ORIGINAL ARTICLE

Efficacy and Safety of an Ad26.RSV.preF–RSV preF Protein Vaccine in Older Adults

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) can cause serious lower respiratory tract disease in older adults, but no licensed RSV vaccine currently exists. An adenovirus serotype 26 RSV vector encoding a prefusion F (preF) protein (Ad26.RSV.preF) in combination with RSV preF protein was previously shown to elicit humoral and cellular immunogenicity.

METHODS

We conducted a randomized, double-blind, placebo-controlled, phase 2b, proof-of-concept trial to evaluate the efficacy, immunogenicity, and safety of an Ad26.RSV.preF–RSV preF protein vaccine. Adults who were 65 years of age or older were randomly assigned in a 1:1 ratio to receive vaccine or placebo. The primary end point was the first occurrence of RSV-mediated lower respiratory tract disease that met one of three case definitions: three or more symptoms of lower respiratory tract infection (definition 1), two or more symptoms of lower respiratory tract infection (definition 2), and either two or more symptoms of lower respiratory tract infection or one or more symptoms of lower respiratory tract infection plus at least one systemic symptom (definition 3).

RESULTS

Overall, 5782 participants were enrolled and received an injection. RSV-mediated lower respiratory tract disease meeting case definitions 1, 2, and 3 occurred in 6, 10, and 13 vaccine recipients and in 30, 40, and 43 placebo recipients, respectively. Vaccine efficacy was 80.0% (94.2% confidence interval [CI], 52.2 to 92.9), 75.0% (94.2% CI, 50.1 to 88.5), and 69.8% (94.2% CI, 43.7 to 84.7) for case definitions 1, 2, and 3, respectively. After vaccination, RSV A2 neutralizing antibody titers increased by a factor of 12.1 from baseline to day 15, a finding consistent with other immunogenicity measures. Percentages of participants with solicited local and systemic adverse events were higher in the vaccine group than in the placebo group (local, 37.9% vs. 8.4%; systemic, 41.4% vs. 16.4%); most adverse events were mild to moderate in severity. The frequency of serious adverse events was similar in the vaccine group and the placebo group (4.6% and 4.7%, respectively).

CONCLUSIONS

In adults 65 years of age or older, Ad26.RSV.preF–RSV preF protein vaccine was immunogenic and prevented RSV-mediated lower respiratory tract disease. (Funded by Janssen Vaccines and Prevention; CYPRESS ClinicalTrials.gov number, NCT03982199.)

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Respiratory syncytial virus (RSV) causes 64 million acute respiratory infections worldwide annually.[1] RSV is a leading cause of lower respiratory tract disease in older adults and in persons with underlying chronic cardiac or pulmonary conditions.[2] RSV in at-risk adults may cause pneumonia and exacerbate underlying conditions, potentially resulting in hospitalization, admission to an intensive care unit, and death.[3-9] Prevention of RSV-mediated lower respiratory tract disease in at-risk adults remains an unmet medical need because there are currently no licensed RSV vaccines.

Reports have suggested that virus-neutralizing antibody and T-cell responses are important in order for an RSV vaccine to provide durable protection from infection.[10-12] The prefusion conformation of RSV F (RSV preF) protein is the most immunogenic RSV protein.[13,14] The investigational vaccine that we evaluated in the trial reported here is made up of a recombinant, replication-incompetent, adenovirus serotype 26 vector encoding a conformation-stabilized RSV preF protein (Ad26.RSV.preF) and recombinant RSV preF protein, with no adjuvant. In preclinical studies, Ad26.RSV.preF induced humoral and T-cell responses[15-17]; the addition of RSV preF protein to Ad26.RSV.preF improved humoral responses while maintaining cellular responses and provided protection from RSV challenge superior to that provided by either component alone.[18] In adults, Ad26.RSV.preF has been shown to have humoral and cellular immunogenicity and to reduce the risk of RSV infection, disease severity, and viral loads after RSV challenge.[19] In a recent clinical study, the addition of RSV preF protein to Ad26.RSV.preF improved humoral immunogenicity without affecting Ad26.RSV.preF-induced cellular immune responses.[20] We evaluated the efficacy, immunogenicity, and safety of an Ad26.RSV.preF–RSV preF protein vaccine for the prevention of RSV-mediated lower respiratory tract disease in adults who were 65 years of age or older.

Methods

Trial Design and Oversight

We conducted CYPRESS, a double-blind, placebo-controlled, phase 2b, proof-of-concept trial, at 40 centers in the United States. The trial protocol, including the amendments, was approved by the ethics committee or institutional review board at each participating center and is available with the full text of this article at NEJM.org. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent. An independent data and safety monitoring committee monitored safety outcomes throughout the trial.

The trial was designed and conducted and the data analyzed and interpreted by Janssen Vaccines and Prevention. Trial-site investigators collected and contributed to interpretation of the data. All the data were available to all authors, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and who collectively decided to submit the manuscript for publication. Agreements with the sponsor requiring the authors to maintain confidentiality of the data were in place. Medical writers, funded by the sponsor, assisted with writing the manuscript.

Trial Participants

Adults 65 years of age or older who were in good or stable health were eligible for participation. We included a subgroup of participants who were at increased risk for severe RSV-mediated lower respiratory tract disease (i.e., those with mild-to-moderate chronic cardiac or pulmonary disease or those who met a broader definition of increased risk that also included chronic kidney disease and diabetes mellitus). Eligibility details are provided in the Supplementary Appendix, available at NEJM.org.

Trial Procedures

Participants were randomly assigned in a 1:1 ratio (with stratification according to risk level [increased or nonincreased risk] and age group [65 to 74 years, 75 to 84 years, or ≥85 years]) to receive one intramuscular injection of Ad26.RSV.preF–RSV preF protein vaccine (1 ml; 1×10^{11} viral particles of Ad26.RSV.preF plus 150 μg of RSV preF protein) or saline placebo on day 1. Injections in both groups occurred between August 5, 2019, and November 13, 2019. Investigators, participants, site personnel, and the sponsor were unaware of the randomization assignments.

Twice-weekly surveillance for new or worsening symptoms of acute respiratory infection was conducted from the time of the injection until the end of the RSV season, which was truncated at March 20, 2020 (from April 30, 2020), as a re-

sult of the emergence of the coronavirus disease 2019 (Covid-19) pandemic. Participants with symptoms of acute respiratory infection completed a daily electronic diary, including the Respiratory Infection Intensity and Impact Questionnaire (RiiQ) and the Return to Usual Health question (a yes-or-no question: "Have you returned to your usual health today?"), from day 1 (i.e., the day of symptom onset) until symptoms resolved or returned to baseline for at least 2 days. On day 1 or 2 of acute respiratory infection, participants obtained their own nasal midturbinate swab samples. On day 3, 4, or 5, midturbinate swab and sputum samples (when possible) were obtained during clinical assessments. Reverse-transcriptase–polymerase-chain-reaction (RT-PCR) confirmation of RSV infection from nasal and sputum samples was conducted centrally with the use of a Food and Drug Administration (FDA)–approved test (Xpert FLU RSV XC assay, Cepheid). Additional details of the trial procedures are provided in the Supplementary Appendix.

EFFICACY ASSESSMENTS

In the absence of a standardized case definition for RSV-mediated lower respiratory tract disease, we evaluated different case definitions that were based on participant- or clinician-reported symptoms. The primary end point was the first occurrence of RT-PCR–confirmed RSV-mediated lower respiratory tract disease according to one of three case definitions: three or more symptoms of lower respiratory tract infection (case definition 1, the most severe disease), two or more symptoms of lower respiratory tract infection (case definition 2), and either two or more symptoms of lower respiratory tract infection or one or more symptoms of lower respiratory tract infection plus at least one systemic symptom (case definition 3); the symptoms are defined in Table S1 in the Supplementary Appendix. Case definitions were nested according to disease severity — that is, cases meeting case definition 1 also met case definitions 2 and 3, and those meeting case definition 2 also met case definition 3.

The per-protocol efficacy population included all participants who underwent randomization and received the assigned injection, excluding participants with protocol deviations that would be expected to affect efficacy, those with onset of RSV-mediated acute respiratory infection within 14 days after the injection, and those who discontinued participation within 14 days after the injection. Prespecified subgroups for the analysis of the primary efficacy end point included participants at increased risk for severe RSV-mediated lower respiratory tract disease, as well as age-based subgroups. The secondary efficacy end point was the first occurrence of any RT-PCR–confirmed RSV-mediated acute respiratory infection. Primary analyses of vaccine efficacy were conducted at the end of the first RSV season. Vaccine efficacy ([1 − incidence rate ratio] × 100) was calculated on the basis of an exact Poisson regression model with the incidence rate (number of cases over the follow-up time) as the dependent variable and the vaccination group, age, and risk status for severe RSV disease as independent variables.

IMMUNOGENICITY ASSESSMENTS

Blood samples were obtained at days 1, 15, 85, and 169 from participants in the per-protocol immunogenicity population (i.e., all participants who underwent randomization and received the assigned injection and for whom immunogenicity data were available, excluding those with protocol deviations that were likely to affect immunogenicity). Samples obtained after an RSV infection and samples obtained outside of prespecified visit windows were excluded from immunogenicity analyses. RSV A2 and RSV B neutralizing antibodies were measured with the use of virus-neutralization assays. Serum preF IgG antibodies were measured with an enzyme-linked immunosorbent assay, and RSV-F–specific T-cell responses were measured with an interferon-γ enzyme-linked immunosorbent spot assay. Details of the assays are provided in the Supplementary Appendix. Prespecified subgroups for immunogenicity analyses included participants at increased risk for severe RSV-mediated lower respiratory tract disease and age-based subgroups.

SAFETY ASSESSMENTS

Data on serious adverse events and adverse events leading to discontinuation of participation in the trial were collected for the primary safety population (i.e., the full analysis population, which included all participants who underwent randomization and received the assigned injection) for 6 months after the injection or until the end of the RSV season, whichever occurred later. Solicited and unsolicited adverse events were recorded for 7 and 28 days after the

injection, respectively, in a safety subpopulation (a subset of the full analysis population in which approximately 50% of participants were at increased risk for severe RSV disease). Adverse events were graded with an adapted FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).[21]

STATISTICAL ANALYSIS

The sample size was determined under the assumption that vaccine efficacy would be 70% (against disease meeting case definition 2), the incidence of RSV-mediated lower respiratory tract disease would be 0.75% (against disease meeting case definition 2) among participants who received placebo, and 10% of the participants would be excluded. Under these assumptions, and with three nested primary end points and a one-sided significance level of 0.05, a total of 2750 participants per group would provide 80% power to detect a vaccine efficacy greater than 0% for case definition 2 (total sample, 5500 participants). Simulations showed that the power to show significance for any case definition, after multiplicity correction to control type I error at 5%, was similar to that for case definition 2 alone without multiplicity correction.

The analysis of the primary efficacy end point evaluated the number of participants with at least one episode of RSV-mediated lower respiratory tract disease (defined according to the three case definitions) in the vaccine group as compared with the placebo group in the per-protocol efficacy population. The null hypothesis (i.e., that vaccine efficacy would be ≤0% for all three case definitions) was tested against the alternative hypothesis (that vaccine efficacy would be >0% for at least one case definition). The significance level for the primary efficacy analysis was controlled at 5% (one-sided) and adjusted to account for multiple end points with the use of a Spiessens–Debois method[22] and for multiple analyses with the use of the Pocock rule; the methods were combined to calculate a defined significance cutoff value. For each primary endpoint case definition, an exact Poisson regression was fitted, with the number of cases during follow-up used as the dependent variable and the randomly assigned group and stratification factors used as independent variables. If the P value was below the cutoff for one or more primary end-point case definitions, proof of concept was shown, and multiplicity-corrected two-sided confidence intervals around the vaccine efficacy value were calculated. As a post hoc analysis, two-sided P values were also calculated. Vaccine efficacy for secondary efficacy end points was analyzed similarly. Sensitivity analyses were performed for vaccine efficacy as described in the Supplementary Appendix. Efficacy and immunogenicity analyses were performed in the overall per-protocol efficacy and immunogenicity populations, respectively, and in subgroups defined according to age and risk level, with no formal adjustments. For participants with RSV-mediated acute respiratory infections, the area under the curve (AUC) of the total RiiQ respiratory and systemic symptom scores was calculated. The time to the return to usual health among participants with RSV-mediated acute respiratory infections was calculated by Kaplan–Meier analysis. All statistical analyses were performed with the use of SAS software, version 9.4.

RESULTS

PARTICIPANTS

Overall, 5782 participants underwent randomization and received the Ad26.RSV.preF–RSV preF protein vaccine or placebo (full analysis population; 2891 participants in each group); the per-protocol efficacy population included 5592 participants, 2791 of whom received vaccine and 2801 of whom received placebo (Fig. 1). In total, 207 participants discontinued participation early (107 in the vaccine group and 100 in the placebo group) (Table S2).

Demographic characteristics were similar in the vaccine and placebo groups (Table 1). The participants were representative of adults who are at risk for severe RSV infection (Table S3). The median age was 71 years; 73.6% of the participants were 65 to 74 years of age, 23.7% were 75 to 84 years of age, and 2.6% were 85 years of age or older. The percentages of participants with additional risk factors for severe RSV-mediated disease were 25.4% when the narrower definition (chronic cardiac or pulmonary disease) was used and 40.1% when the broader definition (chronic cardiac or pulmonary disease, chronic kidney disease, or diabetes mellitus) was used.

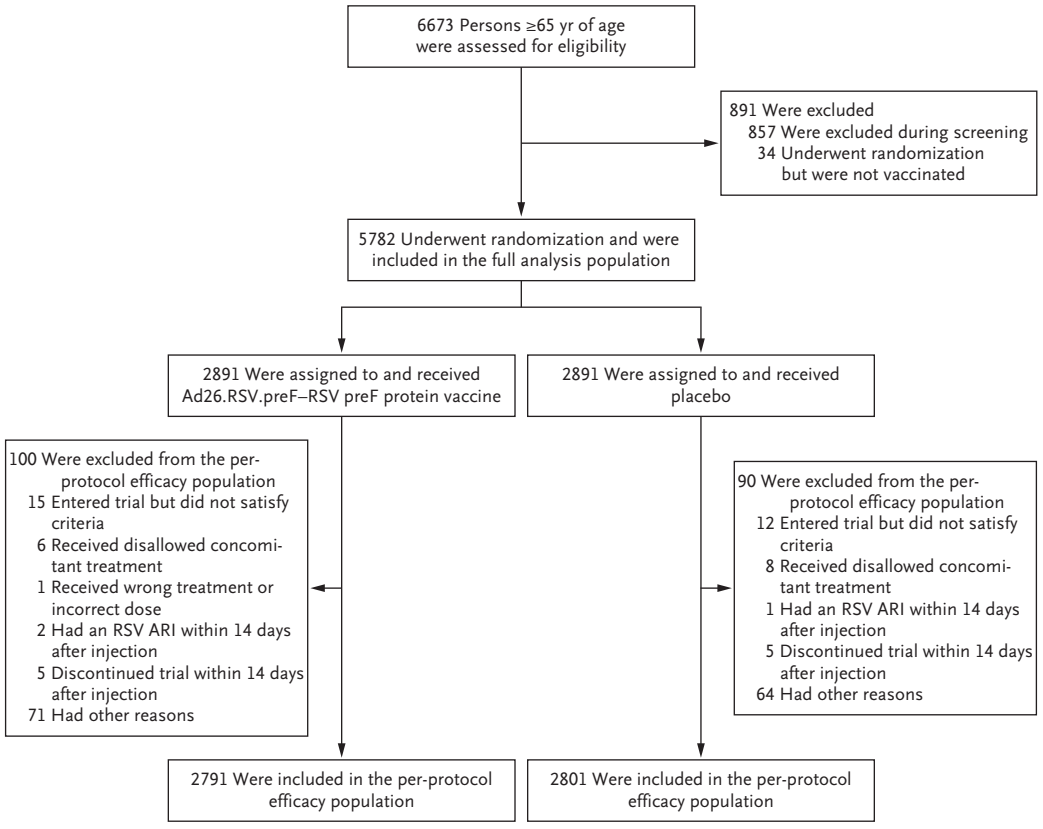

Figure 1. Enrollment and Randomization.

Ad26 denotes adenovirus serotype 26 vector, ARI acute respiratory infection, preF prefusion conformation–stabilized RSV F protein, and RSV respiratory syncytial virus.

EFFICACY

In the per-protocol efficacy population, 13 RSV acute respiratory infections were reported in the vaccine group, as compared with 43 in the placebo group. RSV-mediated lower respiratory tract disease meeting case definition 1 was reported in 6 participants who received vaccine and in 30 participants who received placebo, for vaccine efficacy against illness meeting case definition 1 of 80.0% (94.2% confidence interval [CI], 52.2 to 92.9; P<0.001) (Fig. 2A). Vaccine efficacy against illness meeting case definition 2 was 75.0% (94.2% CI, 50.1 to 88.5; P<0.001). For case definition 3, which captured all RSV-mediated acute respiratory infections in our trial, vaccine efficacy was 69.8% (94.2% CI, 43.7 to 84.7; P<0.001). The results of sensitivity analyses, including the analysis in the full analysis population, were in agreement with those of the primary analysis (Fig. S1). The vaccine was efficacious in subgroups defined according to age (Fig. S2) and risk level for severe RSV-mediated lower respiratory tract disease (Fig. S3).

For participants with RSV-mediated acute respiratory infections, the total RiiQ respiratory and systemic symptom scores were lower (indicating less severe symptoms) among vaccine recipients than among placebo recipients (median AUC [expressed as score × hour], 39 [interquartile range, 11 to 74] vs. 128 [interquartile range, 58 to 242]) (Fig. 2B). In addition, the median time to the return to usual health after RSV-mediated acute respiratory infections was 19 days in the vaccine group, as compared with 30 days in the placebo group (hazard ratio, 2.81; 95% CI, 1.01 to 7.86) (Fig. 2C).

IMMUNOGENICITY

The immunogenicity population included 195 participants (97 in the vaccine group and 98 in

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

Characteristic	Vaccine (N=2891)	Placebo (N=2891)	Total (N=5782)
Median age (range) — yr	71 (65–94)	71 (65–98)	71 (65–98)
Age distribution — no. (%)			
65–74 yr	2126 (73.5)	2132 (73.7)	4258 (73.6)
75–84 yr	688 (23.8)	685 (23.7)	1373 (23.7)
≥85 yr	77 (2.7)	74 (2.6)	151 (2.6)
Sex — no. (%)			
Female	1640 (56.7)	1694 (58.6)	3334 (57.7)
Male	1251 (43.3)	1197 (41.4)	2448 (42.3)
Race or ethnic group — no. (%)†			
White	2658 (91.9)	2690 (93.0)	5348 (92.5)
Black	169 (5.8)	148 (5.1)	317 (5.5)
Asian	15 (0.5)	17 (0.6)	32 (0.6)
American Indian or Alaska Native	8 (0.3)	9 (0.3)	17 (0.3)
Native Hawaiian or other Pacific Islander	16 (0.6)	5 (0.2)	21 (0.4)
Multiple	9 (0.3)	14 (0.5)	23 (0.4)
Not reported, unknown, or missing data	16 (0.6)	8 (0.3)	24 (0.4)
Hispanic or Latino ethnic group			
Hispanic or Latino	84 (2.9)	97 (3.4)	181 (3.1)
Not Hispanic or Latino	2779 (96.1)	2773 (95.9)	5552 (96.0)
Not reported, unknown, or missing data	28 (1.0)	21 (0.7)	49 (0.8)
Smoking status — no. (%)			
Smoker	1297 (44.9)	1255 (43.4)	2552 (44.1)
Nonsmoker	1594 (55.1)	1635 (56.6)	3229 (55.8)
Not reported	0	1 (<0.1)	1 (<0.1)
Increased risk of severe RSV disease, narrower definition — no. (%)‡	740 (25.6)	727 (25.1)	1467 (25.4)
Congestive heart failure	58 (7.8)	54 (7.4)	112 (7.6)
Other chronic cardiac disease	330 (44.6)	330 (45.4)	660 (45.0)
Chronic obstructive pulmonary disease	219 (29.6)	208 (28.6)	427 (29.1)
Asthma	266 (35.9)	250 (34.4)	516 (35.2)
Other chronic pulmonary disease	30 (4.1)	37 (5.1)	67 (4.6)
Increased risk of severe RSV disease, broader definition — no. (%)§	1184 (41.0)	1136 (39.3)	2320 (40.1)

* The vaccine was an adenovirus serotype 26 vector encoding a prefusion F (preF) protein (Ad26.RSV.preF) in combination with respiratory syncytial virus (RSV) preF protein. The full analysis population included all participants who underwent randomization and received the assigned injection. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participants.
‡ Participants were considered to be at increased risk for severe RSV-mediated lower respiratory tract disease if they had chronic cardiac or pulmonary conditions, such as congestive heart failure, chronic obstructive pulmonary disease, or asthma.
§ The broader definition of an increased risk of severe RSV-mediated lower respiratory tract disease included chronic kidney disease and diabetes in addition to the conditions included in the narrower definition.

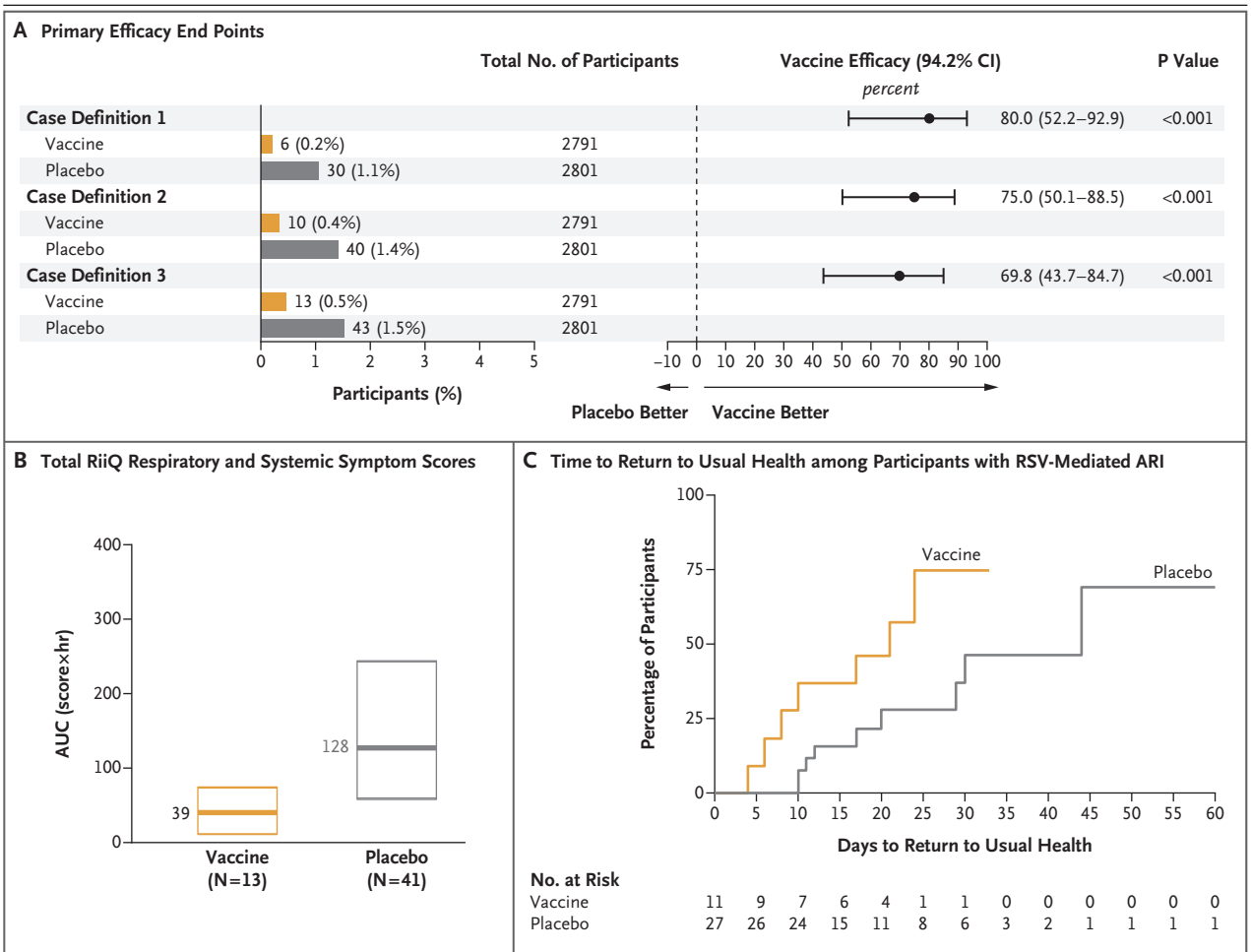

Figure 2. Vaccine Efficacy.

Panel A shows the efficacy of Ad26.RSV.preF–RSV preF protein vaccine for the prevention of reverse-transcriptase–polymerase chain reaction (RT-PCR)–confirmed RSV-mediated lower respiratory tract disease according to three different case definitions: three or more symptoms of lower respiratory tract infection (definition 1), two or more symptoms of lower respiratory tract infection (definition 2), and either two or more symptoms of lower respiratory tract infection or one or more symptoms of lower respiratory tract infection plus at least one systemic symptom (definition 3). Case definition 3 captured all RT-PCR–confirmed RSV-mediated acute respiratory infections in this trial. Vaccine efficacy was calculated with the use of a Poisson regression, including the randomly assigned group and stratification variables as covariates. To control the false positivity rate for multiplicity, the Spiessens–Debois method was applied. The confidence interval for vaccine efficacy is a 90% confidence interval corrected for multiplicity. The multiplicity-corrected alpha level used to define significance was 0.02895 (one-sided) or 0.0579 (two-sided). The one-sided (prespecified) and two-sided (post hoc) P values were less than 0.001 for all three case definitions used for the primary end point. Panel B shows the total respiratory and systemic symptom severity among participants with RT-PCR–confirmed RSV-mediated acute respiratory infections as measured with the Respiratory Infection Intensity and Impact Questionnaire (RiiQ); higher area-under-the-curve (AUC) values indicate greater symptom severity. The top and bottom of the box indicate the third and first quartiles, respectively, and the thick horizontal line indicates the median. Panel C shows the time to the return to usual health for participants with RT-PCR–confirmed RSV-mediated acute respiratory infection.

the placebo group), among whom 48 (24.6%) were at increased risk for severe RSV disease because they had chronic cardiac or pulmonary disease, 64 (32.8%) were at increased risk because they had chronic cardiac or pulmonary disease, chronic kidney disease, or diabetes mellitus (i.e., the broader definition of increased risk), and 53 (27.2%) were at in-

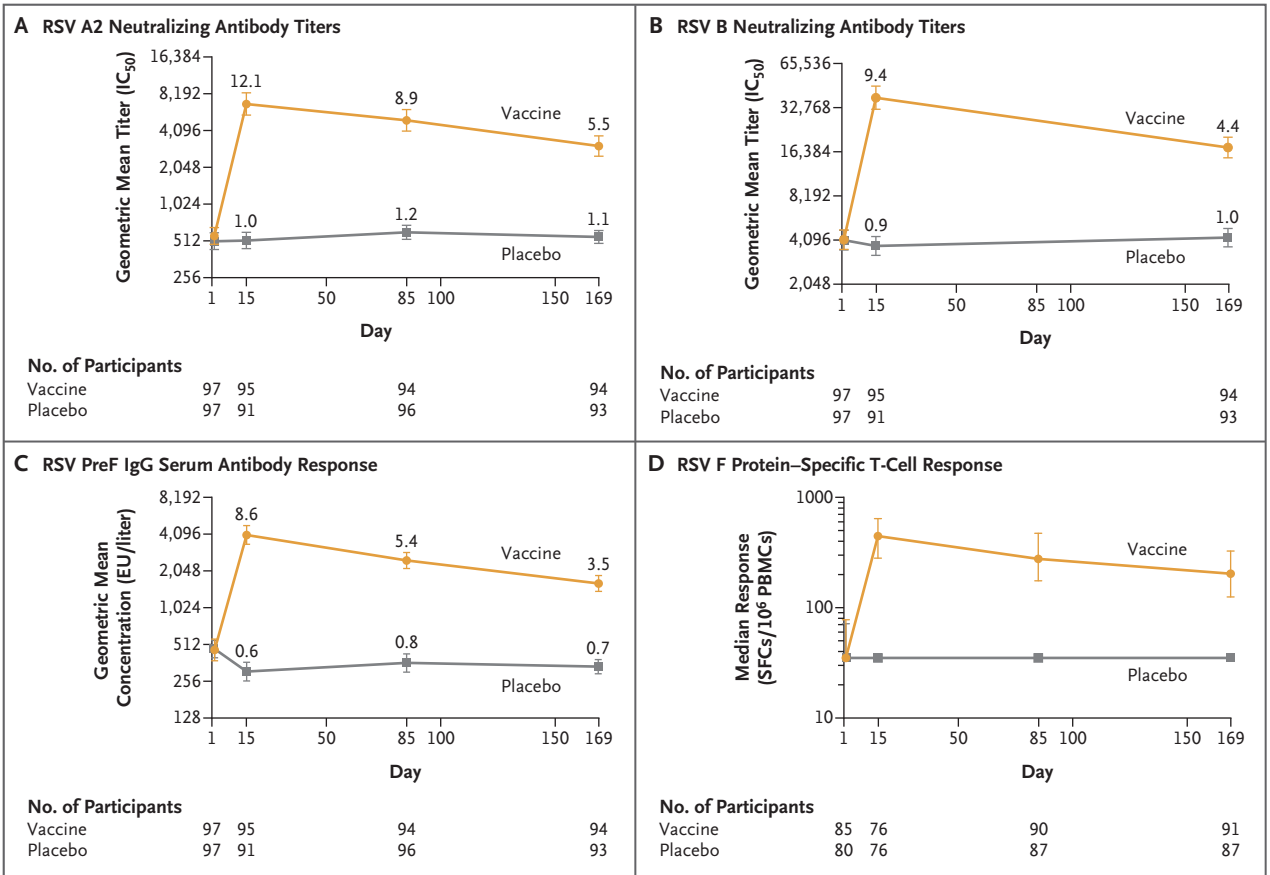

Figure 3. Immunogenicity of the Ad26.RSV.preF–RSV preF Protein Vaccine.

Panel A shows RSV A2 neutralizing antibodies, Panel B RSV B neutralizing antibodies, Panel C the RSV preF IgG serum antibody response (measured by enzyme-linked immunosorbent assay [ELISA]), and Panel D the RSV F protein–specific T-cell response (measured by interferon-γ enzyme-linked immunospot assay) at days 1, 15, and 169 in the immunogenicity population. The data points in Panels A, B, and C are geometric means; I bars indicate the 95% confidence interval. The data points in Panel D are medians; I bars indicate the interquartile range. Numbers associated with data points in Panels A, B, and C are the geometric mean factor increases at the indicated time points. EU denotes ELISA units, IC_{50} 50% inhibitory concentration, PBMC peripheral blood mononuclear cell, and SFC spot-forming cell.

creased risk because they were 75 years of age or older.

In the vaccine group, the geometric mean titer of RSV A2 neutralizing antibodies increased by a factor of 12.1 from baseline to day 15 and remained at 5.5 times the baseline value at day 169 (Fig. 3A). Similar results were observed for RSV B neutralizing antibodies (Fig. 3B). The geometric mean concentration of serum preF IgG antibodies had increased by a factor of 8.6 at day 15 and remained at 3.5 times the baseline level at day 169 (Fig. 3C). The median RSV-F–specific T-cell frequency increased from 34 spot-forming cells per 10^6 peripheral blood mononuclear cells (PBMCs) (interquartile range, 34 to 75) at baseline to 444 spot-forming cells per 10^6 PBMCs (interquartile range, 279 to 641) at day 15 and remained above baseline at day 169 (201 spot-forming cells per 10^6 PBMCs; interquartile range, 123 to 324) (Fig. 3D). No changes in immunogenicity measures were observed in the placebo group (Fig. 3). No effect of age or risk factors on vaccine-induced immunogenicity was observed (Figs. S4 through S7), and limited data suggested that there was no effect of preexisting Ad26-neutralizing antibodies (Fig. S8).

SAFETY

Safety outcomes are summarized in Table 2. In the primary safety population, the percentages of participants who had a serious adverse event were similar in the vaccine group and the placebo group (4.6% and 4.7%, respectively), as

Table 2. Summary of Adverse Events.*

Adverse Event	Vaccine	Placebo
	no. of participants with event/total no. (%)	
Solicited adverse events (safety subpopulation, within 7 days after injection)		
Any event	179/348 (51.4)	70/347 (20.2)
Event of grade ≥3	11/348 (3.2)	2/347 (0.6)
Local event†	132/348 (37.9)	29/347 (8.4)
Local event of grade ≥3†	6/348 (1.7)	1/347 (0.3)
Systemic event‡	144/348 (41.4)	57/347 (16.4)
Systemic event of grade ≥3‡	7/348 (2.0)	1/347 (0.3)
Unsolicited adverse events (safety subpopulation, within 28 days after injection)		
Any event	58/348 (16.7)	50/347 (14.4)
Event of grade ≥3	6/348 (1.7)	5/347 (1.4)
Event thought to be related to vaccine or placebo	18/348 (5.2)	8/347 (2.3)
Serious adverse events and adverse events leading to discontinuation of participation in trial (primary safety population)		
Serious adverse event	132/2891 (4.6)	136/2891 (4.7)
Serious adverse event thought to be related to vaccine or placebo	0	0
Adverse event with fatal outcome	8/2891 (0.3)	12/2891 (0.4)
Adverse event with fatal outcome thought to be related to vaccine or placebo	0	0
Adverse event leading to permanent discontinuation of participation in trial	10/2891 (0.3)	15/2891 (0.5)

* The primary safety population was the full analysis population (all participants who underwent randomization and received the assigned injection). The safety subpopulation was a subgroup of the full analysis population in which approximately 50% of participants were at increased risk for severe RSV disease.
† Solicited local adverse events included erythema, injection-site pain or tenderness, and swelling.
‡ Solicited systemic adverse events included fatigue, headache, myalgia, nausea, and pyrexia.

were the percentages of participants who had adverse events leading to early discontinuation (0.3% and 0.5%, respectively) or fatal adverse events (0.3% and 0.4%, respectively); none of the events were considered by the investigator to be related to the vaccine or placebo. Details of the serious adverse events are provided in Table S4, and details of the adverse events leading to discontinuation of participation in the trial are provided in Table S5.

The safety subpopulation included 695 participants (348 in the vaccine group and 347 in the placebo group), 48.0% of whom were at increased risk because of chronic cardiac or pulmonary disease. Solicited local adverse events were reported by 37.9% of the participants who received vaccine and by 8.4% of those who received placebo; events of grade 3 or higher were reported by 1.7% and 0.3%, respectively (Fig. S9A). The most common solicited local adverse event was injection-site pain or tenderness. The median duration of solicited local adverse events was 1 to 2.5 days.

In the safety subpopulation, solicited systemic adverse events were reported by 41.4% of participants who received vaccine and by 16.4% of those who received placebo; events of grade 3 or higher were reported by 2.0% and 0.3%, respectively. The most common solicited systemic adverse events included fatigue, headache, and myalgia (Fig. S9B). The median duration of solicited systemic adverse events was 1 to 2 days. Unsolicited adverse events were reported by 16.7% of the participants who received vaccine and by 14.4% of those who received placebo. Details of the unsolicited adverse events of grade 3 or higher are provided in Table S5. No safety signal was observed in the subgroup of participants who were at increased risk for severe disease (Table S6).

DISCUSSION

In this trial, one dose of the Ad26.RSV.preF–RSV preF protein vaccine was efficacious against RSV-mediated lower respiratory tract disease in adults 65 years of age or older. Vaccine efficacy in the overall study population was 80.0% for case definition 1, the case definition indicating the most severe disease, and was 69.8% for any RSV acute respiratory infection. In addition, vaccine recipients who had RSV acute respiratory infections reported less severe symptoms and a faster return to usual health than placebo recipients.

Immunogenicity results were consistent with those of previous studies of Ad26.RSV.preF–RSV preF protein.[20] Titers of neutralizing antibodies against RSV A and RSV B, levels of serum RSV preF IgG antibodies, and RSV-F–specific interferon-γ T-cell frequencies were increased among vaccine recipients at day 15 and stayed above baseline for at least 6 months.

An incomplete understanding of the aspects of immunity critical for protection from RSV infection has hindered vaccine development and complicated interpretation of vaccine-induced serologic immune responses. Although no correlate of protection from RSV infection is universally accepted, the available evidence from studies in animals and in humans suggests that, in addition to neutralizing antibodies, RSV-specific T-cell responses may be important for protective immunity.[23-25] Some studies have shown that older adults have lower RSV-F–specific T-cell responses than persons in younger age groups,[26,27] which suggests that impairment of T-cell responses with age may contribute to age-related RSV disease severity. Thus, the RSV-F–specific T-cell responses that were observed in our trial may have contributed to the efficacy of the Ad26.RSV.preF–RSV preF protein vaccine.

The Ad26.RSV.preF–RSV preF protein vaccine maintained vaccine efficacy for the prevention of RSV-mediated lower respiratory tract disease among participants who were 75 years of age or older and among participants with additional risk factors for severe RSV disease; however, these subgroups included fewer participants, which resulted in wide confidence intervals. The humoral and cellular immune responses across age groups are notable, given that some vaccines (e.g., vaccines against influenza,[28] pneumococcal illnesses,[29,30] and Covid-19[31]) show reduced immunogenicity and efficacy in older persons. Although the data are limited, it is encouraging that vaccine efficacy and immunogenicity were maintained in the subgroup of participants with an increased risk of severe disease.

The Ad26.RSV.preF–RSV preF protein vaccine had an acceptable safety profile. No vaccine-related severe adverse events were reported. Safety outcomes were consistent with those that have previously been reported,[19,32] despite the inclusion of participants who were at increased risk for severe disease. No cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) have been identified in Janssen clinical studies in the RSV vaccine program[19,32,33] or in other non–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Ad26-vectored vaccine programs, including vaccine-development programs for Ebola virus,[34-38] human immunodeficiency virus,[39-42] human papillomavirus, and Zika virus,[43] or during the Ebola vaccination campaigns; these observations are based on an overall experience of more than 290,000 recipients of Ad26-vectored vaccines as of September 2022, although with variable follow-up.

The positive results of this trial contrast with those of previous clinical trials of RSV postfusion F (postF)–based vaccines, which may have been insufficiently immunogenic.[44-48] Two clinical trials involving adults 60 years of age or older (evaluating an RSV postF–based vaccine[49] and a nanoparticle-based RSV-F vaccine[50]) did not show protection against RSV-mediated illness. RSV preF elicits a stronger immune response in humans[13,14]; recent phase 1 and 2 clinical studies of other RSV preF–based vaccines have also shown encouraging immunogenicity and efficacy results.[51-54]

The major strengths of this trial are the large sample size and the inclusion of participants at increased risk for severe RSV-mediated disease, who are often excluded from clinical trials because of the potential for excessive adverse events and decreased immune responses. The acceptable safety profile and efficacy in this subgroup is reassuring for care providers who may eventually recommend the vaccine. One limitation of the trial was the shortened surveillance period during the first RSV season. In addition, few participants 85 years of age or older were enrolled in the trial, and low numbers of infections in this subgroup precluded meaningful analyses of efficacy and immunoge-

nicity. Our trial also had overrepresentation of White participants and underrepresentation of other demographic groups, including Black, Asian, and Hispanic participants, as compared with the U.S. population. The ongoing phase 3 trial recruited participants worldwide, with efforts to increase participant diversity. Further trials, including this trial, are ongoing, with extended follow-up periods to strengthen the evidence of the efficacy, immunogenicity (including detailed immunoprofiling of vaccine-induced T-cell responses), and safety of the Ad26.RSV.preF–RSV preF protein vaccine and the durability of vaccine efficacy, including evaluations in populations at increased risk for severe disease.

In this trial, the Ad26.RSV.preF–RSV preF protein vaccine was efficacious against RSV-mediated lower respiratory tract disease and elicited humoral and cellular immune responses, with an acceptable safety profile, in adults who were 65 years of age or older. Vaccine efficacy, immunogenicity, and safety were maintained across subgroups defined according to age and the presence of additional risk factors for severe RSV-mediated disease. These results have led to continued evaluation of this vaccine in phase 3 trials.

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