GSK RSV OA candidate vaccine clinical development

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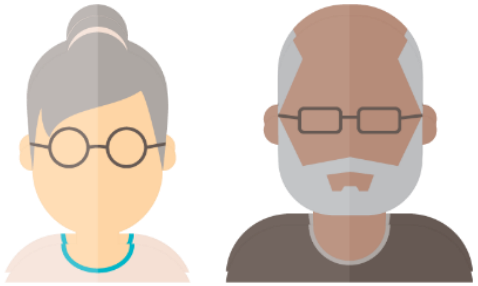
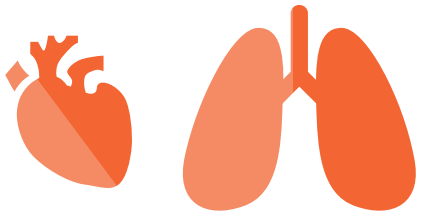
RSV disease remains a significant unmet medical need among adults

- Every year, RSV cases in adults result in substantial clinical and economic burden[1,2,3]
- Older adults and adults with underlying conditions are at increased risk of RSV

Risk factors for severe RSV infection



Older age[1, 4]
Especially for those aged ≥60 years



Comorbidities[1]
Adults at highest risk include those with chronic heart or lung disease

Weak immune status[1]
Adults with weakened immune systems are particularly vulnerable

1.CDC, 2020. RSV in older adults and adults with chronic medical conditions. https://www.cdc.gov/rsv/high-risk/older-adults.html (accessed November 2021); 2. Amand C et al. *BMC Health Serv Res* 2018;18:294.
3. Falsey AR et al. *N Engl J Med* 2005;352:1749–1759 4. Belongia EA *et al. Open Forum Infect Dis* 2018;27;5:ofy316

Key Phase 3 trials

AReSVi-004 study[1]

Older adults ≥60 YOA

Safety, reactogenicity, immunogenicity, persistence & revaccination

AReSVi-006 study[2]

Older adults ≥60 YOA

Pivotal efficacy study

RSV-007 study[3]

Older adults ≥60 YOA

Safety, reactogenicity, immunogenicity when co-administered with FLU-QIV

QIV, Inactivated quadrivalent influenza vaccine; YOA, years of age.

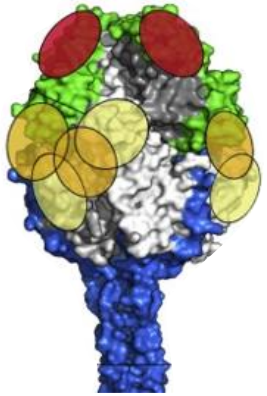
1. ClinicalTrials.gov, 2022 NCT04732871. https://clinicaltrials.gov/ct2/show/NCT04732871; 2. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596;
3. ClinicalTrials.gov, 2022. NCT04841577. https://clinicaltrials.gov/ct2/show/NCT04841577. URLs accessed Oct 2022.

GSK's RSV older adult vaccine

The combination of RSVPreF3 (120 µg) and $AS01_E$ is designed to induce a robust humoral and cellular immune response, to help protect older adults and those with underlying comorbidities

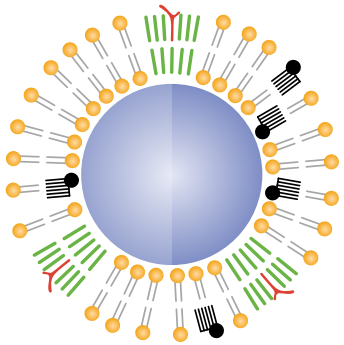
RSVPreF3 OA Vaccine

RSVPreF3 Antigen (120 µg)



Antigen engineered to preferentially maintain the pre-fusion conformation and display potent neutralizing epitopes to boost humoral immune response in older adults[1,2]

$AS01_E$ Adjuvant System



Boosts cellular immune response and restores the RSVPreF3 CD4+ T-cell level in older adults[2]

$AS01_E$, Adjuvant System 01_E (25 µg *Quillaja saponaria* Molina, fraction 21, 25 µg 3-Odesacyl-4'- monophosphoryl lipid A); OA, older adults.
Image of F protein reproduced from Graham BS, et al. *Curr Opin Immunol* 2015;35:30–38, Copyright 2015, with permission from Elsevier.
1. Graham BS, et al. *Curr Opin Immunol.* 2015;35:30–38; 2. Leroux-Roels I, et al. *J Infect Dis*. 2022:jiac327.

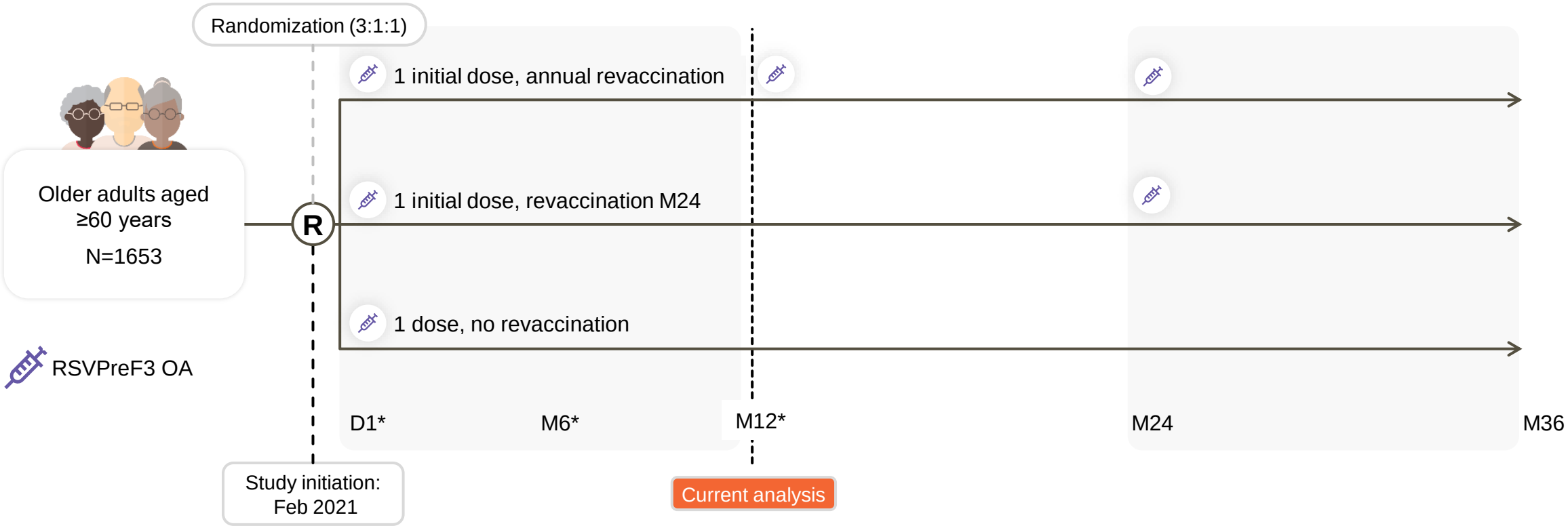
Open-label study of immunogenicity, safety, reactogenicity, and persistence

AReSVi-004: Immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and older

RSV OA=ADJ-004
NCT04732871

AReSVi-004 Phase 3 trial design[1]

Open-label study evaluating immunogenicity, safety, reactogenicity, and persistence of single-dose and different vaccination schedules



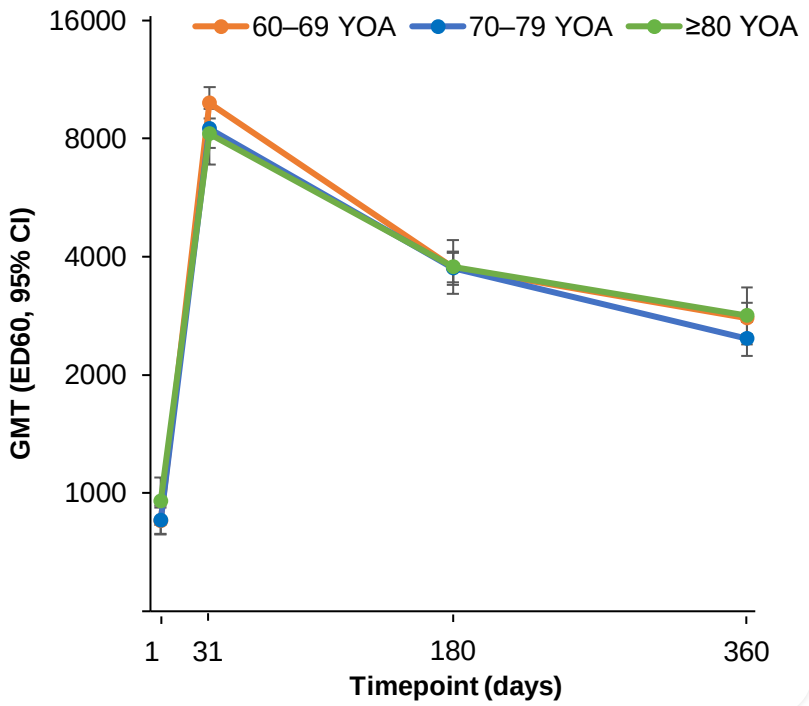
Primary objective: To evaluate humoral immune response following a 1-dose primary schedule up to 12 months post-dose 1*.

Key secondary objectives: To evaluate humoral and CMI† responses following 1-dose primary schedule and revaccination doses, up to study end (M36).

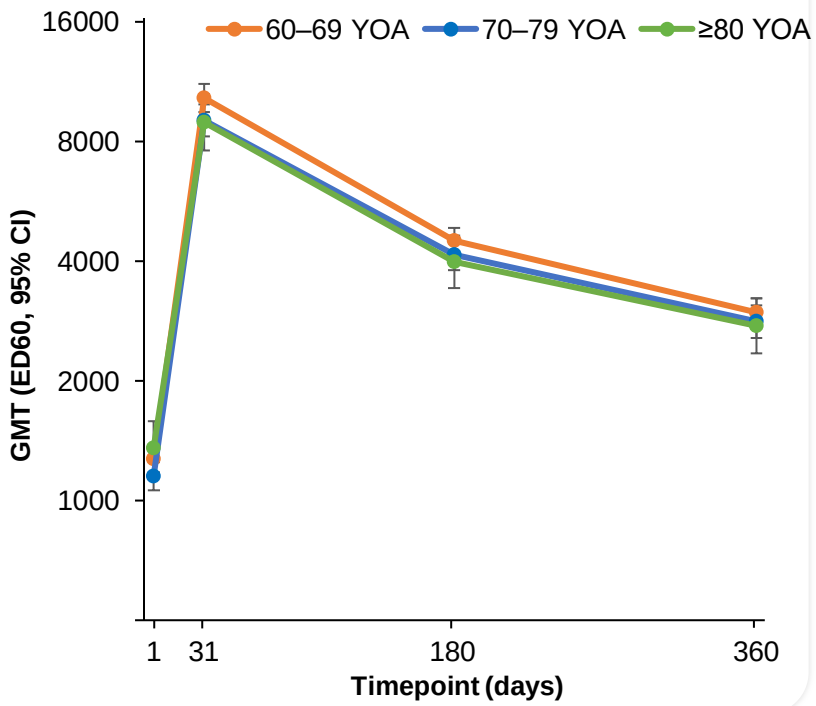
*Primary endpoints are NAb geometric mean titers (RSV-A and RSV-B) at Day 1 (pre-vaccination), D31, M6, and M12 post-dose 1; †CMI response in terms of frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells expressing at least 2 activation markers. AE, adverse event; CD, cluster of differentiation; CMI, cell-mediated immune; D, day; M, month; NAb, neutralizing antibody. 1. ClinicalTrials.gov. 2021. NCT04732871. https://clinicaltrials.gov/ct2/show/NCT04732871 (accessed October 2022).

Durable RSV-A, RSV-B neutralizing antibody and CD4+ T-cell responses across all age groups, 12 months post vaccination

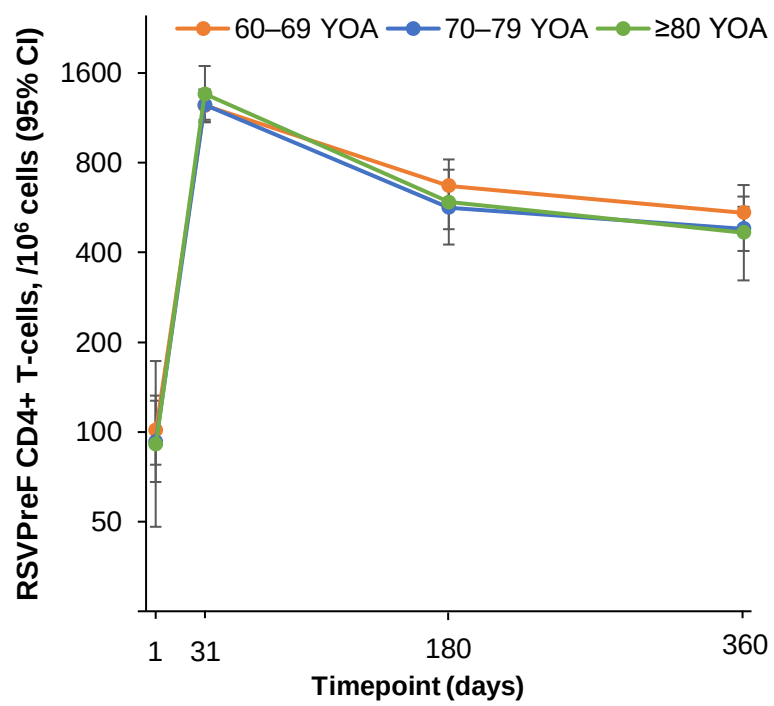
RSV-A NAb



RSV-B NAb



RSVPreF3-specific CD4+ T-cells*



*CD4+ T-cells expressing ≥2 activation markers including ≥1 cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17 (events/10^6 cells; by intracellular staining). Data at each timepoint for all 3 groups combined: Day 1 N=985 for RSV A, N=986 for RSV B, and N=471 for RSVPreF-specific CD4+ T-cells; Day 31 N=937 for RSV A and B, and N=408 for RSVPreF-specific CD4+ T-cells; Month 6=924 for RSV A and B and N=436 for RSVPreF-specific CD4+ T-cells; Month 12 N=870 for RSV A and B, and N=438 for RSVPreF-specific CD4+ T-cells; NCT0473287. CD, cluster of differentiation; CI, confidence interval; ED, Estimated Dilution; ED60, serum dilution inducing 60% inhibition in plaque-forming units; GMT, geometric mean titer; IL, interleukin; NAb, neutralizing antibody; TNF, tumor necrosis factor; YOA, years of age.

1. https://clinicaltrials.gov/ct2/show/NCT04732871 (accessed October 2022).

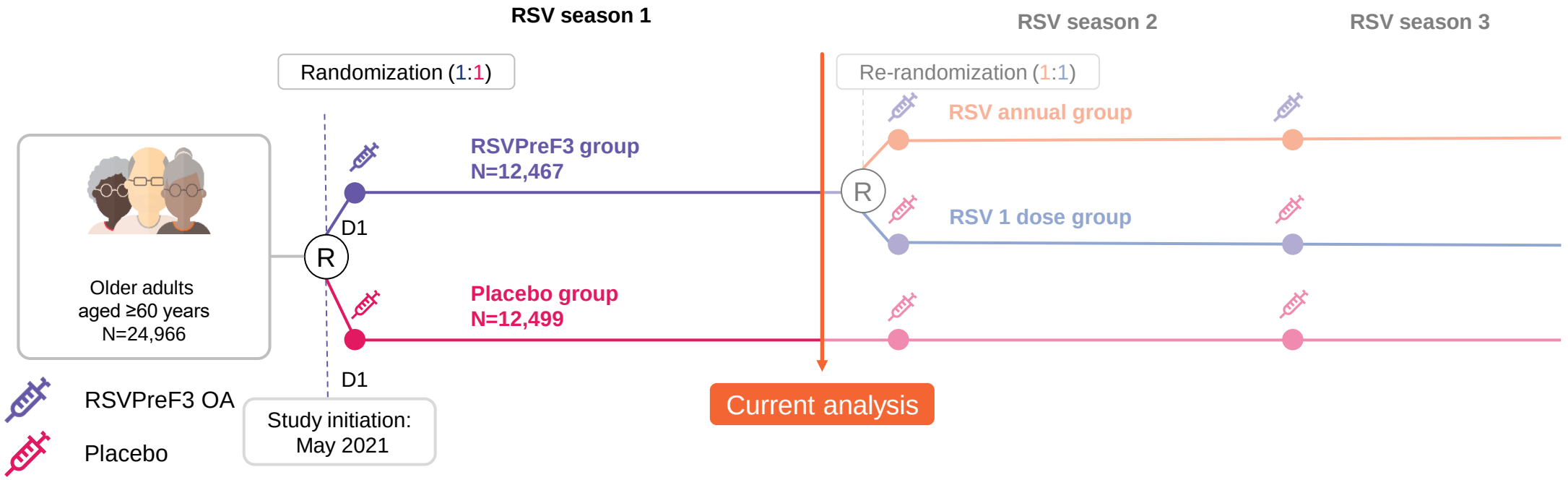
Pivotal efficacy study

AReSVi-006: Phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above

AReSVi-006 study
NCT04886596

Ongoing AReSVi-006 Phase 3 trial design

A randomized, placebo-controlled, observer-blind, multi-country efficacy study



Primary endpoint: To demonstrate the efficacy of RSVPreF3 OA vaccine in the prevention of RSV*-LRTD† in adults ≥60 years of age during the first season.

All RSV-LRTD cases were adjudicated by an independent external adjudication committee

*RT-PCR confirmed; †LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours. D, day; LRTD, lower respiratory tract disease; RT-PCR, reverse transcriptase polymerase chain reaction. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed October 2022).

Demographic characteristics

Demographic characteristics were balanced between study groups (Exposed Set)

Characteristic	RSVPreF3 OA (N=12,467)	Placebo (N=12,499)
Mean age, years (SD)	69.5	69.6
Age category, n (%)		
≥60 years of age	12,467 (100.0)	12,499 100.0)
60–69 years of age	6963 (55.9)	6980 (55.8)
70–79 years of age	4487 (36.0)	4491 (35.9)
≥80 years of age	1017 (8.2)	1028 (8.2)
Female, n (%)	6488 (52.0)	6427 (51.4)
Male, n (%)	5979 (48.0)	6072 (48.6)
Race, n (%)		
White	9887 (79.3)	9932 (79.5)
Black or African American	1064 (8.5)	1101 (8.8)
Asian	953 (7.6)	956 (7.6)
Other*	563 (4.5)	510 (4.1)
Frailty status, n (%)†		
Frail	189 (1.5)	177 (1.4)
Pre-frail	4793 (38.4)	4781 (38.3)
Fit	7464 (59.9)	7521 (60.2)
Unknown	21 (0.2)	20 (0.2)
Comorbidity of interest, n (%)‡		
≥1 pre-existing comorbidity of interest	4937 (39.6)	4864 (38.9)

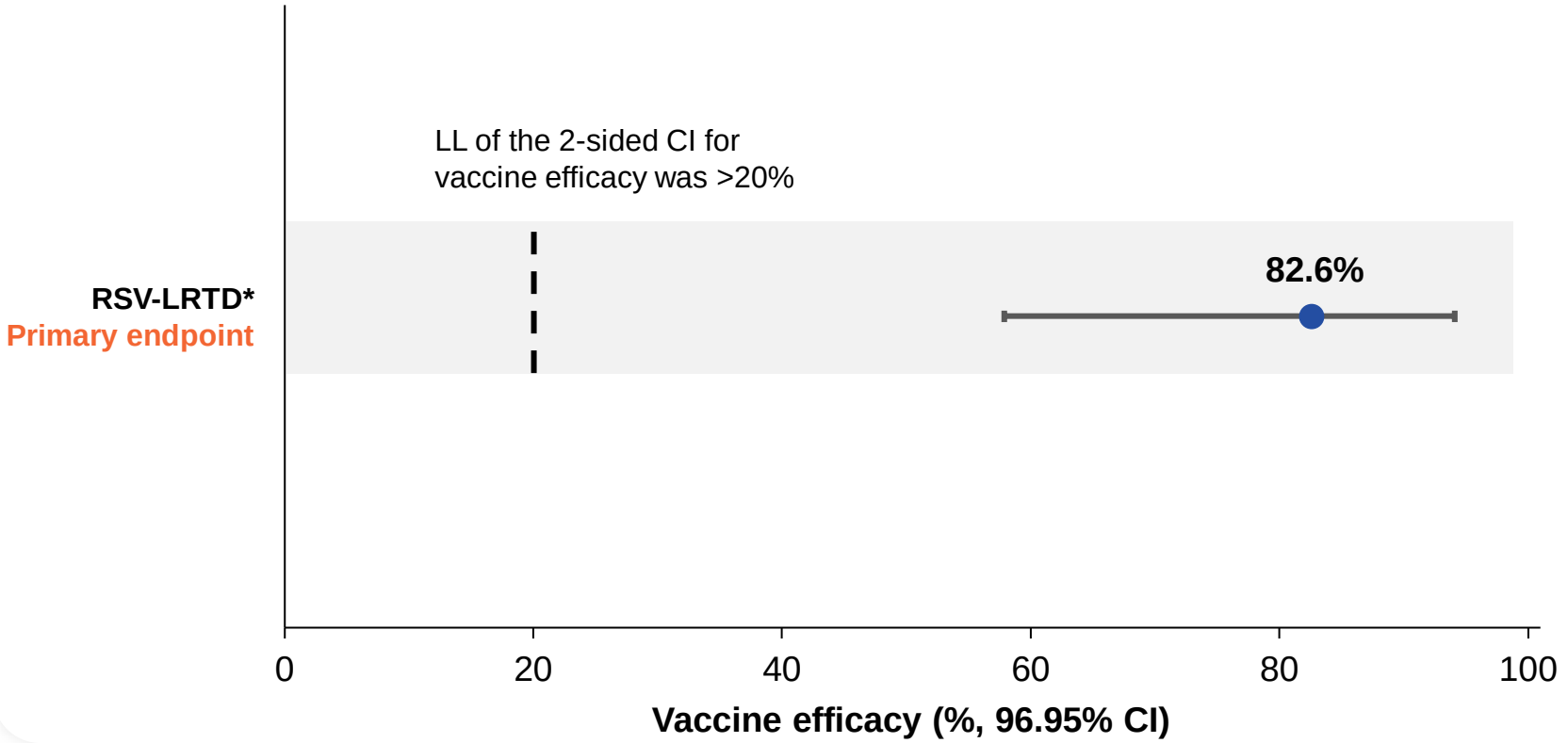
United States (N= 6949; 27.8% of total Exposed Set):

Characteristic	N	%
60-69 YOA	4290	61.7
70-79 YOA	2275	32.7
≥80 YOA	384	5.5
Hispanic or Latino	636	9.2
Black or African American	1025	14.8
Native Hawaiian or Pacific Islander	9	0.1
Other	65	0.9
White	5728	82.4

Around 39% of participants in each group had ≥1 pre-existing comorbidity of interest associated with an increased risk of severe RSV disease‡

*Includes Native American, Alaska Native, Native Hawaiian and other Pacific Islanders; †assessed by a gait speed test; ‡COPD, asthma, any chronic respiratory/pulmonary disease, diabetes type 1 or type 2, chronic heart failure, advanced liver or renal disease. COPD, chronic obstructive pulmonary disease; SD, standard deviation; YOA, years of age. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed Oct 2022).

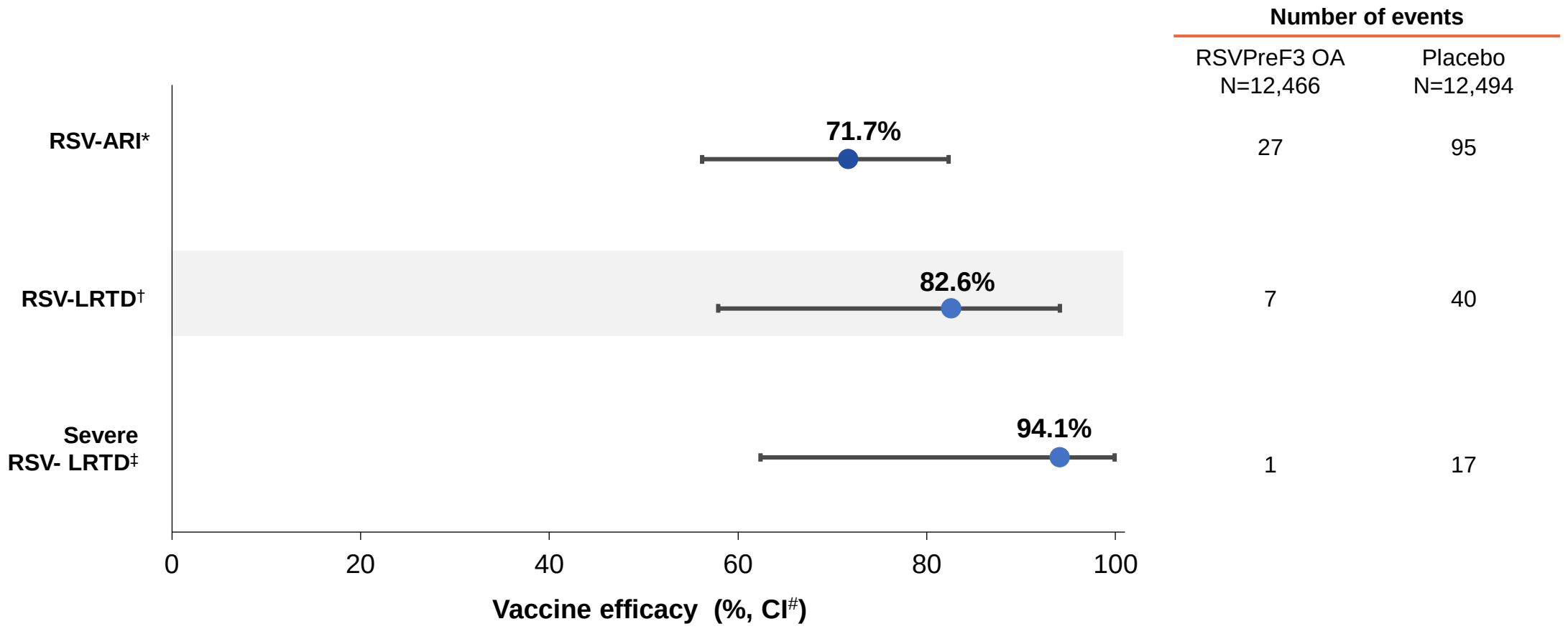
The primary endpoint was demonstrated; a single dose of RSVPreF3 OA is highly efficacious in the prevention of RSV-LRTD



Number of events	
RSVPreF3 OA N=12,466	Placebo N=12,494
7	40

*LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours; all RSV cases confirmed by RT-PCR; CI, confidence interval; LL, lower limit; LRTD, lower respiratory tract disease; RT-PCR, reverse transcriptase polymerase chain reaction. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed Oct 2022).

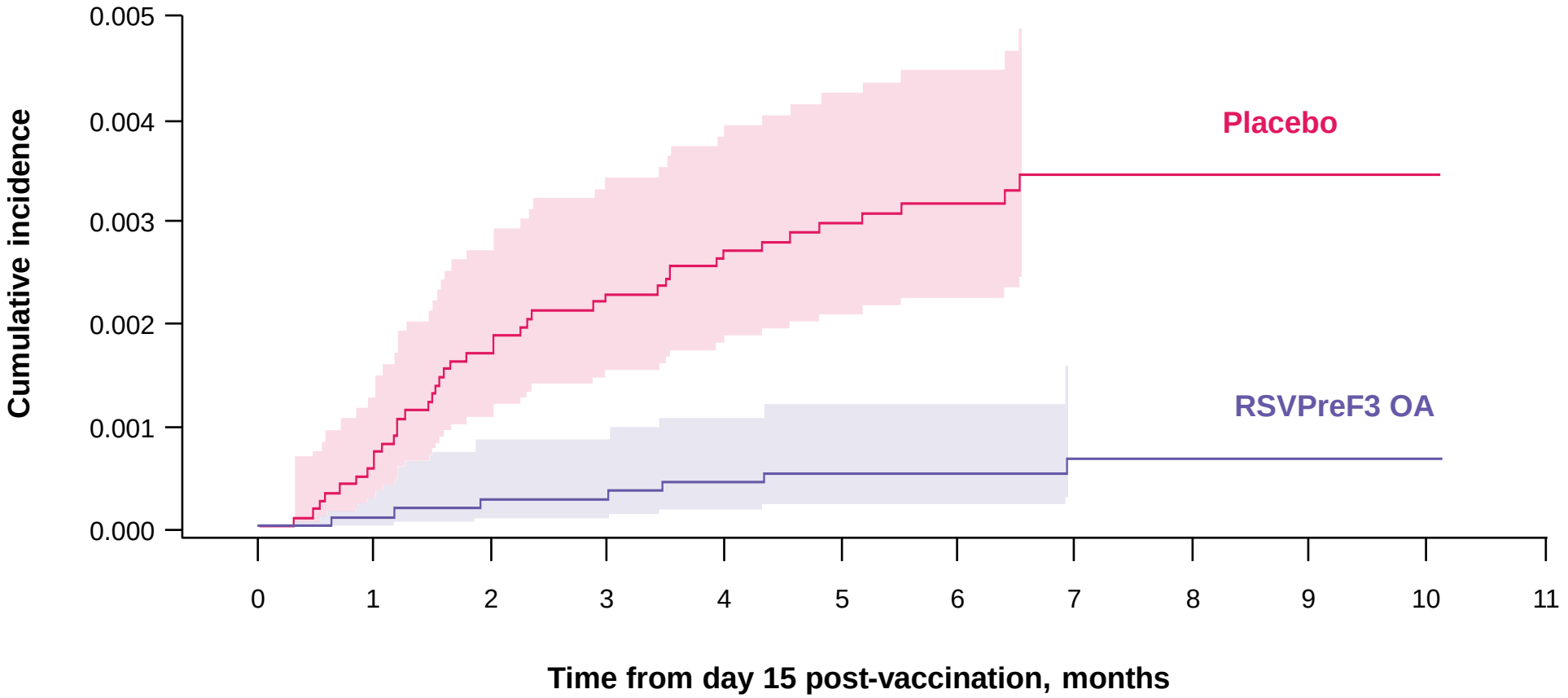
Consistently high vaccine efficacy across the full spectrum of RSV disease



*ARI defined as ≥2 respiratory symptoms/signs for ≥24 hours or ≥1 respiratory symptom/sign + 1 systemic symptom/sign for ≥24 hours; †LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign or ≥3 lower respiratory symptoms for ≥24 hours; ‡ severe LRTD defined as LRTD with ≥2 LRTD signs or assessed as severe by the Investigator. All RSV cases confirmed by RT-PCR; # 96.95% Confidence Interval (CI) for primary endpoint, 95% CI for all secondary endpoints; ARI, acute respiratory infection; LRTD, lower respiratory tract disease; RT-PCR, reverse transcriptase polymerase chain reaction. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed October 2022).

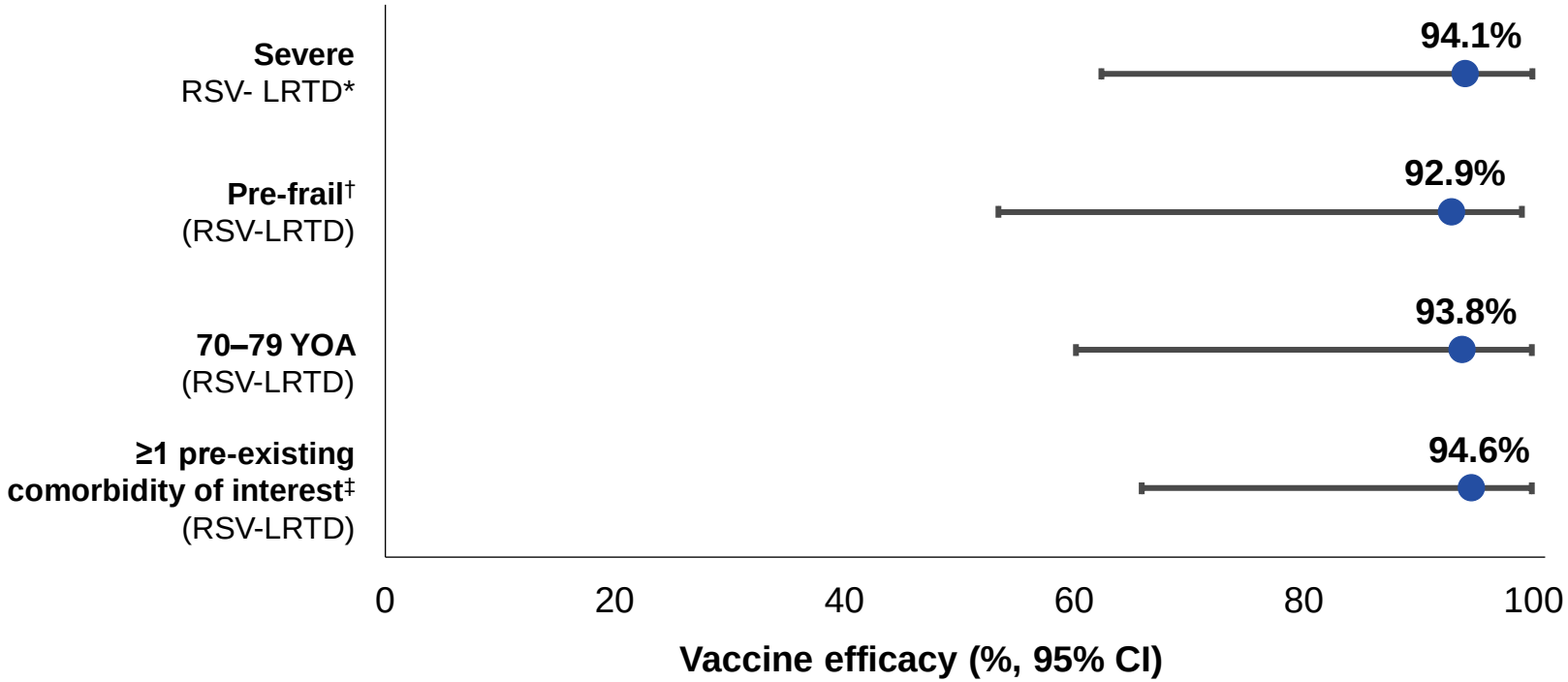
High vaccine efficacy against RSV-LRTD observed over 6.7-month follow-up, supporting efficacy over the course of an RSV season

Cumulative incidence curve for RSV-LRTD



The shaded areas represent 96.95% CI.
LRTD, lower respiratory tract disease; VE, vaccine efficacy. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed October 2022).

Very high and consistent vaccine efficacy against severe RSV disease and in older adults at increased risk



	number of events/N	
	RSVPreF3 OA	Placebo
Severe RSV- LRTD*	1 / 12,466	17 / 12,494
Pre-frail† (RSV-LRTD)	1 / 4792	14 / 4778
70–79 YOA (RSV-LRTD)	1 / 4487	16 / 4487
≥1 pre-existing comorbidity of interest‡ (RSV-LRTD)	1 / 4937	18 / 4861

Due to too few cases observed in adults aged 80 years and older, and those considered frail we cannot conclude on VE.

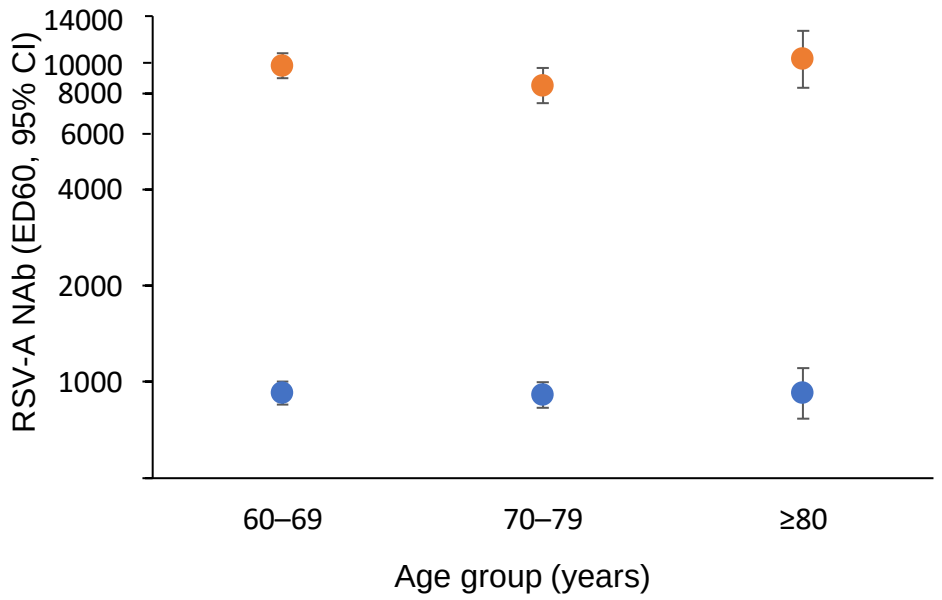
- ≥80 YOA (number of events / N): **RSVPreF3 OA** (2 / 1016); **Placebo** (3 / 1028)
- Frail (number of events / N): **RSVPreF3 OA** (1 / 189); **Placebo** (1 / 177)

*LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign or ≥3 lower respiratory symptoms for ≥24 hours; severe LRTD defined as LRTD with ≥2 LRTD signs or assessed as severe by the Investigator. All RSV cases confirmed by RT-PCR. †Frailty was assessed by a gait speed test. ‡COPD, asthma, any chronic respiratory/pulmonary disease, diabetes type 1 or type 2, congestive heart failure, advanced liver or renal disease; CI, confidence interval; LRTD, lower respiratory tract disease; RT-PCR, reverse-transcriptase polymerase chain reaction; VE, vaccine efficacy; YOA, years of age. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed October 2022).

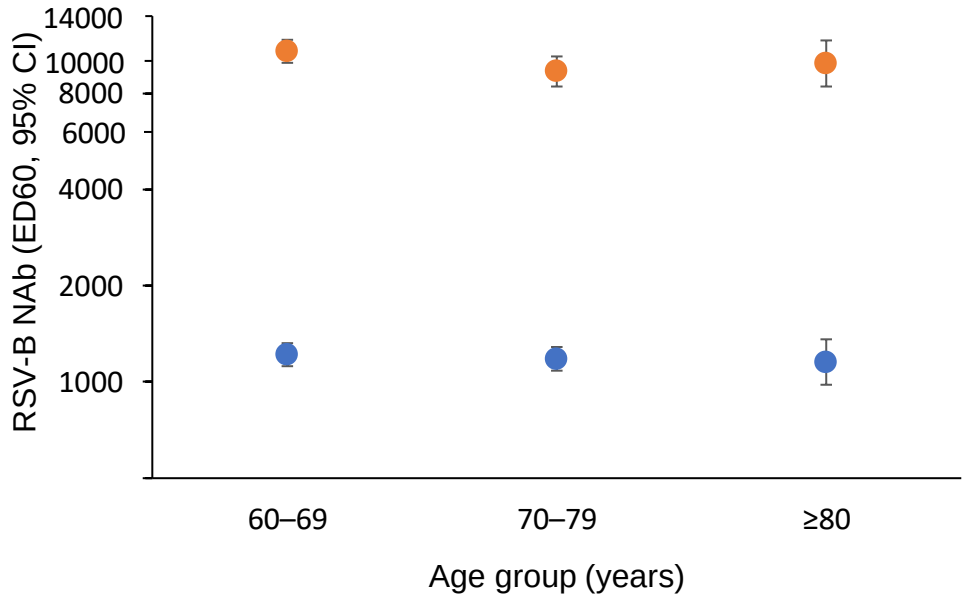
Robust immune response to RSV-A and RSV-B regardless of age

RSVPreF3 RSV-A and RSV-B neutralizing antibodies (ED60) by age (30 days post vaccination)

RSV-A NAb



RSV-B NAb

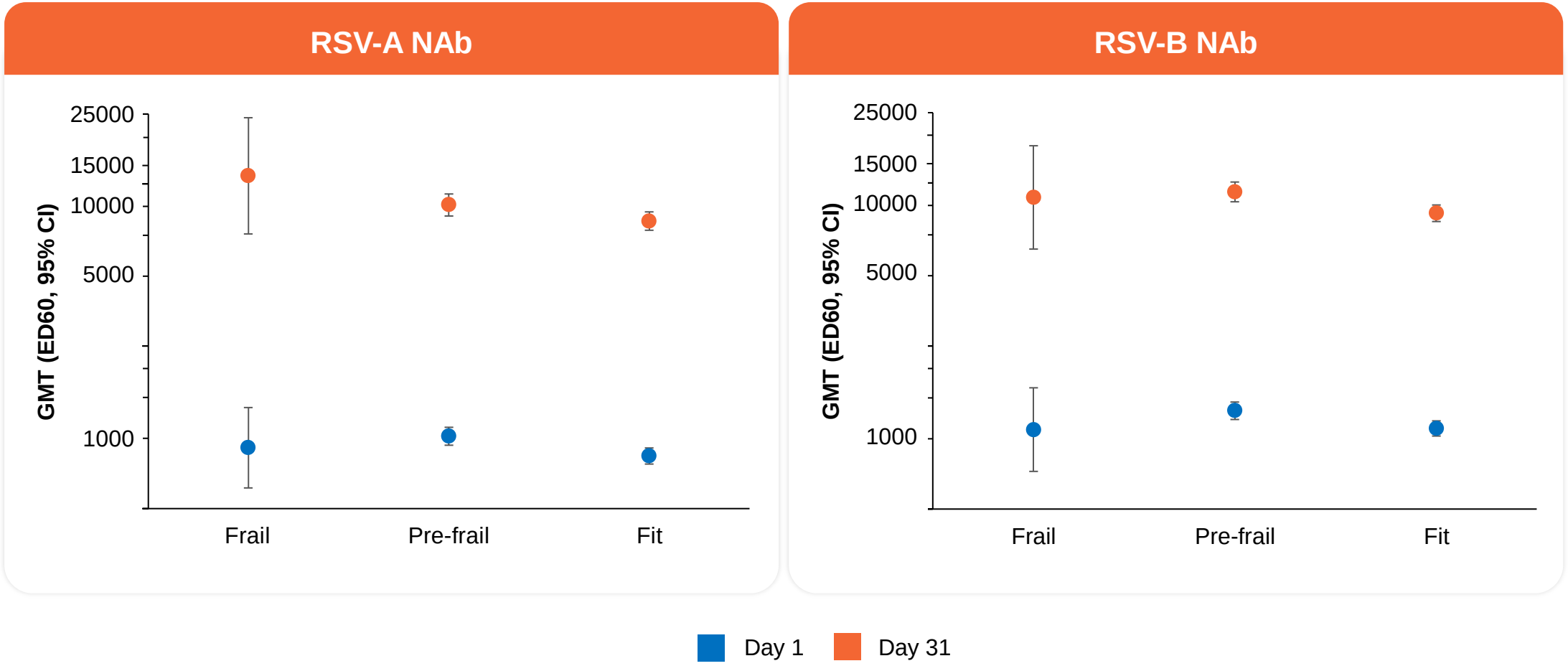


Day 1 Day 31

CI, confidence interval; ED, estimated dilution; GMT, geometric mean titer; MGI, mean geometric increase; NAb, neutralizing antibody; PPSi, per-protocol set for immunogenicity; ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed Oct 2022).

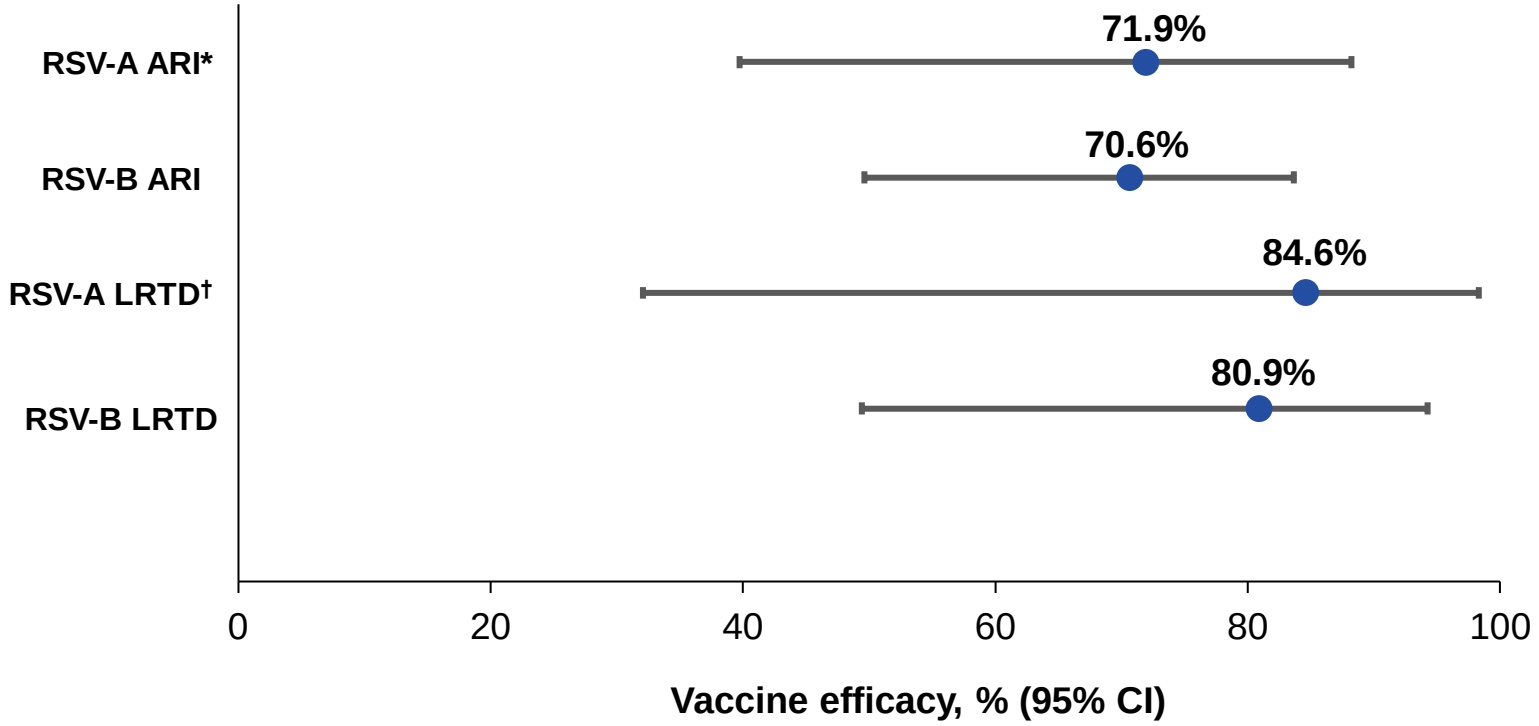
Robust immune response to RSV-A and RSV-B regardless of frailty* status

RSVPreF3 RSV-A and RSV-B neutralizing antibodies (ED60) by baseline frailty status (30 days post vaccination)



* Frailty assessed by a gait speed test ; CI, confidence interval; ED, estimated dilution; GMT, geometric mean titer; NAb, neutralizing antibody; PPSi, per-protocol set for immunogenicity. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed Oct 2022).

Consistently high vaccine efficacy against RSV-A- and RSV-B-associated disease



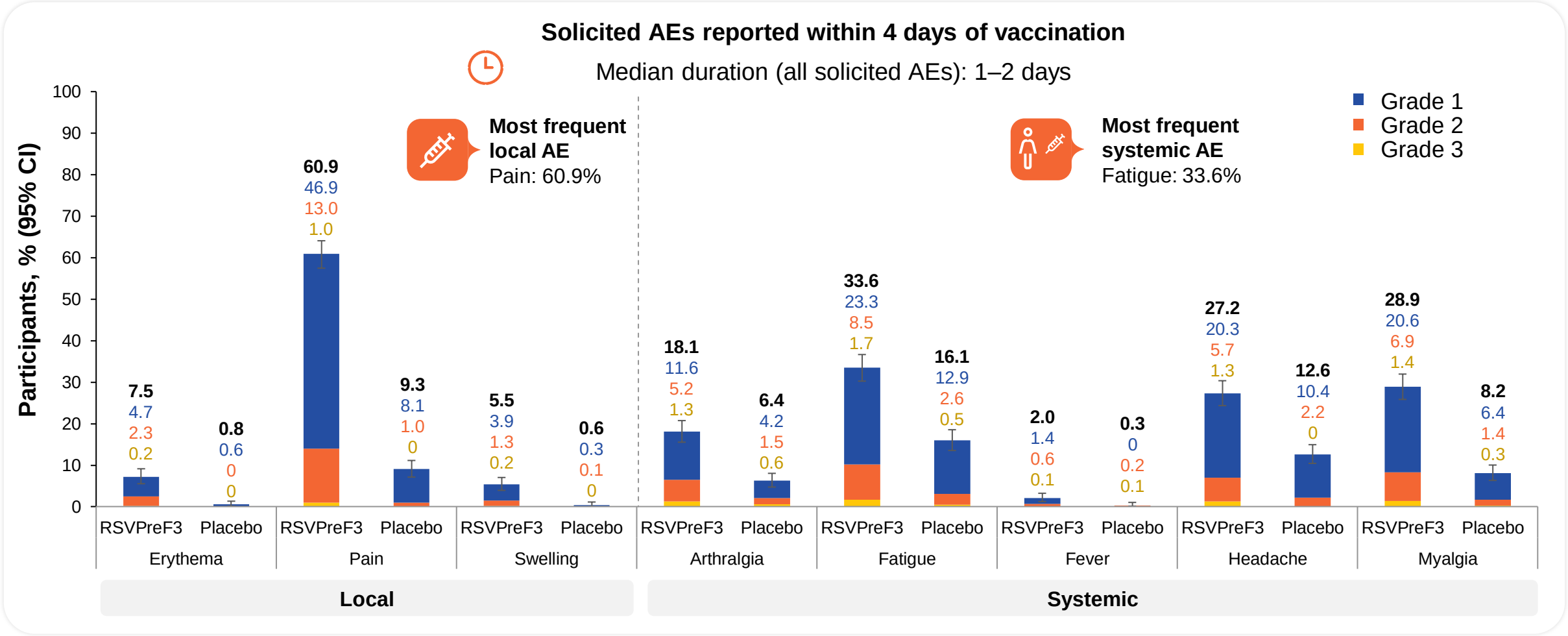
	Number of events	
	RSVPreF3 OA N=12,466	Placebo N=12,494
RSV-A ARI*	9	32
RSV-B ARI	18	61
RSV-A LRTD†	2	13
RSV-B LRTD	5	26

2/3 of RSV-LRTD cases were associated with RSV-B

*ARI defined as ≥2 respiratory symptoms/signs for ≥24 hours or ≥1 respiratory symptom/sign + 1 systemic symptom/sign for ≥24 hours; †LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign or ≥3 lower respiratory symptoms for ≥24 hours. All RSV cases confirmed by RT-PCR. ARI, acute respiratory infection; CI, confidence interval; LRTD, lower respiratory tract disease; RT-PCR, reverse transcriptase polymerase chain reaction. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed Oct 2022).

RSVPreF3 OA was well tolerated: most events were mild to moderate and transient

Solicited AEs reported within 4 days of vaccination (solicited safety set)

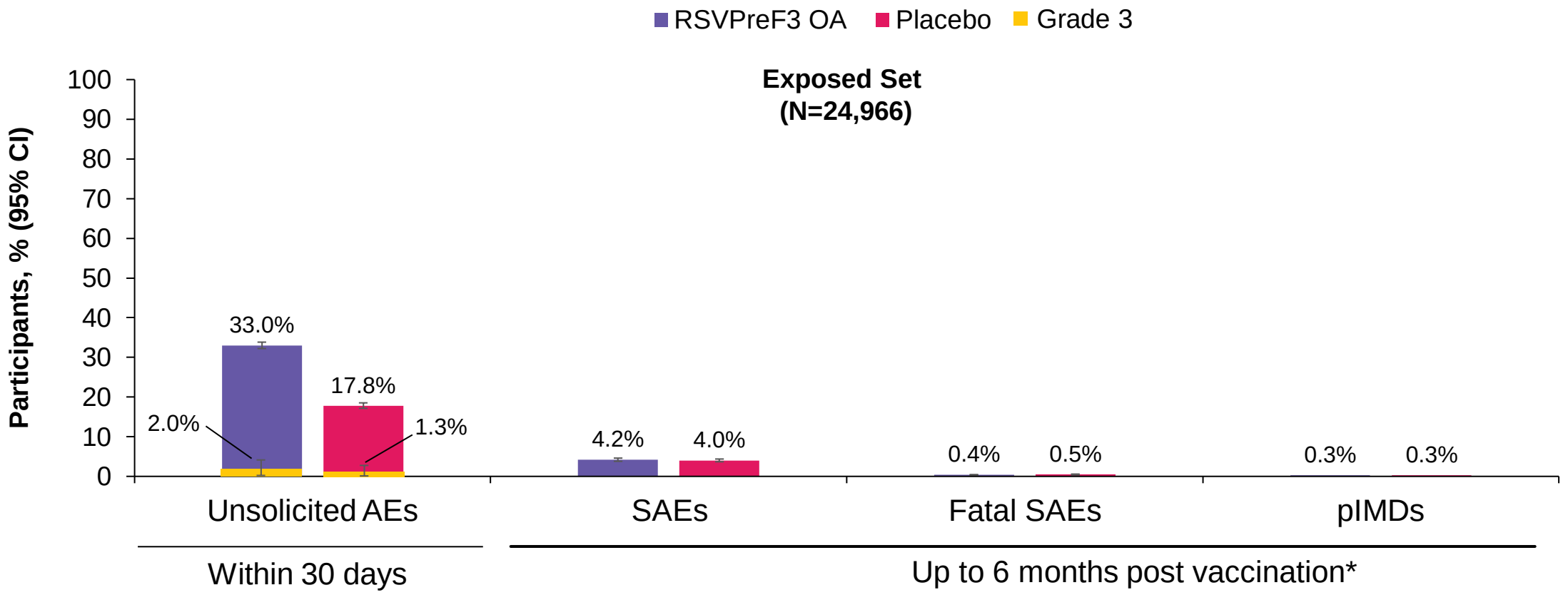


Error bars show 95% CIs for total AEs. Solicited safety set (N=1757); AE, adverse event; CI, confidence interval; Grade 3 Erythema and swelling is >100 mm ; Grade 3 pain defined as significant pain at rest; preventing normal everyday activities; Grade 3 fever defined as > 39.0°C/102.2°F; Grade 3 headache, fatigue, myalgia, arthralgia is defined as events preventing normal activity

Safety: Unsolicited AEs, SAEs, fatal SAEs, and pIMDs

The majority of unsolicited AEs were mild to moderate and transient

The overall rate of SAEs, fatal SAEs, and pIMDs were balanced between groups



IDMC have not identified any safety concern during their regular review of the unblinded safety data

*Follow-up is on-going until the end of the study. AE, adverse event; CI, confidence interval; IDMC, Independent Data Monitoring Committee; pIMD, potential immune-mediated disease; SAE, serious adverse event. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed Oct 2022).

RSVPreF3 OA & FLU-QIV co-administration study

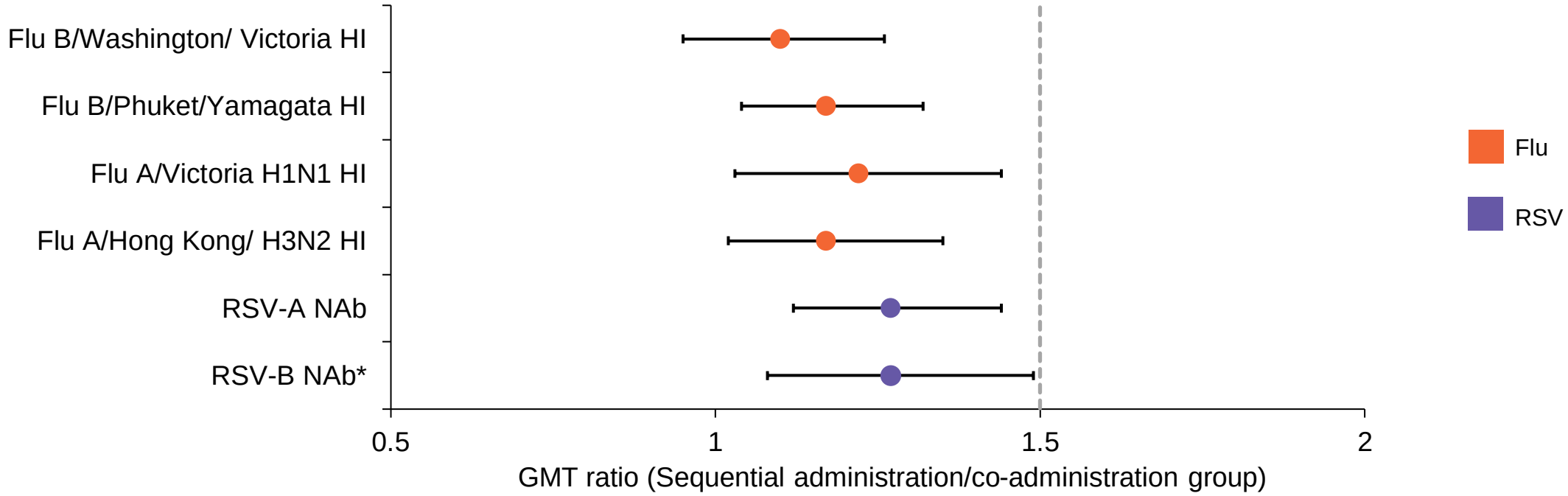
RSV-007: Open-label, randomized, controlled, multi-country study to evaluate immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU vaccines in adults aged 60 years and above

RSV OA=ADJ-007
NCT04841577

Coprimary endpoints met for both FLU-QIV and RSV

Non-inferior immunogenicity of FLU-QIV and RSVPreF3 OA co-administration versus administration of each vaccine alone

Ratio of RSV-A NAb GMTs and HI GMTs between the control group (sequential administration) and the co-administration group,1 month after vaccination



Success Criteria: Upper limit ≤1.5 of the 2-sided 95% CI for the group GMT ratio (RSV-A NAb titers and HI antibody titers in the control group (sequential administration) divided by the co-administration group) for RSV vaccine and for each of the flu vaccine strains

*RSV-B NAb was a descriptive and secondary endpoint. CI, confidence interval; GMT, geometric mean titer; HI, hemagglutinin inhibition; NAb, neutralizing antibodies; QIV, Inactivated Quadrivalent Influenza Vaccine. ClinicalTrials.gov. 2022. NCT04841577. https://clinicaltrials.gov/ct2/show/NCT04841577.

GSK's RSV candidate vaccine for older adults

Conclusion

Efficacy

- RSVPreF3 OA provides high and consistent efficacy across the full spectrum of RSV disease regardless of RSV A or RSV B
- Efficacy over an entire RSV season

82.6%	94.1%	94.6%	93.8%
RSV-LRTD (≥60 YOA)	Severe RSV-LRTD (≥60 YOA)	RSV-LRTD (≥1 with comorbidity of interest*)	RSV-LRTD (70−79 YOA)

Immune Response

- RSVPreF3 OA induces a robust and persistent humoral and T-cell immune response
- Can be co-administered with FLU-QIV

Safety

- RSVPreF3 OA is well tolerated with a favorable safety profile

Public Health Impact

- RSVPreF3 OA has the potential to meaningfully impact clinical outcomes in older adults

*COPD, asthma, any chronic respiratory/pulmonary disease, diabetes type 1 or type 2, congestive heart failure, advanced liver or renal disease. $AS01_E$, Adjuvant System 01_E; IDMC, Independent Data Monitoring Committee; LRTD, lower respiratory tract disease; QIV, Inactivated Quadrivalent Influenza Vaccine; YOA, years of age.

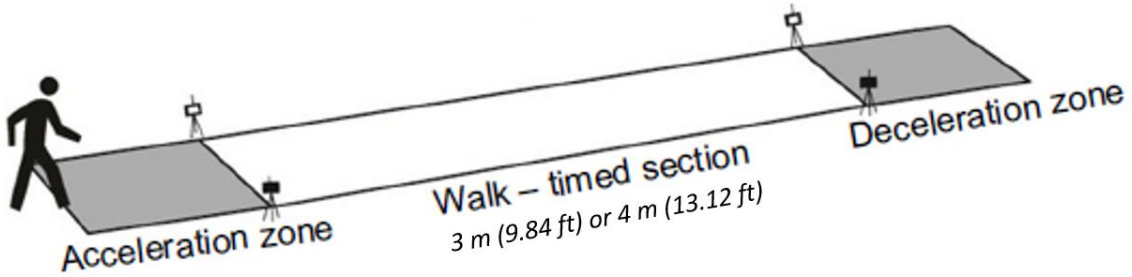
1. ClinicalTrials.gov, 2022 NCT04732871. https://clinicaltrials.gov/ct2/show/NCT04732871; 2. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596; 3. ClinicalTrials.gov, 2022. NCT04841577. https://clinicaltrials.gov/ct2/show/NCT04841577. URLs accessed Oct 2022.

Backup

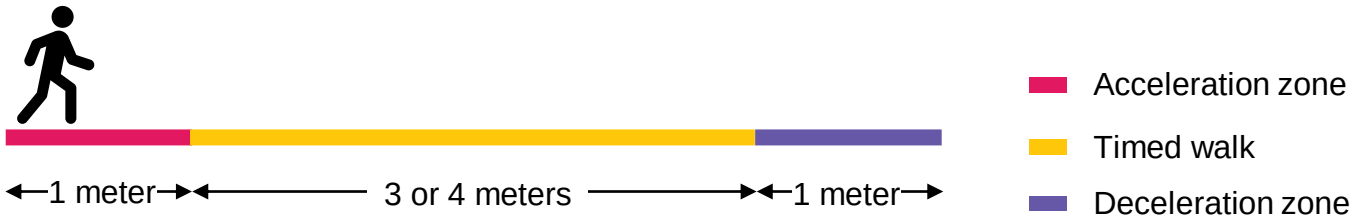
Frailty Assessment

The physical frailty status of each participant has been assessed at Visit 1 by the Gait Speed test[1]

- The test allows 2 length of walk; 3 meters (9.84 feet) or 4 meters (13.12 feet).
- Participant walks down a hallway through a 1-metre zone for acceleration, a central 4- metre “testing” zone, and a 1-metre zone for deceleration.



- Timing has been recorded and reported in the eCRF and further grouped as follows:
  - Frail, participants with a walking speed <0.4 m/s or not able to perform the test (reasons might include: Tried but unable, Could not walk unassisted, Not attempted – study staff or participant felt unsafe, participants unable to understand the instructions)
  - Pre-frail, participants with a walking speed of 0.4–0.99 m/s
  - Fit, participants with a walking speed ≥1 m/s



[1]: Gait Speed test is one component of the Short Physical Performance Battery (SPPB) measurement