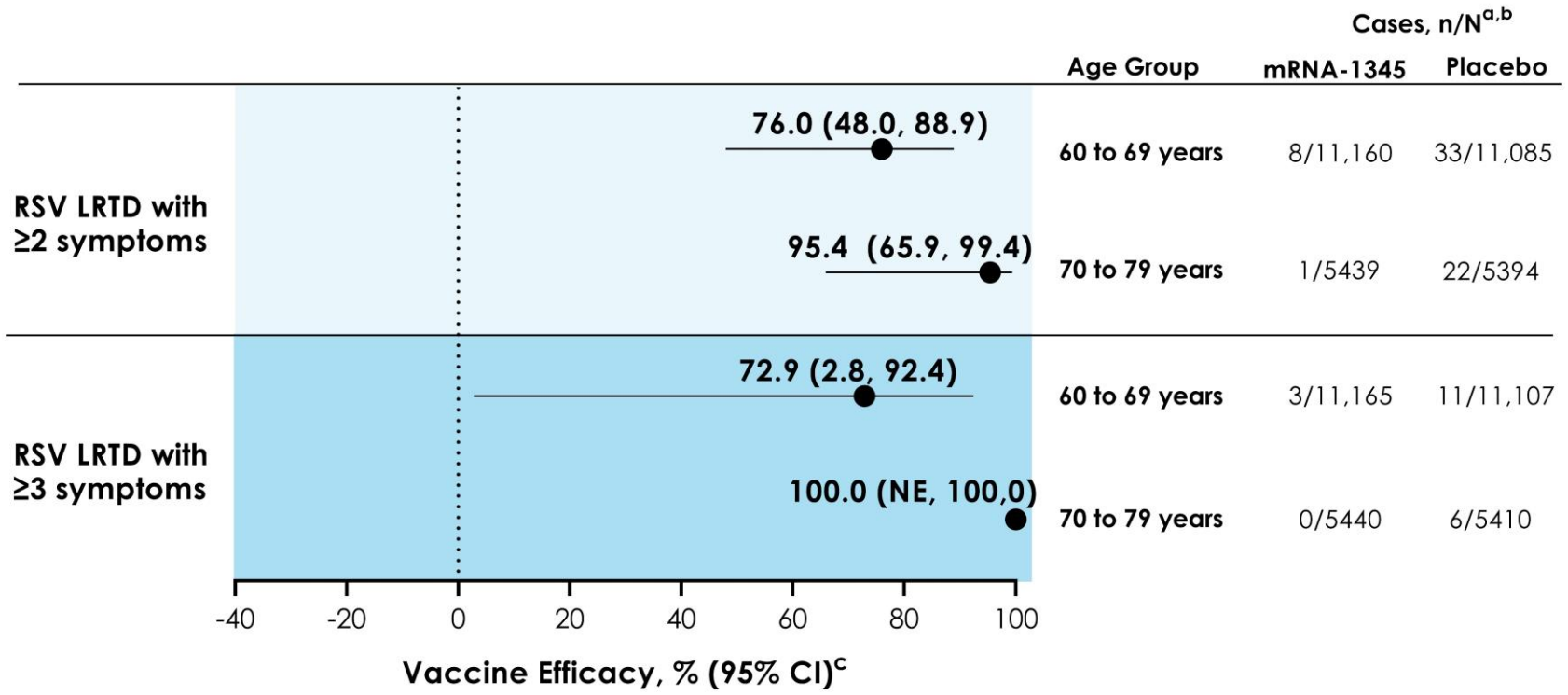
Efficacy of mRNA-1345 Against RSV LRTD Across Age Groups



- In adults ≥80 years, no cases of RSV LRTD with ≥2 or ≥3 symptoms were observed (mRNA-1345, n/N=0/964; PBO, n/N=0/982)

Note: Data are from the Per-Protocol Efficacy Set analysis population, 14 days to 12 months post-injection.
CI, confidence interval; LRTD, lower respiratory tract disease; mRNA, messenger ribonucleic acid; NE, not evaluated; PBO, placebo; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction; VE, vaccine efficacy
[a]Protocol-defined RSV-LRTD with ≥2 and ≥3 symptoms is based on eligible symptoms onset within a timeframe of +/- 14 days from positive RSV RT-PCR collection date.
[b]The time to first occurrence of protocol-defined RSV-LRTD with ≥2 and ≥3 symptoms will be calculated as date of case — date of randomization + 1.
[c]VE is defined as 100% x (1 — hazard ratio [mRNA-1345 vs. placebo]). The CI for VE is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a fixed effect, adjusting for stratification factors at randomization.

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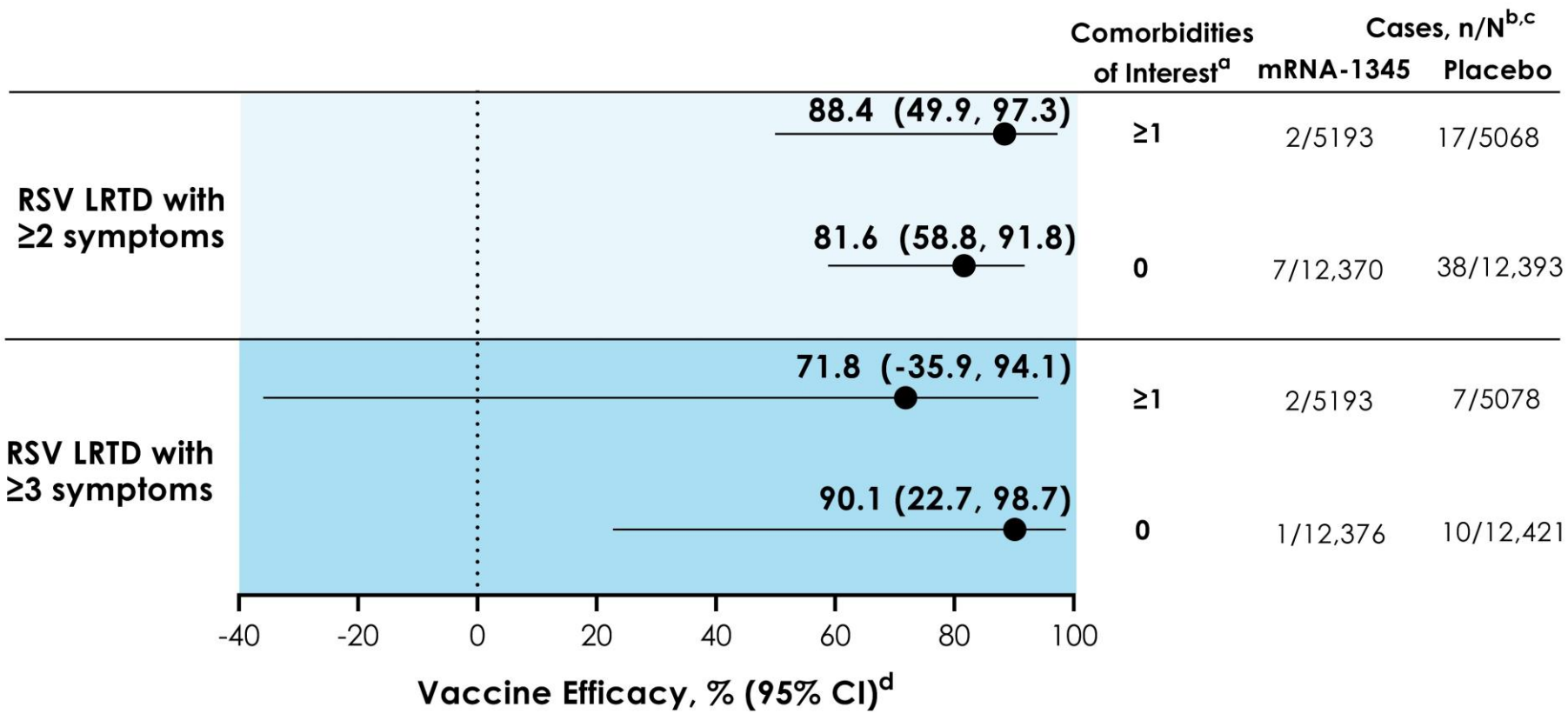
Efficacy of mRNA-1345 Against RSV LRTD in Participants With Pre-existing Comorbidities



Note: Data are from the Per-Protocol Efficacy Set analysis population, 14 days to 12 months post-injection.
CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction; VE, vaccine efficacy.
[1]Comorbidities of interest include COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease. [2]Protocol-defined RSV-LRTD with ≥2 and ≥3 symptoms is based on eligible symptoms onset within a timeframe of +/- 14 days from positive RSV RT-PCR collection date. [3]The time to first occurrence of protocol-defined RSV-LRTD with ≥2 or ≥3 symptoms will be calculated as date of case — date of randomization + 1. [4]VE is defined as 100% x (1 — hazard ratio [mRNA-1345 vs. placebo]). The CI for VE is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a fixed effect, adjusting for stratification factors at randomization.

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Conclusions

- mRNA-1345 was well tolerated and had an acceptable safety profile; solicited adverse reactions were mostly grade 1 or grade 2 in severity
- A single dose of mRNA-1345 50 µg is efficacious in preventing RSV LRTD with ≥2 or ≥3 symptoms in adults aged ≥60 years within 14 days to 12 months following injection
- Vaccine efficacy was consistently high across all age groups and in participants with pre-existing comorbidities
- The phase 3 clinical trial of mRNA-1345 in adults aged ≥60 years is ongoing, with additional supportive analyses planned through 24 months

LRTD, lower respiratory disease; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus.

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Safety and efficacy of a respiratory syncytial virus vaccine (mRNA-1345), against a spectrum of symptomatic disease in adults aged ≥60 years

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16 April 2023
33rd European Congress of Clinical Microbiology & Infectious Diseases (ECCMID); 15-18 April 2023
Copenhagen, Denmark

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Disclosures, Acknowledgments, and Abstract Plain Language Summary

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Overview of Respiratory Syncytial Virus (RSV)

- RSV is a common and highly infectious respiratory pathogen that co-circulates as two different subtypes, RSV-A and RSV-B[1]
- The burden of RSV in older adults is underestimated due to inconsistent and insensitive diagnostic testing, limited data from low- and middle-income regions and lack of standardized case definition[2,3,4]
- Across high-income countries in 2019, RSV caused an estimated ~5.2 million cases, 470,000 hospitalizations, and 33,000 in-hospital deaths in adults aged ≥60 years[2]
- After adjusting for under detection, a recent study estimated that the United States sees 1.36 million RSV-associated outpatient visits in adults aged ≥65 years, and 1.08 million RSV-associated outpatient visits in adults aged 50-64 each year[3]

Potential impact of RSV infection sequelae[3]

Severe acute respiratory infection and lower respiratory tract infections

Exacerbation of asthma and chronic obstructive pulmonary disease

Higher 1 year mortality after severe illness with RSV than influenza

Griffiths C et al. 2017. *Clin Microbiol Rev*; 30(1):277-319. 2. Savic, M et al. 2022. *Influenza Other Respi Viruses;*17(1):e13031. 3. McLaughlin JM et al. *Open Forum Infec Dis*. 2022; 9(7):ofac300. 4. Nguyen-Van-Tam, JS et al. 2022. *Eur Respir Rev;* 31: 220105

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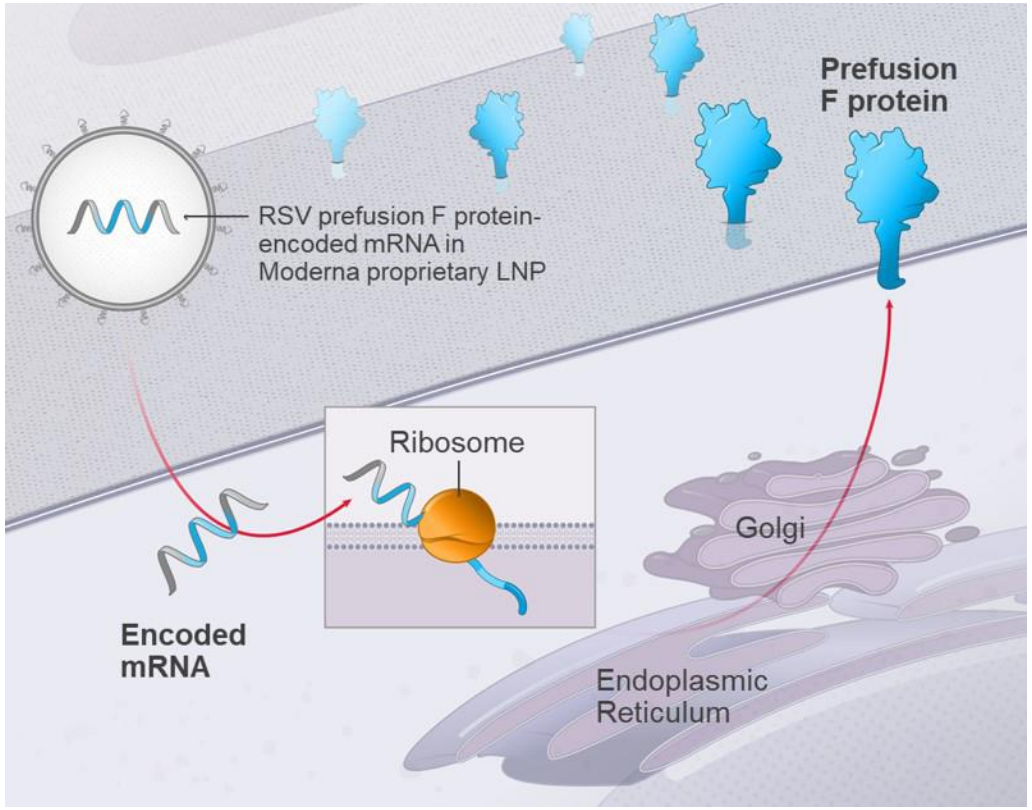
mRNA-1345, an mRNA-based RSV Vaccine, Encodes for a Stabilized Prefusion F Glycoprotein

- **mRNA-1345** is an mRNA-based RSV vaccine candidate consisting of a single mRNA sequence encoding the membrane-anchored RSV F glycoprotein stabilized in the prefusion conformation

  Prefusion F elicits superior neutralizing antibody responses compared to post-fusion F[1,2]

  F protein antibodies cross-react between RSV-A and RSV-B[3]

  Phase 1 data show that mRNA-1345 is well tolerated and boosts antibody levels through 6 months[4]



F, fusion; LNP, lipid nanoparticle; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus.

1. Crank MC, et al. *Science*. 2019;365:505-509. 2. McKekkan JS, et al. *Science*. 2013;342(6158):592-598. 3. Aranda SS, Polack FP. *Front Immunol*. 2019;10:1006. 4. Chen GL, et al. *Open Forum Infect Dis*. 2022;9(suppl 2):ofac492.312.

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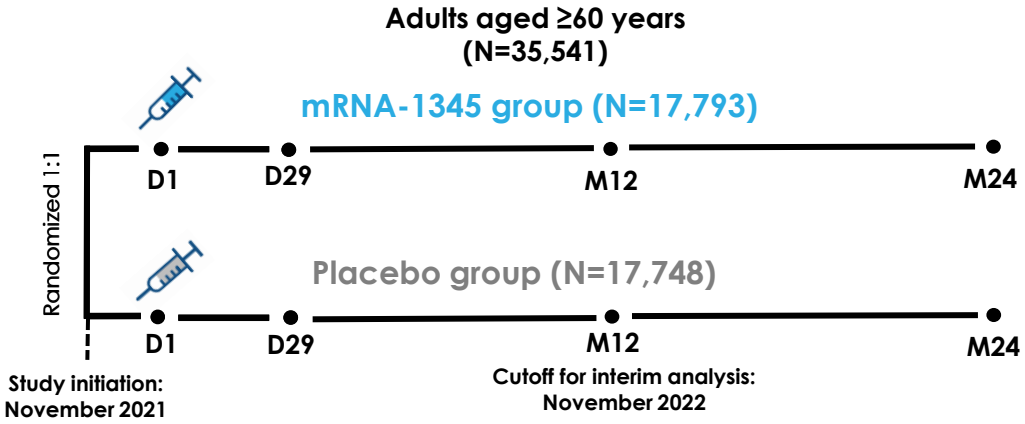
mRNA-1345 Pivotal Phase 2/3 Clinical Trial

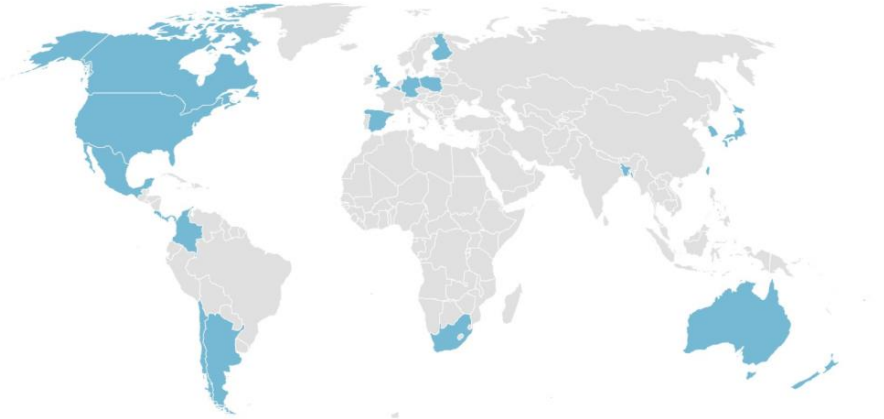
ConquerRSV

- In this ongoing phase 2/3, randomized, double-blind, placebo-controlled, case-driven study in adults aged ≥60 years (NCT05127434),[1] 35,541 participants from 22 countries were randomized 1:1 to receive 1 dose of mRNA-1345 50 µg or placebo[2]
  - Healthy participants were included, as well as medically stable participants with ≥1 comorbidities of interest

Study Schedule – Phase 3



Trial Sites



269 trial sites across 22 countries

Key Efficacy Endpoints

- Vaccine efficacy of mRNA-1345 to **prevent a first episode of RSV lower respiratory tract disease (LRTD) with ≥2 or ≥3 symptoms** between 14 days to 12 months following injection
- Vaccine efficacy of mRNA 1345 to **prevent a first episode of RSV acute respiratory disease (ARD)** within the period of 14 days post-injection up to 12 months post-injection

Note: Study schedule data are from the Randomization Set analysis population. Data cut-off for analysis was 30 November 2022.
Solicited local and systemic adverse reactions were collected up to 7 days post-injection; unsolicited adverse events were collected up to 28 days post-injection; medically attended adverse events, adverse events of special interest, serious adverse events, and adverse events leading to withdrawal are collected up to 24 months post-injection.
ARD, acute respiratory disease; D, day; LRTD, lower respiratory tract disease; M, month; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus.

1. ClinicalTrials.gov. NCT05127434. https://clinicaltrials.gov/ct2/show/NCT05127434.
2. Enrolment numbers as of 31 October 2022

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Definitions of ARD and LRTD

Phase 2/3 Safety and Efficacy Study of mRNA-1345

ConquerRSV

RT-PCR Confirmed RSV +

RSV Acute Respiratory Disease (ARD)

New or Worsening of ≥1 of Following Symptoms for ≥24 Hours

Sinus pain	Hoarseness	Stuffy Nose	Tachypnea	Shortness of breath	Sputum production	Wheezing and/or rales and/or rhonchi
Sore Throat	Runny Nose	Chills	Hypoxemia	Fever	Pleuritic chest pain	
				Cough		

RSV Lower Respiratory Tract Disease (LRTD)

New or Worsening of ≥2 or ≥3 of Following Symptoms for ≥24 Hours

Tachypnea	Shortness of breath	Sputum production	Wheezing and/or rales and/or rhonchi
Hypoxemia	Fever and/ or Cough	Pleuritic chest pain	

LRTD cases are a subset of the ARD cases

In case of inability to fully assess other clinical parameters, radiologic evidence of pneumonia with RT-PCR-confirmed RSV infection also can be used to confirm RSV-ARD or RSV-LRTD

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Demographics and Baseline Characteristics

	mRNA-1345 N=17,793	Placebo N=17,748
Age at Enrollment (Years), Mean (SD)	68.1 (6.19)	68.1 (6.20)
Age Group, n (%)[a]		
60 to 69 Years	11,315 (63.6)	11,270 (63.5)
70 to 79 Years	5493 (30.9)	5478 (30.9)
≥80 Years	985 (5.5)	1000 (5.6)
Sex, n (%)		
Male	9100 (51.1)	9004 (50.7)
Female	8693 (48.9)	8744 (49.3)
Comorbidities of Interest, n (%)[b]		
0	12,535 (70.4)	12,593 (71.0)
≥1	5258 (29.6)	5155 (29.0)

	mRNA-1345 N=17,793)	Placebo N=17,748
Race Groups, n (%)		
White	11,285 (63.4)	11,254 (63.4)
Black	2210 (12.4)	2173 (12.2)
Asian	1541 (8.7)	1535 (8.6)
Other[c]	2688 (15.1)	2680 (15.1)
Unknown/Not Reported	69 (0.4)	106 (0.6)
Ethnicity, n (%)		
Hispanic or Latino	6112 (34.4)	6162 (34.7)
Not Hispanic or Latino	11,495 (64.6)	11,377 (64.1)
Unknown	27 (0.2)	22 (0.1)
Not Reported	159 (0.9)	187 (1.1)

- Demographics and baseline characteristics were well-matched across groups

Note: Data are from the Randomization Set analysis population.
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; mRNA, messenger ribonucleic acid; SD, standard deviation.
[a]Derived from age and risk collected on electronic case report forms. [b]Comorbidities of interest include COPD, asthma, chronic respiratory disease, diabetes, CHF, advanced liver disease, or advanced renal disease. [c]Other race includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, or Multiple.

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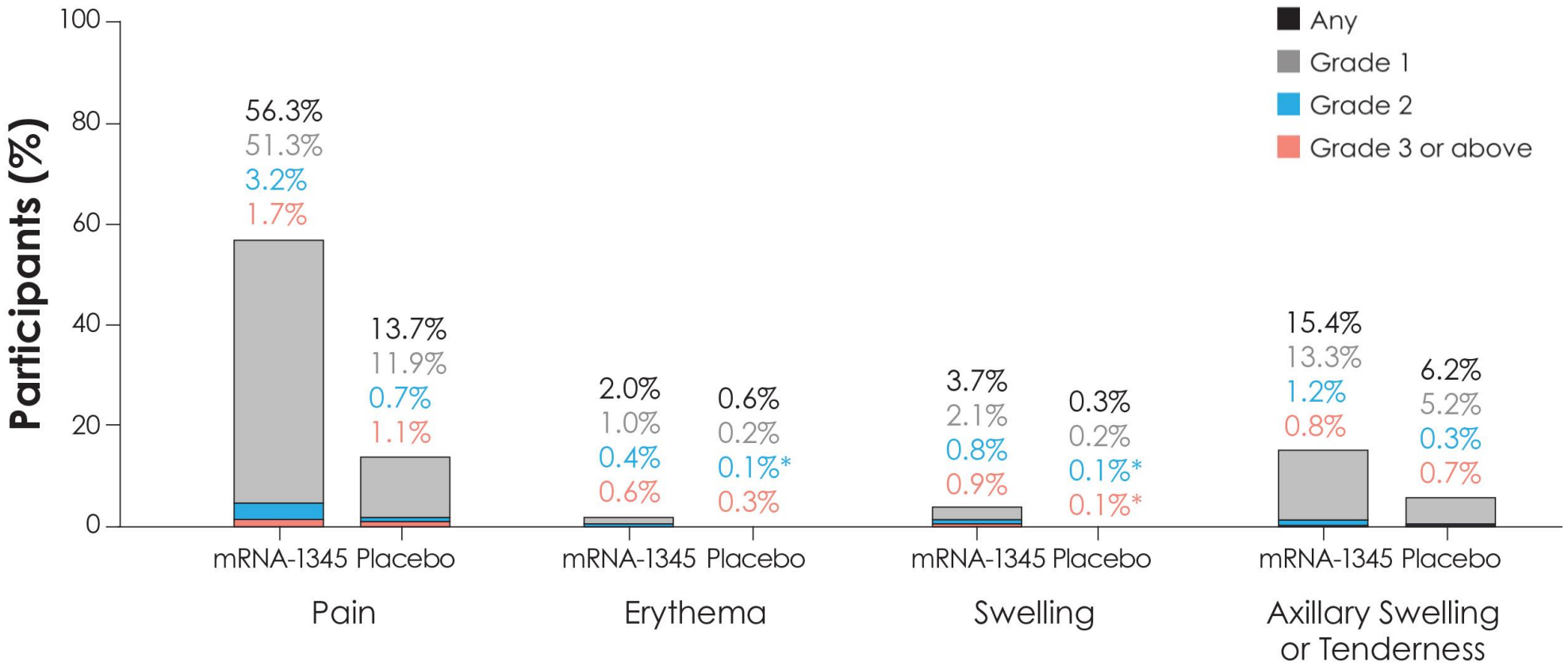
Percentage of Participants With Solicited Local Adverse Reactions Within 7 Days



- Pain at the injection site (mostly grade 1) was the most frequently reported local adverse reaction

Note: Data are from the Solicited Safety Set analysis population as of 30 November 2022.
Summary of participants with solicited adverse reactions within 7 days after injection by grade; placebo (n = 17,598); mRNA-1345 50 µg (n = 17,665).
*For placebo, grade 2 for erythema and grade 2 and grade 3 or above for swelling are <0.1%.
mRNA, messenger ribonucleic acid.

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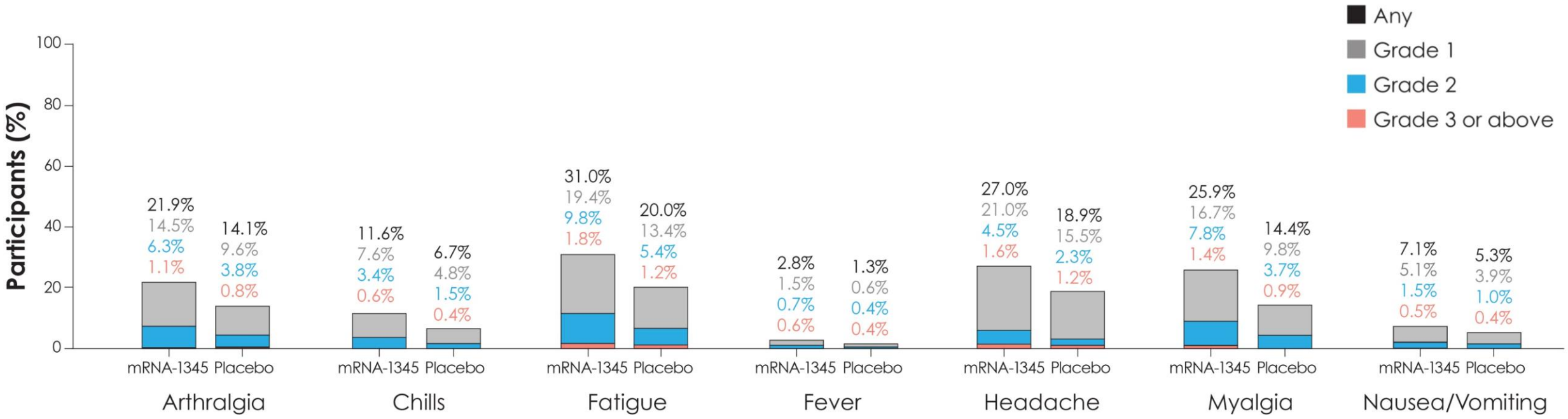
Percentage of Participants With Solicited Systemic Adverse Reactions Within 7 Days



- Arthralgia, fatigue, headache, and myalgia were the most frequently reported systemic adverse reactions

Note: Data are from the Solicited Safety Set analysis population as of 30 November 2022.
Summary of participants with solicited adverse reactions within 7 days after injection by grade: placebo (n=17,598); mRNA-1345 50 µg (n=17,665).
mRNA, messenger ribonucleic acid.

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Unsolicited Treatment-Emergent Adverse Events Within 28 Days After Injection, Regardless of Relationship to Vaccine/Placebo

	mRNA-1345 50 µg (N=17734)		Placebo (N=17679)	
	n	%	n	%
All	3624	**20.4%**	3331	**18.8%**
Serious	102	**0.6%**	93	**0.5%**
Fatal	2	**<0.1%**	4	**<0.1%**
Medically Attended	1842	**10.4%**	1739	**9.8%**
Leading to Study Discontinuation	2	**<0.1%**	9	**<0.1%**
Severe/≥ Grade 3	124	**0.7%**	119	**0.7%**
Non-Serious[a]	3522	**19.9%**	3238	**18.3%**
Any Adverse Event of Special Interest (AESI)	3	**<0.1%**	8	**<0.1%**

- No significant imbalances in any of these events between vaccine & placebo recipients

Note: Data are from the Safety Set analysis population as of 30 November 2022.
A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Severe TEAEs include both unsolicited severe TEAEs and ≥ grade 3 solicited ARs that meet SAE criteria or last beyond 7 days after injection.
Medically Attended TEAEs include ED/urgent care, outpatient physician visits and per-protocol illness visits.
[a]Participants who did not report any serious TEAE are included in the summary of "non-serious."
AR, adverse reaction; ED, emergency department; mRNA, messenger RNA; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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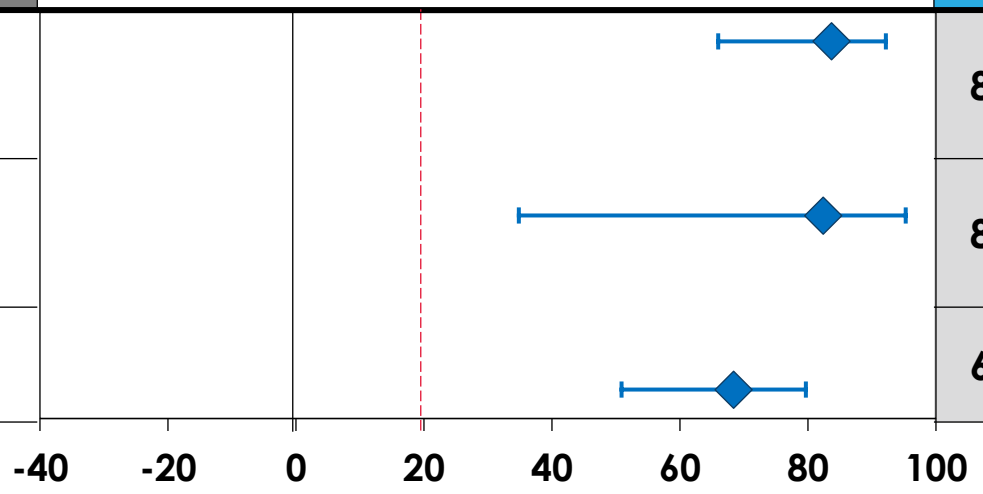
Vaccine Efficacy Against RSV-LRTD With ≥2 and ≥3 Symptoms and RSV-ARD

	Numbers of Events		
	mRNA-1345 N=17,572	Placebo N=17,516	Vaccine Efficacy (CI*)
RSV-LRTD ≥2 Symptoms	**9**	**55**	**83.7%** (66.0, 92.2)
RSV-LRTD ≥3 Symptoms	**3**	**17**	**82.4%** (34.8, 95.3)
RSV-ARD	**26**	**82**	**68.4%** (50.9, 79.7)



Data are from the Per-Protocol Efficacy Set analysis population.
VE is defined as 100% x (1 — hazard ratio (mRNA-1345 vs placebo).
*CI for VE is based on a stratified Cox proportional hazard model, with Efron's method of tie handling and with treatment group as a fixed effect, adjusting for stratification factors at randomization.
Red dotted reference line indicates lower bound used to declare success for VE.
Adjusted CIs: Overall RSV-LRTD with ≥2 symptoms, 95.88%; Overall RSV-LRTD with ≥3 symptoms, 96.36%; Overall RSV-ARD, 95% CI.
ARD, acute respiratory disease; CI, confidence interval; LRTD, lower respiratory tract disease; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus; VE, vaccine efficacy.

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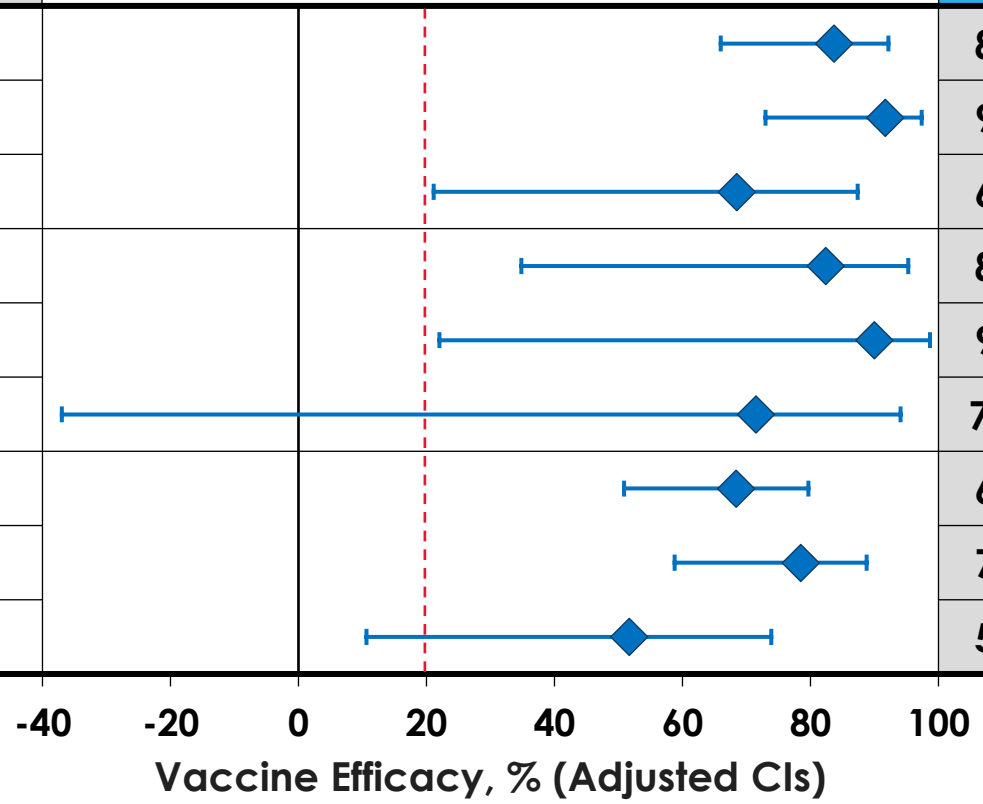
Vaccine Efficacy Against RSV-A and RSV-B by Endpoint Among Adults ≥60 Years

		Numbers of Events		Vaccine Efficacy (CI*)
		mRNA-1345 N = 17,572	Placebo N = 17,516	
RSV-LRTD ≥ 2 Symptoms	Overall	9	55	**83.7%** (66.0, 92.2)
	RSV-A	3	36	**91.7%** (73.0, 97.4)
	RSV-B	6	19	**68.5%** (21.1, 87.4)
RSV-LRTD ≥ 3 Symptoms	Overall	3	17	**82.4%** (34.8, 95.3)
	RSV-A	1	10	**90.0%** (22.0, 98.7)
	RSV-B	2	7	**71.5%** (-37.0, 94.1)
RSV-ARD	Overall	26	82	**68.4%** (50.9, 79.7)
	RSV-A	11	51	**78.5%** (58.8, 88.8)
	RSV-B	15	31	**51.7%** (10.6, 73.9)



Data are from the Per-Protocol Efficacy Set analysis population.
VE is defined as 100% x (1 — hazard ratio (mRNA-1345 vs placebo).
*CI for VE is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with treatment group as a fixed effect, adjusting for stratification factors at randomization
Red dotted reference line indicates lower bound used to declare success for VE.
Adjusted CIs: Overall RSV-LRTD with ≥2 symptoms, 95.88%; Overall RSV-LRTD with ≥3 symptoms, 96.36%; RSV-A and B subtype, 95% CI.
CI, confidence interval; LRTD, lower respiratory tract disease; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus; VE, vaccine efficacy.

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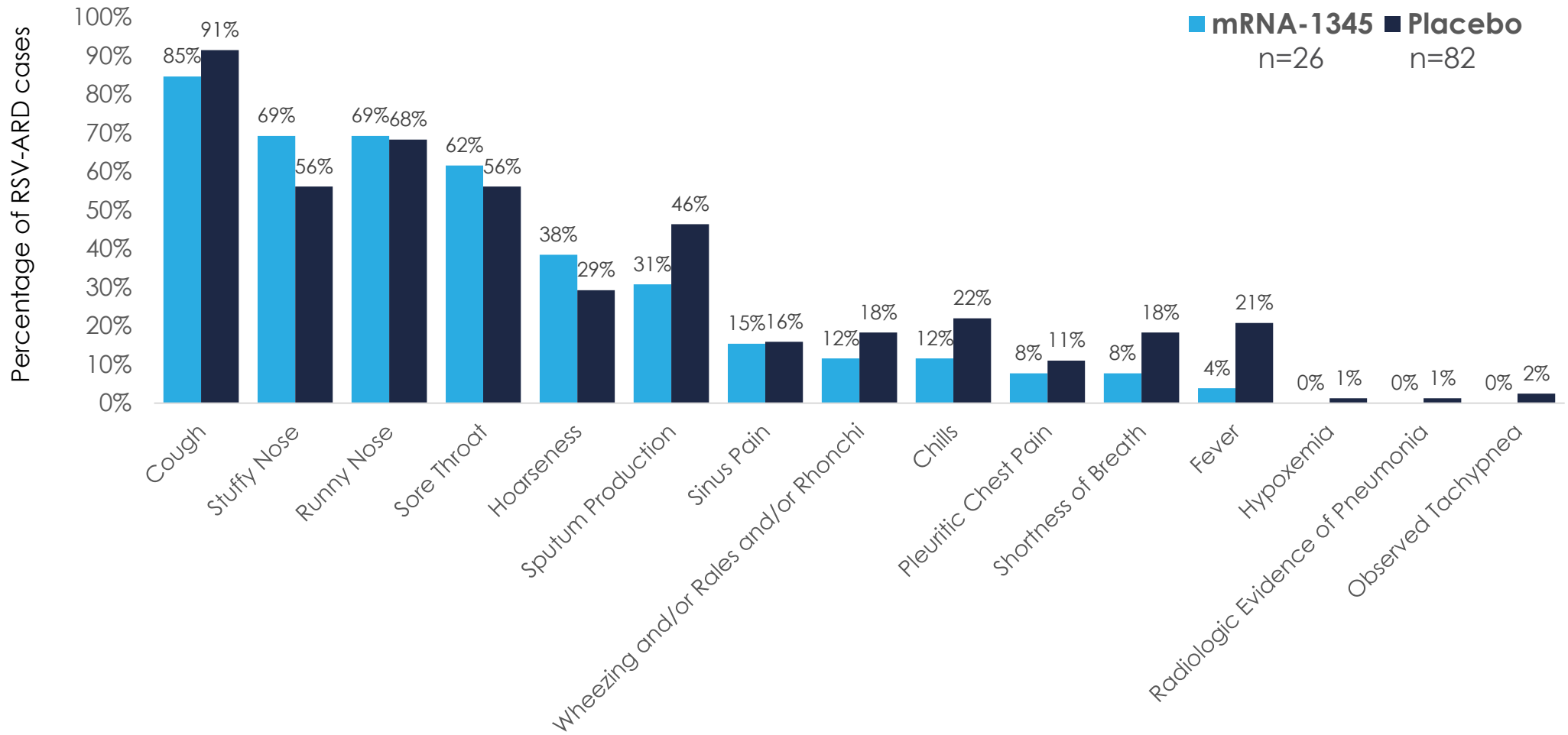
Summary of Signs/Symptom Assessment for First Occurrence of RSV-ARD Cases With ≥1 Signs/Symptom(s) Between 14 Days and 12 Months Following Injection



Data are from the Per-Protocol Efficacy Set analysis population.
ARD, acute respiratory disease; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus.

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Conclusions

- The global trial population was racially diverse, with a sizeable enrollment of participants outside of North America/Europe as well as those with comorbidities that put them at risk for RSV
- A single 50-µg dose of mRNA-1345 showed consistently high efficacy across the clinical spectrum of RSV disease in adults aged ≥60 years, including LRTD with ≥2 or ≥3 symptoms, ARD with ≥1 symptom, and across RSV-A and RSV-B subtypes within 14 days to 12 months following injection
- mRNA-1345 was well-tolerated and had an acceptable safety profile in adults aged ≥60 years
- These preliminary data suggest that the symptom profile, including symptoms indicative of severity, occur at a lower frequency in vaccinated than in placebo groups
- The phase 3 clinical trial of mRNA-1345 in adults aged ≥60 years is ongoing, with additional supportive analyses planned through 24 months

LRTD, lower respiratory disease; mRNA, messenger ribonucleic acid; RSV, respiratory syncytial virus.

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RSV vaccine (mRNA-1345) Phase 1 in pediatric and adult populations

Overview

- Evaluating the tolerability and reactogenicity of mRNA-1345 in younger adults, older adults, children, older adults of Japanese descent and women of child-bearing potential

Outcome measures

- Safety and immunogenicity
  - Neutralizing antibody titers against RSV

Phase 1 Trial Design

Cohorts 1-4 ✓	**Younger Adults** (18-49 years)
Cohorts 5-6 ✓	**RSV Seropositive Children** (12-59 months)
Cohorts 7-11 ✓	**Older Adults** (65-79 years)
Cohorts 12-14 ✓	**Women of Child-Bearing Potential** (18-40 years)
Cohorts 15 ✓	**Japanese Descent Older Adults** (≥ 60 Years)

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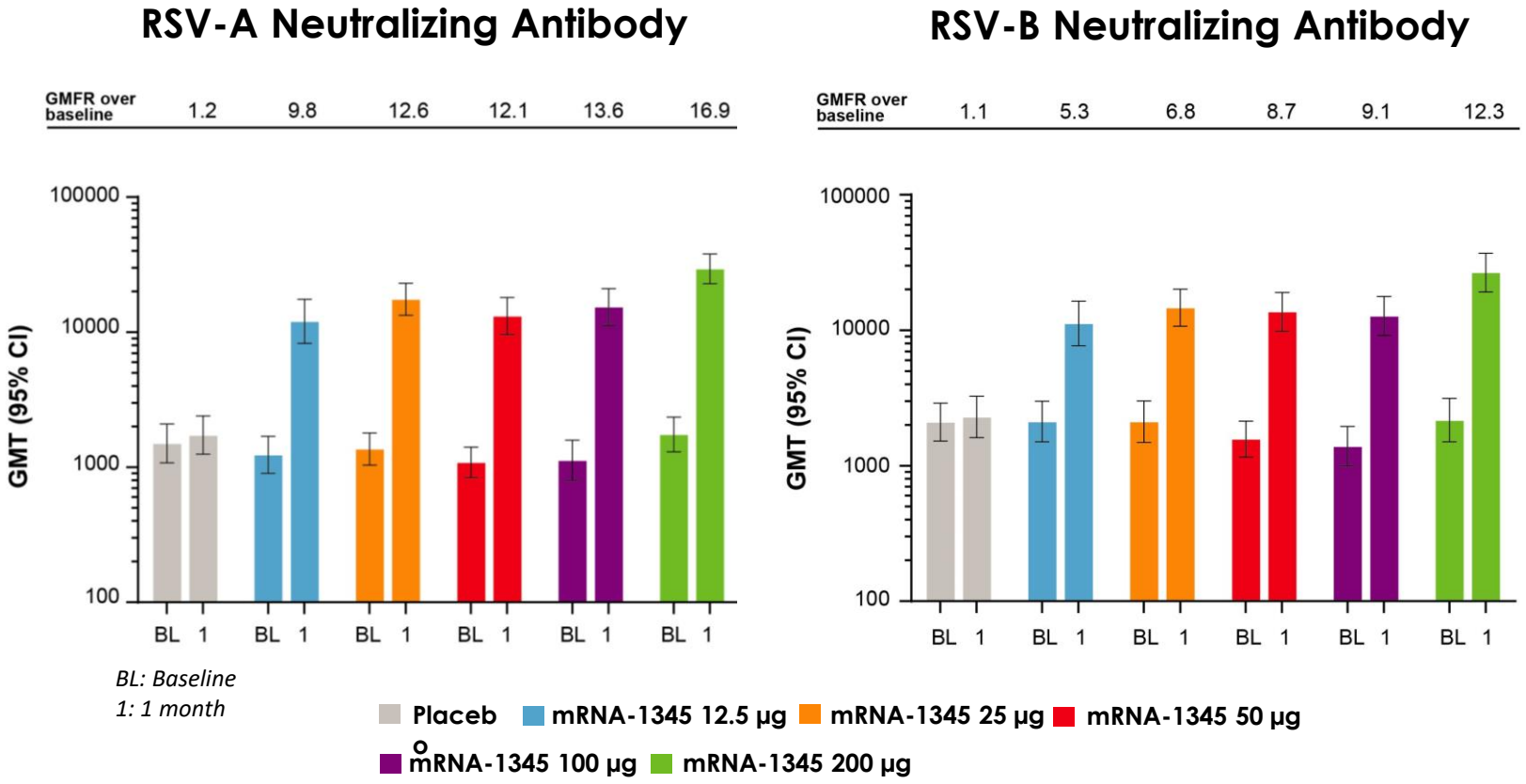
In older adults, mRNA-1345 boosts RSV neutralizing antibodies



- All participants had nAb against RSV at baseline (BL) before study injections, suggesting prior exposure to RSV
- mRNA-1345 boosted RSV-A and RSV-B nAb GMTs
- GMFR over BL at 1 month were 9.8–16.9 and 5.3–12.3 for RSV-A and RSV-B, respectively
- Minimal dose-response was observed for nAb GMTs

Interim data, Per-Protocol analysis set.
Participants were randomised to receive one dose of mRNA-1345 (12.5, 25, 50, 100, or 200 µg; n=47–48 each) or placebo (n=59). 1/2 of the participants dosed with mRNA will get a booster at the same dose-level as the initial dose, at 12 months

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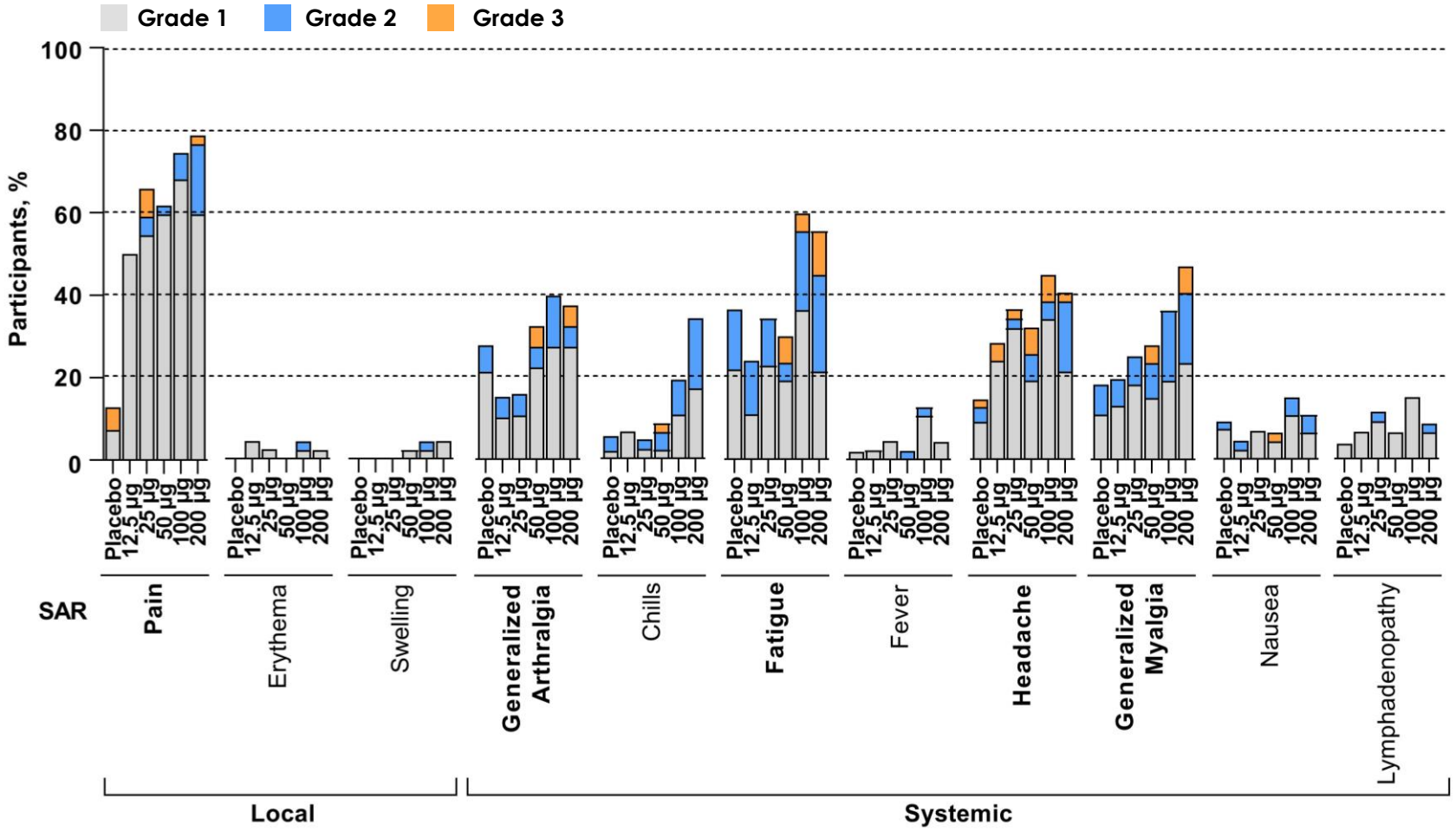
In older adults, mRNA-1345 is well-tolerated at all dose levels

Local and Systemic Solicited Adverse Reactions (SARs) in Older Adults Within 7 Days of Receiving 1 Dose



- Local SARs were reported in 50.0%–78.7% and 12.7% of mRNA-1345 and placebo recipients, respectively
  - Pain at the injection site (mostly grade 1) was the most frequently reported
- Systemic SARs were reported in 50.0%-78.7% and 45.5% of mRNA-1345 and placebo recipients, respectively
  - Headache, fatigue, arthralgia, and myalgia were the most frequently reported
- Treatment related unsolicited AEs were reported by 6.7% (16/239) of mRNA-1345 and 10.2% (6/59) of placebo recipients
- Unsolicited severe AEs were reported by 7 (2.9%) of the RNA-1345 recipients with none reported in the placebo group
- No related SAE or AESI were reported

SAR, solicited adverse reactions; AEs, adverse events; SAE, severe adverse events; AESI, adverse events of special interest
Placebo (n = 55); mRNA-1345 12.5 µg (n = 46); mRNA-1345 15 µg (n = 44); mRNA-1345 50 µg (n = 47); mRNA-1345 100 µg (n = 47); mRNA-1345 200 µg (n = 47)

Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding: the vaccine efficacy of mRNA-1345; the potential for mRNA-1345 to reduce disease burden from RSV; the safety and tolerability profile of mRNA-1345; potential market size; clinical trials; and enrollment in the pivotal Phase 3 trial of mRNA-1345 in older adults. In some cases, forward-looking statements can be identified by terminology such as "may," "should," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward -looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties and other factors include those described in Moderna's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date referenced on the first page.

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