ORIGINAL ARTICLE

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) is an important cause of acute respiratory infection, lower respiratory tract disease, clinical complications, and death in older adults. There is currently no licensed vaccine against RSV infection.

METHODS

In an ongoing, international, placebo-controlled, phase 3 trial, we randomly assigned, in a 1:1 ratio, adults 60 years of age or older to receive a single dose of an $AS01_E$-adjuvanted RSV prefusion F protein–based candidate vaccine (RSVPreF3 OA) or placebo before the RSV season. The primary objective was to show vaccine efficacy of one dose of the RSVPreF3 OA vaccine against RSV-related lower respiratory tract disease, confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR), during one RSV season. The criterion for meeting the primary objective was a lower limit of the confidence interval around the efficacy estimate of more than 20%. Efficacy against severe RSV-related lower respiratory tract disease and RSV-related acute respiratory infection was assessed, and analyses according to RSV subtype (A and B) were performed. Safety was evaluated.

RESULTS

A total of 24,966 participants received one dose of the RSVPreF3 OA vaccine (12,467 participants) or placebo (12,499). Over a median follow-up of 6.7 months, vaccine efficacy against RT-PCR–confirmed RSV-related lower respiratory tract disease was 82.6% (96.95% confidence interval [CI], 57.9 to 94.1), with 7 cases (1.0 per 1000 participant-years) in the vaccine group and 40 cases (5.8 per 1000 participant-years) in the placebo group. Vaccine efficacy was 94.1% (95% CI, 62.4 to 99.9) against severe RSV-related lower respiratory tract disease (assessed on the basis of clinical signs or by the investigator) and 71.7% (95% CI, 56.2 to 82.3) against RSV-related acute respiratory infection. Vaccine efficacy was similar against the RSV A and B subtypes (for RSV-related lower respiratory tract disease: 84.6% and 80.9%, respectively; for RSV-related acute respiratory infection: 71.9% and 70.6%, respectively). High vaccine efficacy was observed in various age groups and in participants with coexisting conditions. The RSVPreF3 OA vaccine was more reactogenic than placebo, but most adverse events for which reports were solicited were transient, with mild-to-moderate severity. The incidences of serious adverse events and potential immune-mediated diseases were similar in the two groups.

CONCLUSIONS

A single dose of the RSVPreF3 OA vaccine had an acceptable safety profile and prevented RSV-related acute respiratory infection and lower respiratory tract disease and severe RSV-related lower respiratory tract disease in adults 60 years of age or older, regardless of RSV subtype and the presence of underlying coexisting conditions. (Funded by GlaxoSmithKline Biologicals; AReSVi-006 ClinicalTrials.gov number, NCT04886596.)

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*A list of the members of the Adult Respiratory Syncytial Virus (AReSVi-006) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Respiratory syncytial virus (RSV) is an important cause of acute respiratory infections during the autumn and winter months in temperate regions and during rainy seasons in tropical regions.[1,2] Most children are infected with RSV by 2 years of age, but reinfection may recur throughout life, typically with mild or no symptoms.[1,3] In older adults or those with coexisting conditions, RSV infection can cause lower respiratory tract disease, which may lead to exacerbation of underlying diseases, hospitalization, and death.[4-8] In 2019, RSV infection accounted for an estimated 5.2 million cases of acute respiratory infection, 470,000 hospitalizations, and 33,000 in-hospital deaths among adults 60 years of age or older in industrialized countries.[9] Reduced RSV-specific T-cell responses in older adults owing to immunosenescence probably contribute to the susceptibility to severe RSV disease in this group.[10]

Treatment for RSV-associated illness is supportive, and there are no licensed vaccines or prophylactic interventions for older adults.[11,12] Most RSV vaccine candidates being tested in clinical trials target the RSV F glycoprotein, which mediates viral fusion and host-cell entry, elicits neutralizing antibodies, and is highly conserved across the two RSV subtypes (A and B).[12,13] A candidate RSV vaccine for older adults (RSVPreF3 OA, GSK [formerly GlaxoSmithKline]) contains F protein stabilized in its prefusion conformation, which exposes epitopes targeted by neutralizing antibodies.[12,14,15] Immunization of mice and macaques with stabilized prefusion forms of the F protein elicited significantly higher neutralizing activity than postfusion forms.[15] Several formulations of the RSVPreF3 OA vaccine (without or with an AS01-based adjuvant) were evaluated in a phase 1–2 study, which showed that the vaccine was associated with an acceptable safety profile and induced neutralizing antibody responses in older adults.[16] AS01-adjuvanted formulations increased RSV-specific CD4+ T-cell frequencies in older adults to levels similar to those observed in young adults after vaccination.[16] Formulations with $AS01_E$ were less reactogenic than those with $AS01_B$ (which contains twice the dose of immunostimulants[17]).[16] Therefore, an $AS01_E$-adjuvanted formulation was selected for further development.[16] We designed the Adult Respiratory Syncytial Virus (AReSVi-006) phase 3 trial to evaluate the efficacy of the RSVPreF3 OA vaccine against RSV-related lower respiratory tract disease in adults 60 years of age or older.

METHODS

TRIAL DESIGN AND OVERSIGHT

We are conducting this ongoing, randomized, placebo-controlled, phase 3 trial in 17 countries in Africa, Asia, Australia, Europe, and North America. Participants are followed for three consecutive RSV seasons in the Northern Hemisphere and for at least two consecutive seasons in the Southern Hemisphere. Here, we present results for the first RSV season in the Northern Hemisphere.

The relevant independent ethics committees or institutional review boards for each trial site approved the protocol and amendments (available with the full text of this article at NEJM.org). All the participants provided written or witnessed informed consent before trial procedures began. The trial has been conducted in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and regulatory requirements. Safety is monitored by an independent data and safety monitoring committee, which regularly reviews unblinded data.

Authors who are employees of GSK were involved in the trial design, and the investigators gathered the data. All the authors critically reviewed drafts prepared by a medical writer and made the decision to submit the manuscript for publication. To maintain participant-level blinding in this ongoing trial, independent external statisticians performed the statistical analyses. All the authors had access to the protocol, statistical analysis plan, and data that did not risk participant-level unblinding. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

We enrolled adults 60 years of age or older who had not previously been enrolled in or were not currently enrolled in another RSV vaccine trial. Persons with chronic medical conditions were eligible if the investigator considered the participant's condition to be medically stable. Inclusion and exclusion criteria and details of the enrollment rules are provided in the protocol and in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION, VACCINATION, AND BLINDING

Before the RSV season began, participants were randomly assigned in a 1:1 ratio, with the use of an automated Internet-based system, to receive either the RSVPreF3 OA vaccine or placebo (see the Supplementary Appendix). Each 0.5-ml dose of reconstituted RSVPreF3 OA vaccine contained 120 μg of RSVPreF3 antigen and the liposome-based $AS01_E$ adjuvant system containing 25 μg of 3-*O*-desacyl-4′-monophosphoryl lipid A and 25 μg of *Quillaja saponaria* Molina, fraction 21 (QS21). The active vaccine or saline placebo was injected into the deltoid muscle of the participant's nondominant arm. Injections were administered by personnel who were not involved in data collection or evaluation. Participants and the trial team members responsible for evaluating end points were unaware of trial-group assignments.

OBJECTIVES

The primary objective of the trial was to evaluate the efficacy of a single dose of the RSVPreF3 OA vaccine with regard to the prevention of RSV-related lower respiratory tract disease during one RSV season among adults 60 years of age or older. Secondary objectives included the evaluation of efficacy against RSV-related acute respiratory infection, severe RSV-related lower respiratory tract disease, and RSV-related lower respiratory tract disease according to RSV subtype (A or B), participant age, the presence or absence of coexisting conditions at baseline, and frailty status (see below) at baseline. Reactogenicity, safety and immunogenicity were also evaluated. Details of the trial objectives are presented in Table S1 of the Supplementary Appendix.

EFFICACY ASSESSMENTS

The primary end point was RSV-related lower respiratory tract disease as confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR). Surveillance for acute respiratory infection was done by means of spontaneous reporting by participants and actively by means of scheduled contacts with participants. Starting from the day of the injection, participants were required to contact the site staff if they had at least two symptoms or signs of acute respiratory infection lasting at least 24 hours. Starting from 30 days after the injection, site staff contacted participants every 2 weeks during the RSV season and every month during the period between RSV seasons to capture data on acute respiratory infections that were not spontaneously reported by participants. For any acute respiratory infection that occurred before 30 days after the injection, participants were required to contact the trial site to plan a visit to assess the acute respiratory infection. Starting from 30 days after the injection, participants had to perform nasal swabbing (preferably within 48 hours after the onset of acute respiratory infection) and contact the site to plan a visit to assess the infection. Regardless of the timing of the onset of acute respiratory infection, during the assessment visit, nasal and throat swabs were obtained by trial personnel if the presence of acute respiratory infection was confirmed. Swabs were tested for RSV A and B subtypes by quantitative RT-PCR. Each case of acute respiratory infection was followed up with additional visits or telephone calls until resolution.

Acute respiratory infection was defined as at least two respiratory symptoms or signs or at least one respiratory and one systemic symptom or sign lasting for at least 24 hours. Lower respiratory tract disease was defined as at least two lower respiratory symptoms or signs (including at least one lower respiratory sign) or at least three lower respiratory symptoms lasting for at least 24 hours (Table S2).

An external adjudication committee reviewed all cases of lower respiratory tract disease that were confirmed to be caused by RSV and that fulfilled the case definition as well as all investigator-reported cases of RSV-related lower respiratory tract disease that did not meet the case definition. The primary efficacy analysis included externally adjudicated cases only. Details on the surveillance and adjudication of acute respiratory infections, quantitative RT-PCR assessment, and coronavirus disease 2019 (Covid-19) mitigation measures are provided in the Supplementary Appendix. Baseline frailty status was assessed with the use of a gait speed test. A walking speed of less than 0.4 m per second or an inability to perform the test indicated frail status, a walking speed of 0.4 to 0.99 m per second indicated prefrail status, and a walking speed of 1 m per second or faster indicated fit status.

SAFETY ASSESSMENTS

Reactogenicity was assessed in the reactogenicity–immunogenicity cohort, in which we planned to include approximately 1800 participants (1620

in the Northern Hemisphere and 180 in the Southern Hemisphere) (see the Supplementary Appendix). Participants in this cohort used paper diaries to record solicited injection-site and systemic reactions starting within 4 days after the injection. Reactions for which data were solicited were followed up until resolution. Unsolicited adverse events starting within 30 days after injection were to be recorded by all the participants in paper diaries. Participants who were not part of the reactogenicity–immunogenicity cohort recorded all adverse events, including reactogenicity events, that started within 30 days after injection as unsolicited adverse events.

The intensity of adverse events was graded from mild (grade 1) to severe (grade 3); grading was done by the participants for solicited events and by the investigators for unsolicited events. Data on serious adverse events and potential immune-mediated diseases were collected from the day of the injection until 6 months after the injection. Serious adverse events and potential immune-mediated diseases that are considered by the investigator to be related to vaccine or placebo, fatal serious adverse events, and adverse events and serious adverse events leading to withdrawal from the trial are being recorded until the end of this ongoing trial.

IMMUNOGENICITY ASSESSMENT

Blood samples were obtained from all the participants before the injection and at 1 month after the injection. Immunogenicity was assessed in the reactogenicity–immunogenicity cohort with the use of an RSVPreF3-specific IgG enzyme-linked immunosorbent assay and RSV A and B neutralization assays (see the Laboratory Assays section in the Supplementary Appendix). We calculated the geometric mean increase by taking the geometric mean of the within-participant ratios of the antibody titer or concentration after injection to that before injection.

STATISTICAL ANALYSIS

We planned to enroll up to 25,000 participants in this trial (Tables S3 and S4 and the Statistical Analyses section in the Supplementary Appendix). The primary efficacy analysis was performed in the modified exposed population, which included all the participants who had received vaccine or placebo and did not report an RSV-related acute respiratory infection before day 15 after injection. Additional analyses were performed in the exposed population, which included all the participants who had received vaccine or placebo. The primary objective would be met if the lower limit of the two-sided confidence interval around the efficacy estimate was greater than 20% (see the Supplementary Appendix).

The current efficacy analysis was performed (as planned) because at least 35 cases of RSV-related lower respiratory tract disease had occurred in the primary cohort for efficacy, on the basis of data available at the end of the first Northern Hemisphere RSV season (April 2022). The type I error was adjusted to maintain the overall significance level, and a two-sided 96.95% confidence interval was calculated for the primary end point (see the Supplementary Appendix). Vaccine efficacy was calculated as 1 minus the relative risk with the use of the conditional exact binomial method based on the Poisson model.[18] Periods at risk ended at the first occurrence of an event or data censoring and started on day 15 after injection for analyses in the modified exposed population and on the day of injection for analyses in the exposed population. If the primary objective was met in the current analysis, the results would be considered to be final.

Safety end points were analyzed in the exposed population, except for solicited reactions, which were analyzed in the solicited safety population. This population included participants in the reactogenicity–immunogenicity cohort who had solicited safety data available.

Immunogenicity was analyzed in the per-protocol immunogenicity cohort. This population included participants in the reactogenicity–immunogenicity cohort who adhered to the protocol and had immunogenicity data available.

No adjustment for multiplicity was applied for the analyses of secondary end points, so no inferences can be made without a hypothesis test. All the statistical analyses were performed with the use of the SAS Life Science Analytics Framework.

RESULTS

TRIAL POPULATION

A total of 26,664 participants were enrolled in the trial between May 25, 2021, and January 31, 2022. Of these participants, 24,966 were included

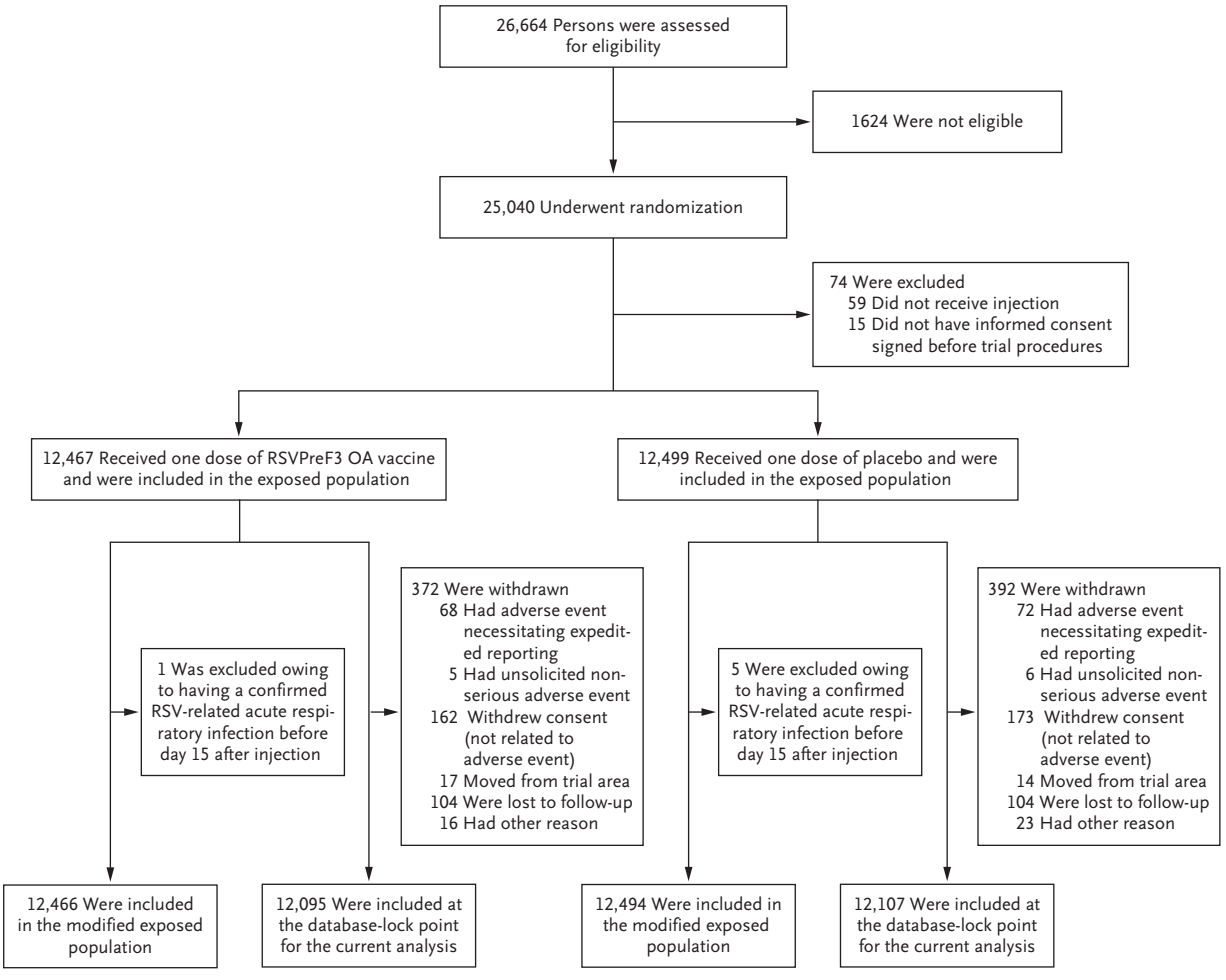


Figure 1. Enrollment and Follow-up of the Participants.

Participants 60 years of age or older were assigned to receive a candidate vaccine against respiratory syncytial virus (RSV) infection (RSVPreF3 OA) or placebo. The exposed population included all the participants who received vaccine or placebo. The modified exposed population included all the participants who received vaccine or placebo and did not report an RSV-related acute respiratory infection before day 15 after injection.

in the exposed population and 24,960 in the modified exposed population. Seven participants who had been randomly assigned to the vaccine group received placebo, and 7 who had been randomly assigned to the placebo group received vaccine. A total of 764 of 24,966 participants (3.1%) were withdrawn before the database lock for the current analysis (Fig. 1).

The demographic characteristics of the participants were similar in the two groups (Table 1). The mean age of the participants was 69.5 years. Approximately 39% of the participants in each group had coexisting conditions at baseline that are known to be associated with an increased risk of severe RSV disease (Table 1). The representativeness of the trial population is presented in Table S5.

VACCINE EFFICACY

In total, 47 participants (7 of 12,466 in the vaccine group and 40 of 12,494 in the placebo group) in the modified exposed population reported an episode of RSV-related lower respiratory tract disease (which was externally adjudicated) during a median follow-up of 6.7 months (maximum follow-up, 10.1 months). All the cases were re-

Table 1. Characteristics of the Participants at Baseline (Exposed Population).*

Characteristic	RSVPreF3 OA Group (N = 12,467)	Placebo Group (N = 12,499)
Age		
Mean — yr	69.5±6.5	69.6±6.4
Distribution — no. (%)		
≥70 yr	5,504 (44.1)	5,519 (44.2)
≥80 yr	1,017 (8.2)	1,028 (8.2)
60–69 yr	6,963 (55.9)	6,980 (55.8)
70–79 yr	4,487 (36.0)	4,491 (35.9)
Female sex — no. (%)	6,488 (52.0)	6,427 (51.4)
Race — no. (%)†		
Black	1,064 (8.5)	1,101 (8.8)
Asian	953 (7.6)	956 (7.6)
White	9,887 (79.3)	9,932 (79.5)
Other	563 (4.5)	510 (4.1)
Geographic region — no. (%)‡		
Northern Hemisphere	11,496 (92.2)	11,522 (92.2)
Southern Hemisphere	971 (7.8)	977 (7.8)
Type of residence — no. (%)		
Community	12,306 (98.7)	12,351 (98.8)
Long-term care facility	161 (1.3)	148 (1.2)
Frailty status — no. (%)§		
Frail	189 (1.5)	177 (1.4)
Prefrail	4,793 (38.4)	4,781 (38.3)
Fit	7,464 (59.9)	7,521 (60.2)
Unknown	21 (0.2)	20 (0.2)
Charlson comorbidity index¶		
Mean	3.2±1.2	3.2±1.2
Distribution — no. (%)		
Low or medium risk	8,235 (66.1)	8,368 (66.9)
High risk	4,232 (33.9)	4,131 (33.1)
Coexisting conditions of interest — no. (%)‖		
Any preexisting condition	4,937 (39.6)	4,864 (38.9)
Cardiorespiratory preexisting condition	2,496 (20.0)	2,422 (19.4)
Endocrine or metabolic preexisting condition	3,200 (25.7)	3,236 (25.9)

* Plus–minus values are means ±SD. The exposed population included all the participants who received a single dose of an $AS01_E$-adjuvanted respiratory syncytial virus (RSV) prefusion F protein–based candidate vaccine (RSVPreF3 OA) or placebo. Percentages may not total 100 because of rounding.

† Race was reported by the participant.

‡ Northern Hemisphere countries that were included in the trial were Belgium, Canada, Estonia, Finland, Germany, Italy, Japan, Mexico, Poland, Russia, Spain, South Korea, the United Kingdom, and the United States. Southern Hemisphere countries were Australia, New Zealand, and South Africa.

§ Frailty status was assessed with the use of a gait speed test. A walking speed of less than 0.4 m per second or an inability to perform the test indicated frail status, a walking speed of 0.4 to 0.99 m per second indicated prefrail status, and a walking speed of 1 m per second or faster indicated fit status.

¶ This trial used an updated Charlson comorbidity index,[19] which is calculated on the basis of 17 conditions, each of which is assigned a weighted score of 0, 1, 2, 4, or 6. Higher scores indicate more coexisting conditions and a higher risk of death; the maximum score is 24. The Charlson comorbidity index was also adjusted for age by the addition of 1 point for each decade after 40 years of age. A baseline score of 3 or less indicated low or medium risk, and a score above 3 indicated high risk. The range of scores that was observed in this trial was 2 to 11.

‖ Coexisting conditions of interest included chronic obstructive pulmonary disease, asthma, any chronic respiratory or pulmonary disease, and chronic heart failure (cardiorespiratory condition) and diabetes mellitus type 1 or type 2 and advanced liver or renal disease (endocrine or metabolic condition).

ported in the Northern Hemisphere (median follow-up, 6.9 months). The vaccine efficacy was 82.6% (96.95% confidence interval [CI], 57.9 to 94.1) (Table 2); thus, the primary objective was met (lower limit of confidence interval, >20%). Similar results were observed in the exposed population (Table S6).

Efficacy against severe RSV-related lower respiratory tract disease (assessed on the basis of clinical signs or by the investigator) was 94.1% (95% CI, 62.4 to 99.9), with 1 case in the vaccine group and 17 cases in the placebo group (Table 2). A total of 122 participants (27 in the vaccine group and 95 in the placebo group) had at least one episode of RSV-related acute respiratory infection, resulting in a vaccine efficacy of 71.7% (95% CI, 56.2 to 82.3) (Table 2). Four participants with RSV-related lower respiratory tract disease (group assignments blinded) received supplemental oxygen. Two participants (group assignments blinded) were hospitalized for RSV-related respiratory disease. No RSV-related deaths were reported. The cumulative incidence curves for RSV-related lower respiratory tract disease and RSV-related acute respiratory infection showed efficacy throughout follow-up (Fig. 2 and Fig. S1).

Two thirds of the cases of RSV-related lower respiratory tract disease and acute respiratory infection were associated with the RSV B subtype. RSV A– and RSV B–specific vaccine efficacy was observed against RSV-related lower respiratory tract disease (84.6% and 80.9%, respectively) and RSV-related acute respiratory infection (71.9% and 70.6%, respectively) (Table 2). Efficacy against RSV-related lower respiratory tract disease was more than 80% among participants 60 to 69 years of age and those 70 to 79 years of age. Among participants 80 years of age or older, too few cases (five) were reported for any conclusion of efficacy to be made (Table 2). Vaccine efficacy was also observed among participants with coexisting conditions (94.6%) and among those with prefrail status (92.9%) (Table 2). Among frail participants, efficacy results were inconclusive because only two cases of RSV-related lower respiratory tract disease occurred.

REACTOGENICITY AND SAFETY

The reactogenicity–immunogenicity cohort included 1799 participants, of whom 1757 were part of the solicited safety population (Fig. S2). In the solicited safety population, pain was the most common injection-site reaction for which data were solicited (in 60.9% of the participants in the vaccine group and in 9.3% of those in the placebo group), and fatigue was the most common solicited systemic reaction (in 33.6% and 16.1%, respectively) (Table 3). Most solicited reactions were mild or moderate and resolved within the 4-day solicitation period (mean duration, 1 to 2 days). In the solicited safety population, the incidence of unsolicited adverse events within 30 days after injection was balanced between the two groups (14.9% in the vaccine group and 14.6% in the placebo group); the incidence of grade 3 unsolicited adverse events was 1.4% in each group (Table 3).

In the exposed population, more participants who received vaccine than those who received placebo reported unsolicited adverse events (33.0% vs. 17.8%) and unsolicited adverse events related to vaccine or placebo (24.9% vs. 5.8%) within 30 days after injection (Table 3). These differences were due largely to reactogenicity events, primarily in participants who were not included in the solicited safety population and thus reported reactogenicity events as unsolicited adverse events.

In the exposed population, 22,666 participants (90.8%) completed 6 months of follow-up. During this period, 4.2% of the vaccine recipients and 4.0% of the placebo recipients reported a serious adverse event (Table 3); the most common system organ class was infections and infestations (Table S7). Until the database lock for the safety analyses, 10 vaccine recipients (0.1%) and 7 placebo recipients (0.1%) had a serious adverse event that was considered by the investigator to be related to vaccine or placebo (most common system organ class, nervous system disorders).

A total of 49 vaccine recipients (0.4%) and 58 placebo recipients (0.5%) died (most common system organ class, cardiac disorders) (Table S8). Three fatal serious adverse events (cardiopulmonary failure, pulmonary embolism, and unknown cause of death, in 1 participant each) were considered by the investigators to be related to vaccine or placebo administration (group assignments blinded). After a blinded assessment, alternative explanations for these deaths were considered to be plausible on the basis of time to onset and the presence of preexisting risk factors. In addition, the independent data and safety

Table 2. Vaccine Efficacy against First Occurrence of RSV-Related Lower Respiratory Tract Disease and RSV-Related Acute Respiratory Infection (Modified Exposed Population).*

End Point	RSVPreF3 OA Group				Placebo Group				Vaccine Efficacy (CI)†
	No. of Participants	No. of Events	Follow-up	Incidence Rate	No. of Participants	No. of Events	Follow-up	Incidence Rate	
			participant-yr	*no. of events/1000 participant-yr*			*participant-yr*	*no. of events/1000 participant-yr*	%
RSV-related lower respiratory tract disease									
Overall	12,466	7	6,865.9	1.0	12,494	40	6,857.3	5.8	82.6 (57.9 to 94.1)
Severe‡	12,466	1	6,867.9	0.1	12,494	17	6,867.7	2.5	94.1 (62.4 to 99.9)
According to RSV subtype§									
RSV A	12,466	2	6,867.4	0.3	12,494	13	6,868.9	1.9	84.6 (32.1 to 98.3)
RSV B	12,466	5	6,866.7	0.7	12,494	26	6,862.3	3.8	80.9 (49.4 to 94.3)
According to age group									
≥70 yr	5,503	3	3,015.0	1.0	5,515	19	3,020.9	6.3	84.4 (46.9 to 97.0)
≥80 yr	1,016	2	551.4	3.6	1,028	3	559.3	5.4	33.8 (–477.7 to 94.5)
60–69 yr	6,963	4	3,850.8	1.0	6,979	21	3,836.4	5.5	81.0 (43.6 to 95.3)
70–79 yr	4,487	1	2,463.6	0.4	4,487	16	2,461.6	6.5	93.8 (60.2 to 99.9)
According to baseline coexisting conditions¶									
Low or medium risk	8,235	4	4,495.8	0.9	8,367	23	4,560.6	5.0	82.4 (48.5 to 95.6)
High risk	4,231	3	2,370.0	1.3	4,127	17	2,296.6	7.4	82.9 (40.8 to 96.8)
No coexisting conditions of interest	7,529	6	4,094.1	1.5	7,633	22	4,148.1	5.3	72.5 (30.0 to 90.9)
≥1 Coexisting condition of interest	4,937	1	2,771.8	0.4	4,861	18	2,709.1	6.6	94.6 (65.9 to 99.9)

According to frailty status									
Frail	189	1	95.8	10.4	177	1	92.9	10.8	14.9 (–6638.7 to 98.9)
Prefrail	4,792	1	2,577.6	0.4	4,778	14	2,545.3	5.5	92.9 (53.4 to 99.8)
Fit	7,464	5	4,182.7	1.2	7,519	25	4,208.5	5.9	80.0 (46.7 to 94.0)
RSV-related acute respiratory infection									
Overall	12,466	27	6,858.7	3.9	12,494	95	6,837.8	13.9	71.7 (56.2 to 82.3)
According to RSV subtype§									
RSV A	12,466	9	6,865.2	1.3	12,494	32	6,862.3	4.7	71.9 (39.7 to 88.2)
RSV B	12,466	18	6,861.7	2.6	12,494	61	6,849.4	8.9	70.6 (49.6 to 83.7)

* The modified exposed population included all the participants who received the RSVPreF3 OA vaccine or placebo and did not report an RSV-related acute respiratory infection before day 15 after injection. Cases were reported up to the efficacy database-lock point of April 11, 2022. Cases of RSV-related lower respiratory tract disease were identified by the adjudication committee. Follow-up time was defined as the period from day 15 after injection until first occurrence of the event, database-lock point, or withdrawal. The incidence rate indicates the number of participants who reported at least one event per 1000 participant-years.

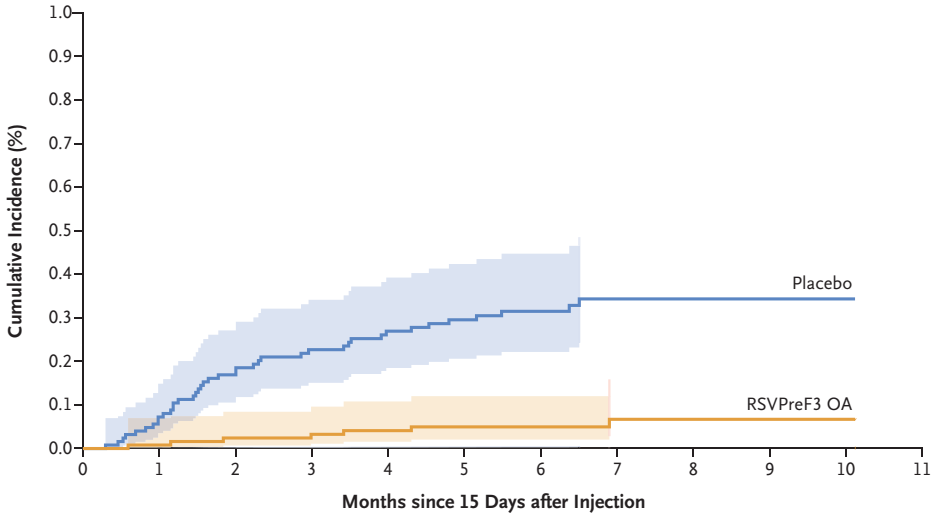
† Vaccine efficacy was estimated with the use of the Poisson method, with adjustment for age and geographic region, except for the analysis according to age, which was adjusted only for geographic region. A 96.95% confidence interval was used for the analysis of the primary end point (overall RSV-related lower respiratory tract disease), and a 95% confidence interval was used for all other end points. There was no adjustment for multiplicity, and the 95% confidence intervals should therefore not be used in place of hypothesis testing.

‡ Severe disease was determined on the basis of either of two case definitions: on the basis of clinical signs or investigator assessment or on the basis of receipt of supportive therapy. All 18 severe cases met the first case definition. Two of the 18 cases were confirmed by the adjudication committee as also meeting the second case definition (group assignments blinded). In addition to these 2 cases, another 2 participants received supplemental oxygen but did not have cases confirmed by the adjudication committee as meeting the second case definition at the time of the efficacy database-lock point.

§ The RSV subtype was unknown in one case of RSV-related lower respiratory tract disease and in two cases of RSV-related acute respiratory infection. All cases with unknown subtype were in the placebo group.

¶ Risk status (low or medium vs. high) was assessed on the basis of the Charlson comorbidity index.

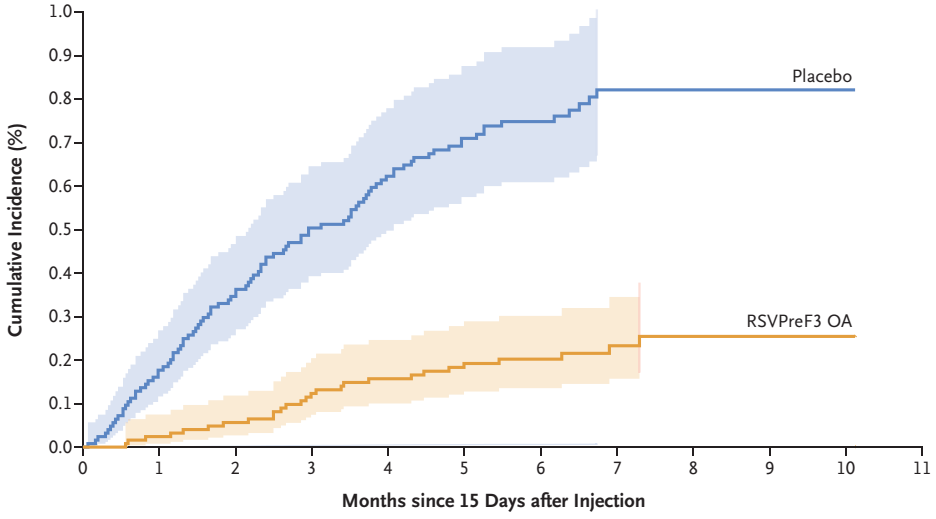
A RSV-Related Lower Respiratory Tract Disease



No. at Risk												
Placebo	12,494	12,403	12,290	11,887	11,640	11,022	8291	5464	2709	559	2	0
RSVPreF3 OA	12,466	12,392	12,286	11,892	11,655	11,046	8320	5495	2727	571	2	0

Cumulative No. of Cases												
Placebo	0	9	21	28	33	36	38	40	40	40	40	40
RSVPreF3 OA	0	1	3	4	5	6	6	7	7	7	7	7

B RSV-Related Acute Respiratory Infection



No. at Risk												
Placebo	12,494	12,390	12,268	11,853	11,597	10,973	8255	5441	2697	554	2	0
RSVPreF3 OA	12,466	12,390	12,282	11,881	11,641	11,029	8305	5481	2717	570	2	0

Cumulative No. of Cases												
Placebo	0	22	43	62	76	86	90	95	95	95	95	95
RSVPreF3 OA	0	3	7	15	19	23	24	26	27	27	27	27

Figure 2 (facing page). Cumulative Incidence of RSV-Related Lower Respiratory Tract Disease and RSV-Related Acute Respiratory Infection (Modified Exposed Population).

Cases were reported until the efficacy database-lock point of April 11, 2022. Cases of RSV-related lower respiratory tract disease were identified by the adjudication committee. Shaded areas indicate 96.95% confidence intervals for the incidence of RSV-related lower respiratory tract disease (Panel A) and 95% confidence intervals for the incidence of RSV-related acute respiratory infection (Panel B). Confidence intervals were computed at each case reported and end at the last reported case in each group.

monitoring committee did not raise concerns after review of the unblinded data. A total of 0.3% of the participants in each group reported potential immune-mediated diseases that started within 6 months after injection (Table 3 and Table S9). Until the database lock for the safety analyses, 7 vaccine recipients (0.1%) and 5 placebo recipients (<0.1%) had a potential immune-mediated disease that was considered by the investigators to be related to the administration of vaccine or placebo (Table 3).

IMMUNOGENICITY

The per-protocol immunogenicity cohort included 1702 participants. Between baseline and 1 month after injection, the concentrations or titers in the vaccine group increased by a factor of 13.1 for RSVPreF3-specific IgG antibodies, by a factor of 10.2 for RSV A neutralizing antibodies, and by a factor of 8.6 for RSV B neutralizing antibodies (Table S10).

DISCUSSION

In this international, phase 3 trial, a single dose of the RSVPreF3 OA vaccine had an efficacy of 82.6% against RSV-related lower respiratory tract disease, 94.1% against severe RSV-related lower respiratory tract disease, and 71.7% against RSV-related acute respiratory infection among adults 60 years of age or older during one RSV season. Vaccine efficacy was similar against the RSV A and B subtypes and was consistently high among participants 60 to 69 years of age and those 70 to 79 years of age, among prefrail older adults, and among those with coexisting conditions. Although mild-to-moderate local reactogenicity around the time of vaccination was common, the RSVPreF3 OA vaccine had an acceptable safety profile. These findings are summarized in plain language in Figure S3.

RSV vaccine development has been ongoing since the 1960s.[13] Previous vaccine candidates in older adults contained RSV F protein that was not stabilized in the prefusion conformation, which is now recognized as an important factor in eliciting potent neutralizing antibodies.[13] With supportive care remaining the clinical standard, an effective RSV vaccine could affect the burden of RSV-associated illness in older adults.

Our results indicate that the RSVPreF3 OA vaccine provided protection across the clinical spectrum of RSV disease, from mild upper respiratory tract infection to severe lower respiratory tract disease. Older adults, particularly those with coexisting conditions, are at increased risk for severe RSV disease and could benefit from an effective vaccine.[4,5,20-25] Although the vaccine efficacy estimates against RSV-related lower respiratory tract disease in the oldest age group (≥80 years) and in frail participants require longer follow-up owing to the lower numbers of participants and RSV cases in these subgroups, the efficacy that was observed among adults 70 to 79 years of age (93.8%), prefrail persons (92.9%), and those with coexisting conditions (94.6%) implies that the RSVPreF3 OA vaccine may be able to protect vulnerable older adults. Our results also indicate that the vaccine protected equally against the RSV A and B subtypes, a finding consistent with the neutralizing antibody response generated against both subtypes. Efficacy against RSV-related lower respiratory tract disease was observed throughout the median follow-up of 6.7 months, a finding that supports the efficacy of the RSVPreF3 OA vaccine over an entire RSV season. The trial is ongoing, including evaluations of the durability of protection beyond the first RSV season and the necessity of annual revaccination.

Other RSV prefusion F–based vaccine candi-

Table 3. Solicited and Unsolicited Adverse Events after Receipt of a Single Dose of the RSVPreF3 OA Vaccine or Placebo.*

Event	RSVPreF3 OA Group		Placebo Group	
	Participants	Incidence (95% CI)	Participants	Incidence (95% CI)
	no.	%	*no.*	%
Solicited safety population	879		878	
Solicited reactions				
Any solicited reaction	632	71.9 (68.8–74.9)	245	27.9 (25.0–31.0)
Any grade 3 solicited reaction	36	4.1 (2.9–5.6)	8	0.9 (0.4–1.8)
Solicited injection-site reactions				
Pain	535	60.9 (57.5–64.1)	81†	9.3 (7.4–11.4)
Erythema	66	7.5 (5.9–9.5)	7†	0.8 (0.3–1.6)
Swelling	48	5.5 (4.1–7.2)	5†	0.6 (0.2–1.3)
Solicited systemic reactions				
Fever‡	18	2.0 (1.2–3.2)	3	0.3 (0.1–1.0)
Headache	239	27.2 (24.3–30.3)	111	12.6 (10.5–15.0)
Fatigue	295	33.6 (30.4–36.8)	141	16.1 (13.7–18.7)
Myalgia	254	28.9 (25.9–32.0)	72	8.2 (6.5–10.2)
Arthralgia	159	18.1 (15.6–20.8)	56	6.4 (4.9–8.2)
Unsolicited adverse events				
Any unsolicited adverse event	131	14.9 (12.6–17.4)	128	14.6 (12.3–17.1)
Grade 3 unsolicited adverse event	12	1.4 (0.7–2.4)	12	1.4 (0.7–2.4)
Exposed population	12,467		12,499	
Unsolicited adverse events§				
Any adverse event	4,117	33.0 (32.2–33.9)	2,229	17.8 (17.2–18.5)
Any grade 3 adverse event	246	2.0 (1.7–2.2)	158	1.3 (1.1–1.5)
Adverse event related to vaccine or placebo	3,105	24.9 (24.1–25.7)	731	5.8 (5.4–6.3)
Grade 3 adverse event related to vaccine or placebo	112	0.9 (0.7–1.1)	25	0.2 (0.1–0.3)
Serious adverse events				
Any serious adverse event	522	4.2 (3.8–4.6)	506	4.0 (3.7–4.4)
Serious adverse event related to vaccine or placebo	10	0.1 (0.0–0.1)	7	0.1 (0.0–0.1)
Fatal serious adverse event	49	0.4 (0.3–0.5)	58	0.5 (0.4–0.6)
Fatal serious adverse event related to vaccine or placebo	3¶	—	3¶	—
Potential immune-mediated disease				
Any potential immune-mediated disease	40	0.3 (0.2–0.4)	34	0.3 (0.2–0.4)
Potential immune-mediated disease related to vaccine or placebo	7	0.1 (0.0–0.1)	5	<0.1 (0.0–0.1)

* The safety analysis included events up to the safety database-lock point of April 30, 2022. The solicited safety population included all the participants in the reactogenicity–immunogenicity cohort (see the Supplementary Appendix) who had solicited safety data available. Solicited reactions were those for which reports were solicited through 4 days after injection. Unsolicited adverse events were included up to 30 days after injection. Serious adverse events and events of potential immune-mediated disease were included up to 6 months after injection, and those that were considered by the investigator to be related to vaccine or placebo were included until the safety database-lock point. Fatal adverse events were included until the safety database-lock point. Grade 3 events of erythema and swelling were defined as erythema or swelling with a diameter of more than 100 mm, and grade 3 fever as a body temperature above 39.0°C. For all other adverse events, grade 3 indicated that normal everyday activities were prevented by the event. Relatedness to the administration of vaccine or placebo was determined by the investigator.

† In the placebo group, data on solicited injection-site reactions were available for 874 participants.

‡ Fever was defined as a body temperature of 38.0°C or higher.

§ Most unsolicited adverse events in the RSVPreF3 OA group were reactogenicity events, primarily in participants who were not included in the reactogenicity–immunogenicity cohort and who thus reported reactogenicity events as unsolicited adverse events.

¶ At the time of the database lock, group assignments for participants with fatal serious adverse events related to vaccine or placebo were still blinded to avoid participant-level unblinding of the trial team. The number of events shown in each group is actually the total number of events across the two groups.

dates for older adults have shown positive results in challenge studies involving younger adults.[26,27] One RSV prefusion F–based adenoviral vector vaccine candidate that elicited RSV-specific humoral and cell-mediated immunity showed promising preliminary efficacy results (estimates of 70 to 80%, depending on the case definition of RSV-related lower respiratory tract disease) in a proof-of-concept trial involving 5782 adults 65 years of age or older.[28] Together with our results, these data support the use of prefusion F as an effective antigen to prevent RSV-related lower respiratory tract disease in older adults.

The RSVPreF3 OA vaccine was more reactogenic than placebo, but most reactions were mild or moderate and transient. No imbalances were observed between the vaccine group and the placebo group in the overall incidences of serious adverse events, injection-related serious adverse events, fatal serious adverse events, potential immune-mediated diseases, or injection-related potential immune-mediated diseases, although careful monitoring is warranted as larger numbers of persons are vaccinated.

Strengths of the trial include its large sample size and the enrollment of a diverse older population (from different geographic areas and of various racial groups, ages, and statuses of coexisting conditions and frailty), which allow for extrapolation to the intended target population. Limitations of the trial include the small proportions of participants 80 years of age or older and frail participants and our limited ability to detect rare side effects. Conducting the trial during the second year of the Covid-19 pandemic posed operational challenges. Moreover, public health measures to limit Covid-19 reduced the spread of RSV and altered the timing of the RSV season, with most cases of RSV-related acute respiratory infection occurring earlier in the season than expected.[29-39] To mitigate these effects, we increased the sample size and started the trial in May, several months before the historical onset of the RSV season in the Northern Hemisphere.

In this trial, we found that a single dose of the RSVPreF3 OA vaccine was efficacious against RSV-related lower respiratory tract disease, RSV-related acute respiratory infection, and severe RSV-related lower respiratory tract disease among adults 60 years of age or older during one RSV season, regardless of RSV subtype and baseline coexisting conditions and frailty status. The vaccine had an acceptable safety profile.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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