Efficacy, safety, and immunogenicity of the AS01$_E$-adjuvanted respiratory syncytial virus prefusion F protein vaccine (RSVPreF3 OA) in older adults over three respiratory syncytial virus seasons (AReSVi-006): a multicentre, randomised, observer-blinded, placebo-controlled, phase 3 trial

Michael G Ison, Alberto Papi*, Eugene Athan, Robert G Feldman, Joanne M Langley, Dong-Gun Lee, Isabel Leroux-Roels, Federico Martinon-Torres, Tino F Schwarz, Richard N van Zyl-Smit, Susanna Cuadripani, Quentin Deraedt, Nancy Dezutter, Catherine Gerard, Laurence Fissette, Stebin Xavier, Marie-Pierre David, Aurélie Olivier, Marie Van der Wielen, Dominique Descamps, on behalf of the AReSVi-006 study group†*

Summary

Background Duration of protection after respiratory syncytial virus (RSV) vaccination is unknown. This study aimed to evaluate efficacy and safety over three RSV seasons of the AS01$_E$-adjuvanted RSV prefusion F protein-based vaccine (RSVPreF3 OA) against RSV-related lower respiratory tract disease (RSV-LRTD) in older adults.

Methods In this randomised, observer-blind, placebo-controlled, phase 3 trial (AReSVi-006), participants aged 60 years or older in 275 centres (ie, GP practices and clinical research sites) across 17 countries in Africa, Asia, Oceania, Europe, and North America were randomly assigned (1:1) to receive RSVPreF3 OA or placebo before RSV season one. RSVPreF3 OA recipients were re-randomly assigned (1:1) before RSV season two to receive a second RSVPreF3 OA dose (RSV revaccination group) or placebo (RSV single-dose group). Recipients of placebo before RSV season one also received placebo before season two (placebo group). The primary objective (efficacy against first occurrence of RSV-LRTD over one RSV season) was reported previously. Confirmatory secondary objectives were to demonstrate efficacy over three RSV seasons of a single RSVPreF3 OA dose and of a first dose followed by revaccination 1 year later, against RSV-LRTD, overall and by RSV subtype (success criteria: lower limits of two-sided CIs around efficacy estimates >20% [RSV-LRTD] and >0% [RSV-LRTD by RSV subtype]). This study is registered with ClinicalTrials.gov, NCT04886596, and is complete.

Findings Participants were enrolled between May 25, 2021, and Jan 31, 2022. Efficacy analyses included 12 468 RSVPreF3 OA recipients and 12 498 placebo recipients. Cumulative efficacy over three seasons of one RSVPreF3 OA dose was 62·9% (97·5% CI 46·7–74·8) against RSV-LRTD, 69·8% (42·2–85·7) against RSV A-related LRTD, and 58·6% (35·9–74·1) against RSV B-related LRTD (median follow-up from day 15 post-dose one 30·6 months [IQR 26·2–32·0]). Efficacy was observed over three seasons among participants aged 60–69 years, participants aged 70–79 years, pre-frail participants (ie, those with a walking speed of 0·4–0·99 m/s in a gait speed test), and participants with pre-existing conditions that increase the RSV-LRTD risk. Efficacy against RSV-LRTD decreased over time. A first RSVPreF3 OA dose followed by revaccination 1 year later had an efficacy that was within the same range as that of one dose. RSVPreF3 OA showed a clinically acceptable safety profile. Between dose one and trial end, eight (<1%) participants in the RSV single-dose group, 12 (<1%) in the RSV revaccination group, and 12 (<1%) in the placebo group had a serious adverse event considered to be related to the trial intervention by the investigator. Five deaths were assessed as related to the trial intervention by the investigator: three in the vaccine groups (cardiopulmonary failure, cardiac arrest, and left ventricular failure) and two in the placebo group (death of unknown cause and pulmonary embolism).

Interpretation A single RSVPreF3 OA dose was efficacious against RSV-LRTD over three RSV seasons in people aged 60 years or older, despite a decrease in efficacy over time. Further research is needed to establish the optimal revaccination strategy. These results support the favourable benefit–risk profile of RSVPreF3 OA to help protect against RSV-LRTD for at least three RSV seasons.

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*Contributed equally

†Members of the AReSVi-006 study group are listed at the end of the article

Bethesda, MD, USA (M G Ison MD); **Pulmonary Division, University of Ferrara, St Anna University Hospital, Ferrara, Italy** (Prof A Papi MD); **Barwon Health, University Hospital Geelong, Geelong, VIC, Australia** (Prof E Athan MD); **Centre for Innovation in Infectious Diseases and Immunology Research, Deakin University, Geelong, VIC, Australia** (Prof E Athan); **Senior Clinical Trials, Laguna Hills, CA, USA** (R G Feldman MD); **Canadian Center for Vaccinology, Dalhousie University, IWK Health and Nova Scotia Health, Halifax, NS, Canada** (Prof J M Langley MD); **Division of Infectious Diseases, Department of Internal Medicine, Vaccine Bio Research Institute, College of Medicine, The Catholic University of Korea, Seoul, South Korea** (Prof D-G Lee MD); **Center for Vaccinology, Ghent University and Ghent University Hospital, Ghent, Belgium** (I Leroux-Roels MD); **Translational Pediatrics and Infectious Diseases, Pediatrics Department, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain** (Prof F Martinon-Torres MD); **Genetics, Vaccines, Infectious Diseases, and Pediatrics Research Group, Instituto de**

Investigación Sanitaria de Santiago, Universidad de Santiago de Compostela, Santiago de Compostela, Spain (Prof F Martinon-Torres); **Consorcio Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain** (Prof F Martinon-Torres); **Institute of Laboratory Medicine and Vaccination Center, Klinikum Würzburg Mitte, Campus Juliusspital, Würzburg, Germany** (Prof T F Schwarz MD); **Division of Pulmonology and University of Cape Town Lung Institute, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa** (Prof R N van Zyl-Smit MD); **GSK, Stevenage, UK** (S Cuadripani MD); **GSK, Wavre, Belgium** (Q Deraedt PhD, N Dezutter PhD, L Fissette MS, M-P David MS, A Olivier PhD, M Van der Wielen MD, D Descamps MD); **GSK, Rixensart, Belgium** (C Gerard PhD); **GSK, Bengaluru, India** (S Xavier MS)

Correspondence to: Dr Marie Van der Wielen, GSK, 1300 Wavre, Belgium **marie.x.van-der-wielen@gsk.com**

Research in context

Evidence before this study

After more than 60 years of research, respiratory syncytial virus (RSV) vaccines became available in 2023. Three vaccines (adjuvanted RSV prefusion F protein-based vaccine [RSVPreF3 OA], bivalent RSV prefusion F protein-based vaccine [RSVPreF], and RSV prefusion F mRNA-based vaccine [mRNA-1345]) are currently approved for preventing RSV-related lower respiratory tract disease (RSV-LRTD) in people aged 60 years or older. Efficacy was shown for each of these vaccines over at least one RSV season, but the duration of protection and optimal strategy for revaccination are unknown. We searched PubMed from database inception to Oct 16, 2024, without language restrictions for articles on randomised controlled trials evaluating the efficacy of RSV vaccines in older adults. We used the search terms "RSV" OR "respiratory syncytial virus" AND "efficacy" AND "vaccin*" and filtered for randomised controlled trials. We identified seven articles that evaluated the efficacy of five different RSV vaccines or vaccine candidates against RSV-LRTD in people aged 60 years or older. Only two articles reported efficacy evaluations beyond the first RSV season: the current phase 3 trial demonstrating efficacy of RSVPreF3 OA over two seasons and a phase 2b trial showing efficacy of an investigational prefusion F adenoviral vaccine (Ad26.RSV.preF) over three seasons. A letter describing efficacy of RSVPreF over two seasons was published after our search. No articles have reported efficacy over three or more RSV seasons for any of the licensed RSV vaccines, and only one trial (the current one) evaluated efficacy after an annual revaccination.

Added value of this study

This phase 3 trial reported the cumulative efficacy over three RSV seasons of a single RSVPreF3 OA dose against RSV-LRTD (62·9% [97·5% CI 46·7–74·8]) in participants aged 60 years or older. Efficacy over three seasons of a first RSVPreF3 OA dose followed by revaccination 1 year later was in the same range as that of a single dose (67·8% [97·5% CI 51·8–79·1]). Safety follow-up over 3 years after RSVPreF3 OA vaccination showed a clinically acceptable safety profile. To the best of our knowledge, this is the first trial to show efficacy of one of the licensed RSV vaccines over three RSV seasons.

Implications of all the available evidence

The results of this randomised, observer-blinded, placebo-controlled, phase 3 trial, reported here and in previous publications after shorter follow-up periods, support the favourable benefit–risk profile of RSVPreF3 OA to help protect people aged 60 years or older against RSV-LRTD over three RSV seasons. Although efficacy decreased over time, the incidence of RSV-LRTD during the third season remained lower in those who received the vaccine compared with the placebo group. A second RSVPreF3 OA dose administered 1 year after the first dose did not appear to provide additional efficacy benefit in the overall trial population. Together with the results of the investigational Ad26.RSV.preF vaccine showing sustained efficacy over three RSV seasons in a phase 2b trial, these data suggest that RSV vaccines can help protect against RSV-LRTD over at least three seasons after a single dose. Further research is needed to establish the optimal revaccination strategy to maintain clinically meaningful protection after the first administration.

Introduction

Respiratory syncytial virus (RSV) is a common seasonal respiratory pathogen that poses a substantial, often underestimated, health burden in older adults.[1–4] Older age and the presence of chronic medical conditions, such as chronic obstructive pulmonary disease (COPD), congestive heart failure, diabetes, or kidney failure increase the risk of RSV-associated hospitalisation and death among older adults.[3–6]

The $AS01_E$-adjuvanted RSV vaccine based on the RSV fusion (F) protein stabilised in its prefusion conformation (RSVPreF3 OA; Arexvy, GSK) was first licensed in 2023 in adults aged 60 years or older on the basis of a favourable benefit–risk profile.[7–9] A single dose of the vaccine was highly efficacious against RSV-related lower respiratory tract disease (RSV-LRTD) in adults aged 60 years or older in the AReSVi-006 phase 3 trial,[10] with efficacy shown over two RSV seasons, including among those with underlying medical conditions that increase the risk of severe RSV disease (eg, COPD, chronic heart failure, diabetes, and advanced kidney or liver disease).[11] The AReSVi-006 trial also showed that a second vaccine dose administered approximately 1 year after the first dose was well tolerated but did not seem to provide additional efficacy benefit in the overall trial population.[11]

Here, we report results of the efficacy and safety over three RSV seasons of a single RSVPreF3 OA dose and of a first dose followed by revaccination 1 year later. Immune persistence after both vaccination regimens was also evaluated.

See Online for appendix

Methods

Study design and participants

The AReSVi-006 study was a randomised, placebo-controlled, observer-blind, phase 3 trial conducted in 275 centres (ie, GP practices and clinical research sites) in 17 countries in Africa, Asia, Oceania, Europe, and North America. This study is registered with ClinicalTrials.gov, NCT04886596, and is complete. Detailed methods were published previously.[10,11] A plain language summary is provided in the appendix (p 39). The protocol (appendix pp 49–246) and protocol amendments were approved by the trial sites' independent ethics committees. The trial was performed in accordance with the Declaration of Helsinki, the Council for

International Organizations of Medical Sciences, Good Clinical Practice, and local laws and regulations. Participant safety was monitored by an independent data and safety monitoring committee.

Participants were adults aged 60 years or older who provided written or witnessed informed consent and whom the investigators considered medically stable; this included individuals with chronic stable medical conditions with or without specific treatment. Detailed eligibility criteria and enrolment rules were published previously.[10]

Randomisation and masking

Randomisation was performed with a centralised automated internet-based system. Before the start of the first RSV season, participants were randomly allocated (1:1) to receive RSVPreF3 OA (RSVPreF3 OA group) or placebo (placebo group). The randomisation algorithm used a stratification by subset (participants included or not in the cohort selected for reactogenicity and immunogenicity analyses; appendix p 3) and a minimisation procedure accounting for centre, age, and region within each subset. Before the start of RSV season two, participants who had received RSVPreF3 OA were re-randomised (1:1) to receive a second RSVPreF3 OA dose (RSV revaccination group) or placebo (RSV single-dose group). The re-randomisation algorithm accounted for the stratification and minimisation factors used for the initial randomisation (appendix p 3).

Participants, investigators, and personnel involved in data collection and sample testing were masked to group allocation. Vaccine and placebo were prepared and administered by unmasked personnel not involved in collecting or evaluating data. Participants who had received placebo before RSV season one received another placebo dose before RSV season two to maintain blinding (placebo group; appendix p 40).

Procedures

Sex, race, and ethnicity data were collected via self-report. Each 0·5 mL dose of reconstituted RSVPreF3 OA contained 120 µg RSVPreF3 antigen and $AS01_E$ adjuvant (appendix p 3). Both vaccine and placebo (NaCl solution) were administered by intramuscular injection in the deltoid muscle, preferably of the non-dominant arm.

In addition to the doses administered before RSV season one and before RSV season two, the trial originally planned for another RSVPreF3 OA dose to be administered before RSV season three to participants in the RSV revaccination group and placebo doses in the other two groups. However, RSV season two results indicated that the second dose administered 1 year post-dose one did not increase the efficacy in the overall trial population compared with a single dose.[11] Therefore, the trial protocol was amended to remove the dose before RSV season three. For some participants, the visit before RSV season three took place before the amendment was approved; hence, they received a vaccine or placebo dose before season three. These participants were included in the safety analyses and the analysis of efficacy of a single RSVPreF3 OA dose; however, for the analysis of the revaccination regimen, they contributed to season one and season two data but were censored at dose three.

Participants in the northern hemisphere were followed up for three consecutive RSV seasons (seasons defined as from Oct 1 to April 30); those in the southern hemisphere for at least two consecutive RSV seasons (seasons defined as from March 1 to Sept 30; appendix p 40). During this follow-up, surveillance for acute respiratory illness was performed via spontaneous reporting by the participants and scheduled site staff contacts at different frequencies during and outside of the RSV seasons.[10] Each time a participant had two or more acute respiratory illness symptoms or signs (appendix p 12), an acute respiratory illness assessment visit had to be scheduled, during which the staff examined the participant and took nasal and throat swabs. Participants also took nasal self-swabs.[10] Both types of swabs were used to assess the presence of RSV A and RSV B by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR).

An acute respiratory illness was defined as at least two respiratory symptoms or signs or at least one respiratory and one systemic symptom or sign, lasting for 24 h or longer. A lower respiratory tract disease (LRTD) 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 24 h or longer. An LRTD was considered severe either based on clinical signs and investigator assessment or on the need for supportive therapy (appendix p 12).[10] All LRTD cases confirmed as RSV-positive by qRT-PCR were reviewed by an adjudication committee; only cases confirmed as LRTD by this committee were included in the analyses.[10]

RSV A and RSV B neutralising titres and RSVPreF3-binding immunoglobulin G concentrations were measured in participants in the reactogenicity-immunogenicity cohort on serum samples collected before dose one, 30 days after dose one, before RSV season two (before dose two), and before RSV season three (appendix p 40). Assays were described previously.[10]

Information about pre-existing medical conditions was gathered by interviewing the participants or reviewing their medical records. Subgroups were generated based on the presence or absence of selected pre-existing medical conditions of interest. These pre-existing medical conditions of interest that increase the risk of severe RSV disease were any chronic respiratory or pulmonary disease (including COPD and asthma),

chronic heart failure, type 1 or type 2 diabetes, and advanced liver or renal disease. To generate the subgroups, the selected medical conditions of interest were identified in the database using a predefined list of Medical Dictionary for Regulatory Activities preferred terms. Frailty status was assessed using a gait speed test, in which frail was defined by a walking speed slower than 0·4 m/s or an inability to perform the test, pre-frail was defined by a walking speed of 0·4–0·99 m/s, and fit was defined by a walking speed of 1 m/s or faster.

Outcomes

A complete list of objectives and endpoints is provided in the appendix (pp 4–8). The trial's primary objective (demonstration of the efficacy of a single RSVPreF3 OA dose against first occurrence of RSV-LRTD during the first RSV season) was reported previously.[10] The demonstration of efficacy over three RSV seasons of a single RSVPreF3 OA dose and of a first dose followed by a second dose 1 year later in preventing first occurrence of RSV-LRTD—overall and for each RSV subtype—were confirmatory secondary objectives. Prespecified descriptive efficacy objectives included the evaluation of efficacy of the two regimens (single dose and revaccination) over three seasons against severe RSV-LRTD and RSV-related acute respiratory illness, and against RSV-LRTD by age, frailty status and presence of any of the selected pre-existing medical conditions of interest. Efficacy was also evaluated descriptively for each season separately. Efficacy against RSV-LRTD and RSV-related acute respiratory illness with medically attended visits was analysed post hoc.

To evaluate the long-term safety after RSVPreF3 OA vaccination, serious adverse events and potential immune-mediated diseases considered by the investigator as related to vaccination and fatal serious adverse events were recorded from dose one until trial end. All serious adverse events and potential immune-mediated diseases occurring within 6 months after each dose and unsolicited adverse events occurring within 30 days after each dose were also collected; these results were reported previously.[10,11]

The safety of the RSVPreF3 OA dose administered before RSV season three was evaluated in participants who had their pre-season three visit before the approval of the final protocol amendment that removed dose three administration. In those participants, solicited adverse events occurring within 4 days post-dose three were only recorded by the subset who were included in the reactogenicity-immunogenicity cohort, whereas unsolicited adverse events (within 30 days post-dose three), serious adverse events and potential immune-mediated diseases (within 6 months post-dose three), and related serious adverse events, related potential immune-mediated diseases, and fatal serious adverse events (from dose three until trial end) were recorded for all.

Statistical analysis

We planned to enrol up to 25 000 participants and assumed a 20% dropout between seasons; approximately 1800 participants were planned to be included in the reactogenicity-immunogenicity cohort.[10,11] Power calculations for the confirmatory secondary objectives are included in the appendix (p 9).

Cumulative efficacy over three RSV seasons was evaluated in participants who received at least the first RSVPreF3 OA or placebo dose (ie, exposed population) and did not report an RSV-related acute respiratory illness within 15 days post-dose one (ie, modified exposed population). Analyses were performed based on the administered intervention. The time at risk started on day 15 post-dose one and ended at the first occurrence of an event, dropout, or end of northern hemisphere season three (April 30, 2024). Participants (in all groups) who did not receive dose two were censored at the end of southern hemisphere season one (Sept 30, 2022). For the analysis of the revaccination regimen, participants who received dose three were censored at dose three. Efficacy during RSV season three only was evaluated in participants who received dose two (vaccine or placebo) and did not report an RSV-related acute respiratory illness within 15 days post-dose two (ie, dose two-modified exposed population); for the analysis of the revaccination regimen, participants who received dose three were excluded. The time at risk began at the start of season three and ended at the first occurrence of an event, dropout, or end of northern hemisphere season three. Additionally, for all efficacy analyses, participants who received an RSV vaccine not planned per protocol were censored at receipt of that vaccine.

Confirmatory secondary objectives were met if the lower limits of the two-sided CIs around the efficacy estimates were more than 20% for efficacy against RSV-LRTD and more than 0% for efficacy against RSV-LRTD by RSV subtype (ie, RSV A or RSV B). To account for multiple comparisons, a Bonferroni correction was applied to evaluate both the single-dose and revaccination regimens simultaneously. Hence, the analyses were conducted using a one-sided significance level (α) of 1·25%, corresponding to a two-sided 97·5% CI. No multiplicity adjustments were applied for the other secondary objectives, which were all analysed descriptively.

Efficacy was defined as 1 – the incidence rate ratio (comparing participants receiving the single-dose or revaccination regimen with those receiving placebo only), calculated using the conditional exact binomial method based on a Poisson model adjusted by age category, region, and season (appendix p 9). Season was included as a covariate to assess efficacy over multiple

seasons to account for potential inter-season differences in incidence rates, efficacy, and follow-up time. A post-hoc analysis without season as a covariate was also performed, in line with efficacy assessments in other RSV vaccine trials that do not account for those potential differences. For the analyses in season three separately, only age and region were included as covariates.

Long-term safety outcomes after a single dose were evaluated on the exposed population. Solicited adverse events post-dose three were evaluated in participants in the reactogenicity-immunogenicity cohort who had received dose three and had solicited safety data available (ie, dose three solicited safety population). Other safety endpoints post-dose three were evaluated on all participants who received dose three. Numbers and percentages (with exact 95% CIs) of participants with adverse events were calculated.

Immunogenicity was evaluated in terms of geometric mean titres and mean geometric increases (MGIs, geometric means of the within-participant ratios of the post-vaccination titres over prevaccination titres) with 95% CIs, on protocol-compliant participants in the reactogenicity-immunogenicity cohort who had immunogenicity data available (ie, per-protocol population for immunogenicity).

Statistical analyses were performed with the SAS Life Science Analytics Framework (SAS Institute, Cary, NC, USA).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Participants were enrolled between May 25, 2021, and Jan 31, 2022. The trial ended on May 31, 2024. The exposed population included 24 972 participants: 12 469 received RSVPreF3 OA and 12 503 received placebo before RSV season one. Of the 12 469 RSVPreF3 OA recipients, 4988 received a placebo dose (RSV single-dose group) and 4968 a second RSVPreF3 OA dose (RSV revaccination group) before RSV season two and were included in the dose two-exposed population, together with 10 033 participants in the placebo group who received a second placebo dose before RSV season two. 5742 participants received an RSVPreF3 OA or placebo dose before RSV season three (1467 in the RSV single-dose group, 1409 in the RSV revaccination group, and 2866 in the placebo group). Overall, 18 726 participants (75% of the exposed population) completed the trial (figure 1). A summary of important protocol deviations is shown in the appendix (pp 13–15).

As reported previously,[10,11] baseline characteristics were balanced between groups (appendix pp 16–17). Mean age

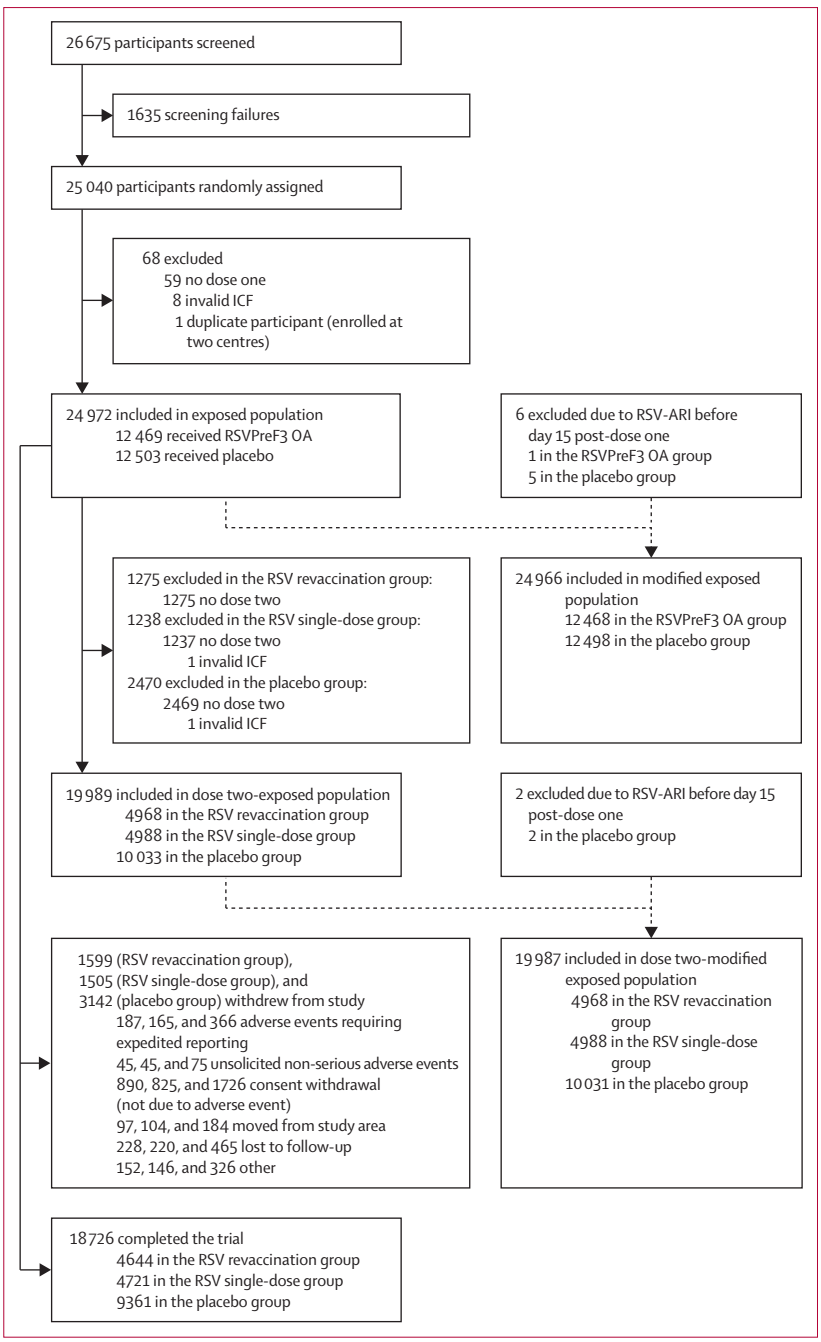

Figure 1: **Trial profile**
RSVPreF3 OA group refers to the participants randomly assigned to receive a dose of RSVPreF3 OA before RSV season one; placebo group refers to the participants randomly assigned to receive placebo; RSV revaccination group refers to the participants who received a first dose of RSVPreF3 OA before season one and were randomly assigned to receive a second RSVPreF3 OA dose (revaccination) before season two; and RSV single-dose group refers to the participants who received a dose of RSVPreF3 OA before season one and were randomly assigned to receive a placebo dose before season two. 5742 participants received a dose before season three: 1406 in the RSV revaccination group received RSVPreF3 OA and three received placebo; and 1467 in the RSV single-dose group and 2866 in the placebo group received placebo. ICF=informed consent form. RSV=respiratory syncytial virus. RSV-ARI=respiratory syncytial virus-related acute respiratory illness. RSVPreF3 OA=respiratory syncytial virus prefusion F protein-based vaccine.

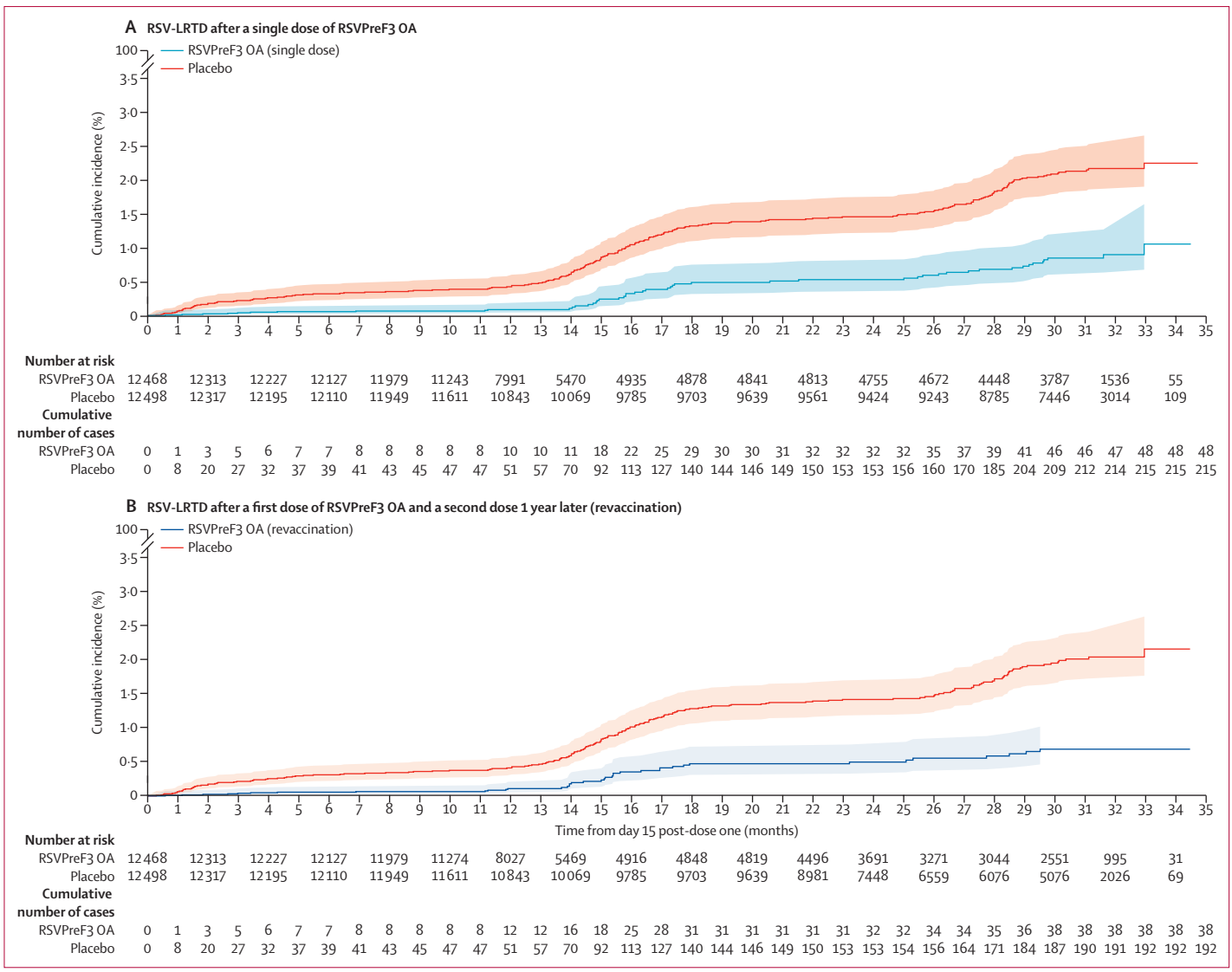

Figure 2: **Cumulative incidence of RSV-LRTD over three RSV seasons (modified exposed population)**
For the analysis of a single dose (A), participants who received RSVPreF3 OA as doses one and two (RSV revaccination group) contributed to RSV season one but were censored at dose two. Log-rank test: p<0·0001. For the analysis of the revaccination regimen (B), participants who received RSVPreF3 OA as dose one and placebo as dose two (RSV single-dose group) contributed to season one but were censored at dose two. Log-rank test: p<0·0001. For both analyses, the time at risk started on day 15 post-dose one and ended at the first occurrence of an event, dropout, or end of northern hemisphere season three (April 30, 2024). Participants (in all groups) who did not receive dose two were censored at the end of southern hemisphere season one (Sept 30, 2022). For the analysis of the revaccination regimen, participants who received dose three were censored at dose three. Additionally, participants who received an RSV vaccine not planned per protocol were censored at receipt of that vaccine. 97·5% CIs (depicted as shaded areas) were computed at each case reported and end at the last reported case in each group. RSV=respiratory syncytial virus. RSV-LRTD=respiratory syncytial virus-related lower respiratory tract disease. RSVPreF3 OA=respiratory syncytial virus prefusion F protein-based vaccine.

of the participants was 69·5 years (SD 6·5), with 11028 (44%) of 24972 participants 70 years or older. 2501 (40%) of 6226 in the RSV single-dose group, 2513 (40%) of 6243 in the RSV revaccination group, and 4954 (40%) of 12503 in the placebo group had at least one pre-existing condition associated with an increased risk of severe RSV disease, and 2358 (38%) of 6226 in the RSV single-dose group, 2437 (39%) of 6243 in the RSV revaccination group, and 4782 (38%) of 12503 in the placebo group were considered pre-frail as evaluated with a gait speed test (appendix pp 16–17).

The modified exposed population included 24966 participants (12468 in the RSVPreF3 OA group [6225 in the RSV single-dose group and 6243 in the RSV revaccination group] and 12498 in the placebo group). The median follow-up from day 15 post-dose one until the end of RSV season three was 30·6 months (IQR 26·2–32·0) for the analysis of efficacy of a single RSVPreF3 OA dose and 27·0 months (21·4–31·3) for the revaccination regimen. During this follow-up, 76 participants in the RSVPreF3 OA-vaccinated groups and 215 in the placebo group had at least one RSV-LRTD.

	RSVPreF3 OA group (single dose)				Placebo group				Vaccine efficacy,% (CI*)	
	N†	n‡	T§, person-years	n/T¶, per 1000 person-years	N†	n‡	T§, person-years	n/T¶, per 1000 person-years	With season as covariate	Without season as covariate
RSV-LRTD										
Overall	12 468	48	19 748·8	2·4	12 498	215	27 363·6	7·9	62·9 (46·7 to 74·8)	69·1 (55·8 to 78·9)
By subtype										
RSV A	12 468	14	19 780·8	0·7	12 498	80	27 524·6	2·9	69·8 (42·2 to 85·7)	75·7 (53·6 to 88·5)
RSV B	12 468	34	19 760·3	1·7	12 498	135	27 454·0	4·9	58·6 (35·9 to 74·1)	65·0 (46·1 to 78·1)
Severe‖	12 468	15	19 778·4	0·8	12 498	75	27 526·4	2·7	67·4 (42·4 to 82·7)	72·3 (51·3 to 85·2)
By age										
60–69 years	6962	28	11 140·1	2·5	6981	117	15 343·9	7·6	60·3 (39·5 to 74·8)	66·9 (49·7 to 78·9)
70–79 years	4489	15	7095·5	2·1	4489	85	9866·4	8·6	70·6 (48·4 to 84·3)	75·6 (57·5 to 86·9)
≥70 years	5506	20	8608·7	2·3	5517	98	12 019·8	8·2	66·0 (44·3 to 80·2)	71·7 (53·9 to 83·4)
≥80 years	1017	5	1513·2	3·3	1028	13	2153·4	6·0	36·2 (–94·0 to 82·5)	45·6 (–62·6 to 84·8)
By pre-existing condition of interest**										
No condition	7454	23	11 814·3	1·9	7547	99	16 629·0	6·0	61·5 (38·6 to 76·7)	67·3 (48·2 to 80·2)
≥1 condition	5014	25	7934·5	3·2	4951	116	10 734·6	10·8	64·7 (45·1 to 78·1)	71·1 (55·2 to 82·0)
≥1 cardiorespiratory condition	2577	17	4048·7	4·2	2504	85	5384·8	15·8	68·1 (45·7 to 82·3)	73·9 (55·8 to 85·5)
≥1 endocrine or metabolic condition	3243	12	5152·9	2·3	3274	55	7143·5	7·7	63·9 (31·4 to 82·5)	69·8 (42·8 to 85·3)
By frailty status										
Frail	189	2	293·5	6·8	176	1	355·2	2·8	–153·6 (–16 323·0 to 88·0)	–159·5 (–15 414·3 to 86·7)
Pre-frail	4794	12	7394·6	1·6	4779	67	10 249·8	6·5	70·1 (43·9 to 85·3)	75·4 (54·0 to 87·9)
Fit	7464	34	12 034·5	2·8	7523	145	16 719·5	8·7	61·0 (42·9 to 74·1)	67·6 (52·6 to 78·4)
RSV-ARI										
Overall	12 468	131	19 654·5	6·7	12 498	428	27 086·0	15·8	51·1 (40·3 to 60·2)	57·9 (48·6–65·6)

Analysis included data collected from day 15 post-dose one until April 30, 2024 (end of northern hemisphere season three) or until Sept 30, 2022 (end of southern hemisphere season one) for participants who did not receive dose two. Participants who received RSVPreF3 OA as dose one and placebo as dose two (RSV single-dose group) and participants in the placebo group contributed to the entire follow-up. Participants who received RSVPreF3 OA as doses one and two (RSV revaccination group) contributed to season one but were censored at dose two. RSV=respiratory syncytial virus. RSVPreF3 OA=respiratory syncytial virus prefusion F protein-based vaccine. RSV-LRTD=respiratory syncytial virus-related lower respiratory tract disease. RSV-ARI=respiratory syncytial virus-related acute respiratory illness. *97·5% CI applies for confirmatory secondary endpoints (RSV-LRTD, overall and by RSV subtype); 95% CI applies for other endpoints. †N refers to the number of participants in the modified exposed population. ‡n refers to the number of participants with ≥1 RSV-LRTD or RSV-ARI. §T refers to the sum of follow-up time (from day 15 post-dose one until first occurrence of the event, data lock point, or dropout). ¶n/T refers to the incidence rate of participants reporting at least one event. ‖Severe disease according to either of the two case definitions (definition one based on clinical signs or investigator assessment or definition two based on supportive therapy; appendix p 12). All severe cases met case definition one; two cases in the RSVPreF3 OA group and five in the placebo group were confirmed by the adjudication committee as also meeting case definition two. **Conditions of interest included cardiorespiratory conditions (any chronic respiratory or pulmonary disease [including chronic obstructive pulmonary disease and asthma] and chronic heart failure) and endocrine or metabolic conditions (type 1 or type 2 diabetes and advanced liver or renal disease).

Table 1: **Vaccine efficacy of a single RSVPreF3 OA dose against first occurrence of RSV-LRTD and RSV-ARI over three RSV seasons (modified exposed population)**

During RSV season one, ten cases were reported in the RSVPreF3 OA-vaccinated groups and 47 in the placebo group; during RSV seasons two and three, respectively, 22 and 16 cases were reported in the RSV single-dose group, 22 and six in the RSV revaccination group, and 107 and 61 in the placebo group. Across the three RSV seasons, RSV B was the predominant subtype, with 182 (62·5%) RSV B-related LRTD cases (47 in the RSVPreF3 OA-vaccinated groups and 135 in the placebo group). RSV-LRTD cases by calendar month throughout the follow-up are reported in the appendix (p 41).

The cumulative efficacy of a single RSVPreF3 OA dose in preventing RSV-LRTD over three RSV seasons was 62·9% (97·5% CI 46·7–74·8; confirmatory objective demonstrated: lower confidence limit >20%); 48 participants in the RSVPreF3 OA group, *vs* 215 participants in the placebo group, had at least one RSV-LRTD case during the follow-up. Cumulative incidence curves showed that a single dose was efficacious during the entire follow-up (figure 2). Vaccine efficacy was also shown (lower confidence limits >0%) against RSV-LRTD due to both RSV A (69·8% [97·5% CI 42·2–85·7]; 14 participants in the RSVPreF3 OA group *vs*

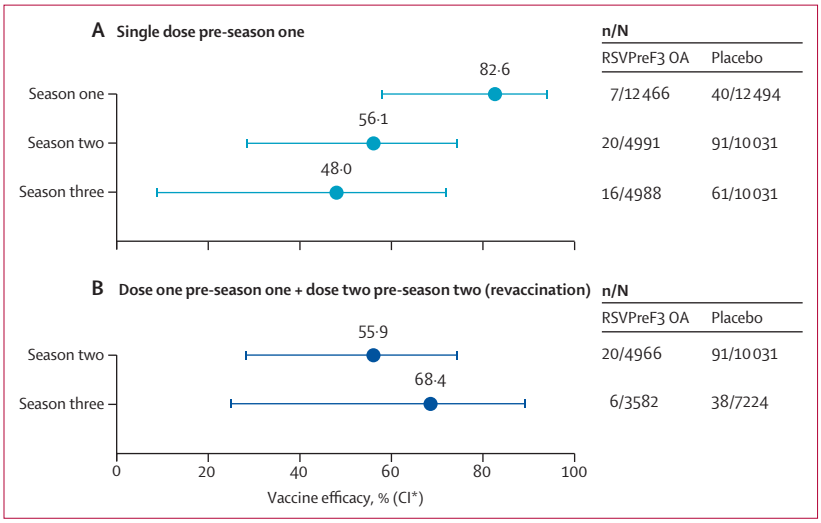

Figure 3: **Vaccine efficacy of a single dose of RSVPreF3 OA or of a first dose followed by a second dose 1 year later (revaccination) against RSV-LRTD during each RSV season (modified exposed populations)**
Season one data included cases reported from day 15 post-dose one until the end of northern hemisphere season one (efficacy database-lock: April 11, 2022).[10] Season two data included cases reported from day 15 post-dose two until the end of northern hemisphere season two (efficacy database-lock: March 31, 2023).[11] Season three data included cases reported from the start (Oct 1, 2023) until the end (efficacy database-lock: April 30, 2024) of northern hemisphere season three. The median follow-up time was 6·7 months (IQR 5·7–7·8) for season one, 6·3 months (5·7–6·8) for season two, and 7·0 months (7·0–7·0) for season three. N refers to number of participants in the modified exposed population (season one) or dose two-modified exposed population (seasons two and three); for the analysis of the revaccination regimen during season three, this excluded participants who received dose three. n refers to the number of participants with at least one RSV-LRTD. RSV=respiratory syncytial virus. RSV-LRTD=respiratory syncytial virus-related lower respiratory tract disease. RSVPreF3 OA=respiratory syncytial virus prefusion F protein-based vaccine. *96·95% CI applies for efficacy of a single dose during season one (primary, confirmatory objective, as published by Papi and colleagues;[10] A); 95% CIs apply for all other endpoints.

80 participants in the placebo group) and RSV B (58·6% [35·9–74·1]; 34 participants in the RSVPreF3 OA group *vs* 135 participants in the placebo group; table 1).

Efficacy over three seasons was 51·1% (95% CI 40·3–60·2) against RSV-related acute respiratory illness (131 participants in the RSVPreF3 OA group *vs* 428 participants in the placebo group with at least one case), 67·4% (42·4–82·7) against severe RSV-LRTD (15 participants in the RSVPreF3 OA group *vs* 75 participants in the placebo group), and 70·2% (50·1–83·1) against RSV-LRTD with medically attended visits (18 participants in the RSVPreF3 OA group *vs* 95 participants in the placebo group; table 1; appendix pp 18–20). Eight hospitalisations due to qRT-PCR-confirmed RSV-related respiratory disease were reported over the entire trial period (two in the RSV single-dose group and six in the placebo group).

A single dose of RSVPreF3 OA showed efficacy over three RSV seasons among participants aged 60–69 years (60·3% [95% CI 39·5–74·8]; 28 participants in the RSVPreF3 OA group *vs* 117 participants in the placebo group) and 70–79 years (70·6% [48·4–84·3]; 15 participants in the RSVPreF3 OA group *vs* 85 participants in the placebo group), among participants with pre-frail status (70·1% [43·9–85·3]; 12 participants in the RSVPreF3 OA group *vs* 67 participants in the placebo group), and among those with pre-existing medical conditions known to increase the risk of severe RSV disease (64·7% [45·1–78·1]; 25 participants in the RSVPreF3 OA group *vs* 116 participants in the placebo group; table 1). Efficacy in participants who were frail and those aged 80 years or older could not be reliably estimated because of the low number of cases in these subgroups. Additional efficacy outcomes are reported in the appendix (pp 10–11, 18–20).

Findings were similar when not accounting for seasonal effects (ie, model without season as a covariate), although efficacy estimates were higher for all evaluated endpoints (table 1).

When evaluating vaccine efficacy in each season separately, a decrease was observed from season one to season three, with a lesser decline between seasons two and three than between seasons one and two; efficacy against RSV-LRTD was 82·6% (96·95% CI 57·9–94·1, as published by Papi and colleagues[10]); seven participants in the RSVPreF3 OA group *vs* 40 participants in the placebo group with at least one case) in season one, 56·1% (95% CI 28·2–74·4; 20 participants in the RSVPreF3 OA group *vs* 91 participants in the placebo group) in season two, and 48·0% (95% CI 8·7–72·0; 16 participants in the RSVPreF3 OA group *vs* 61 participants in the placebo group) in season three (figure 3). Efficacy in season three against RSV-LRTD by subtype, severity, and in the different subpopulations is reported in the appendix (pp 21–22).

Vaccine efficacy of the revaccination regimen (dose one given pre-season one followed by dose two given pre-season two) in preventing RSV-LRTD over three RSV seasons post-dose one was shown for RSV-LRTD due to either subtype (67·8% [97·5% CI 51·8–79·1]; 38 participants in the RSVPreF3 OA group *vs* 192 participants in the placebo group with at least one case), due to RSV A (55·1% [16·5–77·5]; 17 participants in the RSVPreF3 OA group *vs* 65 participants in the placebo group), and RSV B (73·6% [55·1–85·4]; 21 participants in the RSVPreF3 OA group *vs* 127 participants in the placebo group; table 2). Cumulative incidence curves showed that efficacy against RSV-LRTD was observed over the entire follow-up (figure 2).

The revaccination regimen showed vaccine efficacy over three seasons for the different endpoints and in the various subpopulations (table 2; appendix pp 18–19). Efficacy of the revaccination regimen was also observed when considering cases reported during season 3 only (68·4% [95% CI 24·6–89·1]; six participants in the RSVPreF3 OA group *vs* 38 participants in the placebo group with at least one case; figure 3; appendix pp 21–22). Efficacy estimates for the revaccination regimen were generally in the same range as those observed for a single dose, although point estimates for the revaccination regimen were higher for several endpoints (table 2; appendix pp 21–22).

	RSVPreF3 OA group (revaccination)				Placebo group				Vaccine efficacy, % (CI*)
	N†	n‡	T§, person-years	n/T¶, per 1000 person-years	N†	n‡	T§, person-years	n/T¶, per 1000 person-years	With season as covariate
RSV-LRTD									
Overall	12 468	38	18 744·4	2·0	12 498	192	25 468·3	7·5	67·8 (51·8 to 79·1)
By subtype									
RSV A	12 468	17	18 766·6	0·9	12 498	65	25 598·2	2·5	55·1 (16·5 to 77·5)
RSV B	12 468	21	18 762·3	1·1	12 498	127	25 540·3	5·0	73·6 (55·1 to 85·4)
Severe‖	12 468	9	18 776·2	0·5	12 498	67	25 599·0	2·6	78·8 (57·1 to 90·8)
By age									
60–69 years	6962	19	10 562·3	1·8	6981	105	14 324·6	7·3	70·6 (51·6 to 83·1)
70–79 years	4489	14	6734·7	2·1	4489	75	9157·3	8·2	69·4 (45·1 to 84·1)
≥70 years	5506	19	8182·1	2·3	5517	87	11 143·7	7·8	64·3 (40·5 to 79·6)
≥80 years	1017	5	1447·4	3·5	1028	12	1986·5	6·0	32·8 (–108·4 to 81·7)
By pre-existing condition of interest**									
No condition	7454	20	11 283·8	1·8	7547	91	15 558·9	5·8	64·2 (41·1 to 79·2)
≥1 condition	5014	18	7460·6	2·4	4951	101	9909·4	10·2	71·2 (51·9 to 83·7)
≥1 cardiorespiratory condition	2577	11	3793·9	2·9	2504	73	4964·0	14·7	75·9 (54·1 to 88·5)
≥1 endocrine or metabolic condition	3243	9	4846·6	1·9	3274	49	6590·0	7·4	69·9 (37·5 to 87·1)
By frailty status									
Frail	189	1	263·1	3·8	176	1	339·5	2·9	13·6 (–6751·4 to 98·9)
Pre-frail	4794	10	7127·0	1·4	4779	63	9610·1	6·6	74·3 (49·3 to 88·3)
Fit	7464	27	11 325·6	2·4	7523	126	15 483·2	8·1	64·8 (46·1 to 77·8)
RSV-ARI									
Overall	12 468	103	18 678·5	5·5	12 498	385	25 236·9	15·3	58·4 (48·1 to 67·0)

Analysis included data collected from day 15 post-dose one until April 30, 2024 (end of northern hemisphere season three) in participants who did not receive dose three, or until dose three administration, or until Sept 30, 2022 (end of southern hemisphere season one) for participants who did not receive dose two. Participants who received RSVPreF3 OA as dose one and placebo as dose two (RSV single-dose group) contributed to season one but were censored at dose two. Participants who received two RSVPreF3 OA doses (RSV revaccination group) or two placebo doses (placebo group) contributed to the entire follow-up. Participants who received dose three (RSVPreF3 OA or placebo) contributed to seasons one and two but were censored at dose three. RSV=respiratory syncytial virus. RSVPreF3 OA=respiratory syncytial virus prefusion F protein-based vaccine. RSV-LRTD=respiratory syncytial virus-related lower respiratory tract disease. RSV-ARI=respiratory syncytial virus-related acute respiratory illness. *97·5% CI applies for confirmatory secondary endpoints (RSV-LRTD, overall and by RSV subtype); 95% CI applies for other endpoints. †N refers to the number of participants in the modified exposed population. ‡n refers to the number of participants with ≥1 RSV-LRTD or RSV-ARI. §T refers to the sum of follow-up time (from day 15 post-dose one until first occurrence of the event, data lock point, dropout, or dose three administration). ¶n/T refers to the incidence rate of participants reporting at least one event. ‖Severe disease according to either of the two case definitions (definition one based on clinical signs or investigator assessment or definition two based on supportive therapy; appendix p 12). All severe cases met case definition one; no cases in the RSVPreF3 OA group and five in the placebo group were confirmed by the adjudication committee as also meeting case definition two. **Conditions of interest included cardiorespiratory conditions (any chronic respiratory or pulmonary disease [including chronic obstructive pulmonary disease and asthma] and chronic heart failure) and endocrine or metabolic conditions (type 1 or type 2 diabetes and advanced liver or renal disease).

Table 2: **Vaccine efficacy of a first RSVPreF3 OA dose followed by a second dose 1 year later (revaccination) against first occurrence of RSV-LRTD and RSV-ARI over three RSV seasons post-dose one (modified exposed population)**

Reactogenicity and other short-term safety outcomes after a single RSVPreF3 OA dose or after a second dose (revaccination) were reported previously[10,11] (appendix pp 23–29, 42–43). Between dose one and trial end, eight (<1%) participants in the RSV single-dose group, 12 (<1%) in the RSV revaccination group, and 12 (<1%) in the placebo group had a serious adverse event considered to be related to the trial intervention by the investigator. Related potential immune-mediated diseases were reported in seven (<1%) participants in the RSV single-dose group, five (<1%) participants in the RSV revaccination group, and nine (<1%) participants in the placebo group (table 3; appendix pp 10–11). 111 (2%) participants in the RSV single-dose group, 120 (2%) in the RSV revaccination group, and 265 (2%) in the placebo group died during the trial (table 3; appendix pp 30–31). Five fatal serious adverse events were assessed as related to the trial intervention by the investigator: three in the vaccine groups (cardiopulmonary failure, cardiac arrest, and left ventricular failure) and two in the placebo group (death of unknown cause and pulmonary embolism). The

	RSV single-dose group (N=6226)		RSV revaccination group (N=6243)		Placebo group (N=12 503)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Related serious adverse event	8	0·1 (0·1–0·3)	12	0·2 (0·1–0·3)	12	0·1 (0·0–0·2)
Fatal serious adverse event	111	1·8 (1·5–2·1)	120	1·9 (1·6–2·3)	265	2·1 (1·9–2·4)
Related pIMD	7	0·1 (0·0–0·2)	5	0·1 (0·0–0·2)	9	0·1 (0·0–0·1)

Related serious adverse events and pIMDs are those considered related to vaccine or placebo administration by investigator assessment; details of these events are provided in the appendix (pp 10–11). The RSV single-dose group consisted of participants who received a single dose of RSVPreF3 OA pre-season one, were randomly assigned to receive placebo pre-season two, and might have received placebo pre-season three. The RSV revaccination group consisted of participants who received a first RSVPreF3 OA dose pre-season one, were randomly assigned to receive a second RSVPreF3 OA dose (revaccination) pre-season two, and might have received RSVPreF3 OA pre-season three. The placebo group consisted of participants who received placebo only. pIMD=potential immune-mediated disease. RSV=respiratory syncytial virus. RSVPreF3 OA=respiratory syncytial virus prefusion F protein-based vaccine. N refers to the number of participants in the exposed population. n/% refers to the number/percentage of participants reporting the event at least once.

Table 3: **Serious adverse events and potential immune-mediated diseases from dose one until the end of the trial (exposed population)**

sponsor identified no safety signals related to these cases, given the presence of pre-existing or concurrent medical conditions or the long time-to-onset from RSVPreF3 OA vaccination (30 days, 656 days, and 842 days). No acute disseminated encephalomyelitis, Guillain-Barré syndrome, or other neuroinflammatory events were reported after RSVPreF3 OA vaccination throughout the trial.

In the subset of participants who received the pre-season three RSVPreF3 OA dose, the reporting rates of solicited adverse events within 4 days, unsolicited adverse events within 30 days, and serious adverse events and potential immune-mediated diseases within 6 months after this dose were similar to those after the first or second dose (appendix pp 23–29, 32–38, 42–44). No imbalance between the trial groups was observed in the occurrence of atrial fibrillation post-dose three (appendix p 11).

RSV A and RSV B neutralising titres increased from baseline to 1 month after the first RSVPreF3 OA dose, with MGIs versus baseline of 10·2 (95% CI 9·4–10·9) for RSV A and 8·6 (8·0–9·1) for RSV B. Titres decreased over time (with a lesser decline between seasons two and three than between seasons one and two) and remained higher than baseline until at least pre-season three, with MGIs versus baseline of 2·3 (95% CI 2·1–2·5; RSV single-dose group) and 3·4 (3·1–3·8; RSV revaccination group) for RSV A, and 1·7 (1·6–1·9; RSV single-dose group) and 2·4 (2·2–2·6; RSV revaccination group) for RSV B (appendix pp 45–46). Similar findings were observed across age groups (appendix p 47).

Discussion

The confirmatory secondary objectives of this multicentre, randomised, observer-blinded, placebo-controlled, phase 3 trial were met, demonstrating that a single dose of RSVPreF3 OA was efficacious in preventing RSV-LRTD over three RSV seasons in adults aged 60 years or older (62·9%, 97·5% lower confidence limit >20%), with efficacy demonstrated for both RSV A (69·8%, 97·5% lower confidence limit >0%) and RSV B (58·6%, 97·5% lower confidence limit >0%). The predominant circulating RSV subtype varies from year to year and across regions in the world,[12–17] highlighting the importance of an RSV vaccine that helps protect against both subtypes. A single dose was efficacious over three consecutive RSV seasons (median follow-up 30·6 months [IQR 26·2–32·0]) among participants aged 60–69 years and 70–79 years, those with various pre-existing conditions that increase the risk of severe RSV disease (including chronic respiratory or pulmonary diseases such as COPD and asthma, chronic heart failure, type 1 or type 2 diabetes, and advanced liver or renal disease), and among participants who were considered pre-frail. Despite a decrease in protection over time, efficacy against RSV-LRTD remained at 48·0% in the third season. Our results indicate that RSVPreF3 OA vaccination can help to protect clinically vulnerable populations from RSV disease for at least three RSV seasons.

To the best of our knowledge, this is the first randomised phase 3 trial to evaluate the durability of efficacy over three full RSV seasons of one of the currently licensed RSV vaccines (GSK's RSVPreF3 OA, Pfizer's RSVPreF, and Moderna's RSVPreF mRNA-based vaccine). A phase 2b trial of an investigational adenoviral vector RSVPreF vaccine (Ad26.RSV.preF, not licensed) showed an efficacy of 78·7% (95% CI 57·3–90·4) against RSV-LRTD across three seasons in people aged 65 years or older.[18] These results cannot be directly compared with those in our trial because of differences in settings, trial periods, case definitions, and analysis methods, but they do support RSV vaccine efficacy over at least three seasons.

Efficacy of a single RSVPreF3 OA dose over three seasons was observed across the clinical spectrum of RSV disease, including RSV-related acute respiratory illness (51·1%) and severe RSV-LRTD (67·4%). Too few RSV-related hospitalisations were reported in the trial to be able to conclude on the vaccine's ability to prevent hospitalisation due to RSV, but efficacy was observed against RSV-LRTD with medically attended visits (70·2%), suggesting that RSVPreF3 OA is likely to reduce severe clinical conditions and the related burden on the health-care system. A recent test-negative, case-control analysis performed in the USA over the first season after licensure of the RSV vaccines RSVPreF3 OA and RSVPreF (October, 2023 to March, 2024) showed an overall adjusted effectiveness for RSVPreF3 OA of 83% (95% CI 73–89) against RSV-associated hospitalisation in immunocompetent adults aged 60 years or older.[19] These results show a protective effect of RSVPreF3 OA against RSV-associated hospitalisations in older adults in real-world settings.

When comparing the efficacy of a single RSVPreF3 OA dose in our trial during the first season (82·6%[10]) with that during the second (56·1%[11]) and third seasons (48·0%), a decrease was noted over time, which was less pronounced between seasons two and three than between seasons one and two. Although humoral immunogenicity does not fully capture immunological protection against RSV, RSV neutralising titres observed in our trial were in line with the efficacy results, showing a steeper decline in the period between 1 month post-dose one and pre-season two than between the pre-season two and pre-season three timepoints, with pre-season three titres remaining higher than those at baseline. The lower efficacy observed in seasons two and three compared with season one might be due to a combined effect of waning efficacy and other factors, such as variations in RSV circulation between seasons, including timing and attack rates. The COVID-19 pandemic altered RSV seasonality, leading to an advanced RSV season onset in 2021 and 2022 in several countries (seasons one and two in this trial).[20–23] Viral co-infections were more frequent during RSV-LRTD episodes in season two compared with seasons one and three, but sensitivity analyses showed that efficacy was not affected by the presence of respiratory co-infections.

The season two results from our trial suggested that a second RSVPreF3 OA dose given 1 year after the initial dose did not provide additional efficacy benefit to the overall trial population.[11] The current analyses over three seasons were generally in line with these findings, although vaccine efficacy point estimates over three seasons and in season three alone were higher for the revaccination regimen than for the single dose for several endpoints. However, CIs largely overlapped, and the trial was not designed to compare efficacy for the two regimens; hence, these comparisons need to be interpreted with caution. Further research is needed to establish how long protection after a single RSVPreF3 OA dose lasts and what the optimal strategy would be for revaccination.

Safety follow-up over 3 years after RSVPreF3 OA vaccination showed a clinically acceptable safety profile, consistent with the previously reported profile,[10,11] with no acute disseminated encephalomyelitis, Guillain-Barré syndrome, or other demyelinating disorders reported after RSVPreF3 OA vaccination. Our results also showed that revaccination with RSVPreF3 OA was well tolerated, with similar reactogenicity and safety profiles observed after RSVPreF3 OA dose three compared with doses one and two.

Limitations of our trial include the low number of RSV-LRTD cases in participants who were frail and in those aged 80 years or older and the low number of RSV-related hospitalisations reported in the trial, precluding reliable efficacy estimates for these endpoints. As previously highlighted,[11] comparisons of efficacy between seasons were complicated by the different group sizes of the RSV single-dose group and RSV revaccination group in seasons two and three versus the RSVPreF3 OA group in season one.

In summary, a single dose of RSVPreF3 OA was efficacious in preventing RSV-LRTD over three RSV seasons in adults aged 60 years or older, including those at increased risk of severe RSV disease. Although efficacy decreased over time, the incidence of RSV-LRTD remained lower in the vaccine group compared with the placebo group during the third season. A revaccination regimen with two RSVPreF3 OA doses given a year apart showed an efficacy that was in the same range as that of a single dose. Further studies are needed to establish the optimal revaccination strategy to maintain clinically meaningful protection after the first dose. The efficacy, safety, and immunogenicity data reported here further support the favourable benefit–risk profile of RSVPreF3 OA to help protect against RSV-LRTD for at least three consecutive RSV seasons.

AReSVi-006 study group members

Adams, Mark; Adams, Michael; Agutu, Clara; Akite, Elaine Jacqueline; Alt, Ingrid; Andrews, Charles; Antonelli-Incalzi, Rafaelle; Asatryan, Asmik; Bahrami, Ghazaleh; Bargagli, Elena; Bhorat, Qasim; Bird, Paul; Borowy, Przemyslaw; Boutry, Céline; Brotons Cuixart, Carles; Browder, David; Brown, Judith; Buntinx, Erik; Cameron, Donald; Cartier, Cyrille; Chinsky, Kenneth; Choi, Melissa; Choo, Eun-Ju; Collete, Delphine; Corral Carrillo, Maria; Davis, Matthew G; de Heusch, Magali; de Looze, Ferdinandus; De Meulemeester, Marc; De Negri, Ferdinando; DeAtkine, David; Dedkova, Viktoriya; Dzongowski, Peter; Eckermann, Tamara; Essink, Brandon; Faulkner, Karen; Ferguson, Murdo; Fuller, Gregory; Galan Melendez, Isabel Maria; Gentile, Ivan; Ghesquiere, Wayne; Grimard, Doria; Gruselle, Olivier; Halperin, Scott; Heer, Amardeep; Helman, Laura; Hotermans, Andre; Jelinek, Tomas; Kamerbeek, Jackie; Kim, Hyo Youl; Kimmel, Murray; Koch, Mark; Kokko, Satu; Koski, Susanna; Kotb, Shady; Lalueza, Antonio; Lee, Jin-Soo; Lins, Muriel; Lombaard, Johannes; Mahomed, Akbar; Malerba, Mario; Marechal, Celine; Marion, Sandie; Martinot, Jean-Benoit; Masuet-Aumatell, Cristina; McNally, Damien; Medina Pech, Carlos Eduardo; Mendez Galvan, Jorge; Mercati, Lise; Mesotten, Dieter; Mitha, Essack; Mngadi, Kathryn; Moeckesch, Beate; Montgomery, Barnaby; Murray, Linda; Nally, Rhiannon; Narejos Perez, Silvia; Newberg, Joseph; Nugent, Paul; Ochoa Mazarro, Dolores; Oda, Harunori; Orso, Maurizio; Ortiz Molina, Jacinto; Pak, Tatiana; Park, Dae Won; Patel, Meenakshi; Patel, Minesh; Pedro Pijoan, Anna Maria; Perez, Alberto Borobia; Perez-Breva, Lina; Perez Vera, Merce; Pileggi, Claudia; Pregliasco, Fabrizio; Pretswell, Carol; Quinn, Dean; Reynolds, Michele; Romanenko, Viktor; Rosen, Jeffrey; Roy, Nathalie; Ruiz Antoran, Belen; Sakata, Hideaki; Sauter, Joachim; Schaefer, Axel; Sein Anand, Izabela; Serra Rexach, Jose Antonio; Shu, David; Siig, Andres; Simon, William; Smakotina, Svetlana; Steenackers, Katie; Stephan, Brigitte; Tafuri, Silvio; Takazawa, Kenji; Tellier, Guy; Terryn, Wim; Tharenos, Leslie; Thomas, Nick; Toursarkissian, Nicole; Ukkonen, Benita; Vale, Noah; Van Landegem, Pieter-Jan; Vanden Abeele, Carline; Vermeersch, Lode; Vitale, Francesco; Voloshyna, Olga; White, Judith; Wie, Seong-Heon; Wilson, Jonathan; Ylisastigui, Pedro; and Zocco, Manuel.

Contributors

ND, LF, AO, MVdW, and DD were involved in the conception or design of the trial. MGI, AP, EA, RGF, JML, D-GL, IL-R, FM-T, TFS, and RNvZ-S participated in the acquisition or generation of the data. LF, SX, and M-PD performed the data analysis. MGI, AP, EA, RGF, JML, D-GL, IL-R, FM-T, TFS, RNvZ-S, SC, QD, ND, CG, LF, SX, M-PD, AO, MVdW, and DD were involved in the interpretation of the data. AP, LF, and

AO accessed and verified the underlying data reported in the manuscript. All authors had access to the data, critically revised the manuscript drafts, approved the final submitted version, and were responsible for the decision to submit this manuscript for publication.

Declaration of interests

MGI declares that research support from GSK was paid to his previous institution, Northwestern University; he received consulting fees paid by Adagio Therapeutics, ADMA Biologics, Adamis Pharmaceuticals, AlloVir, Atea, Cidara Therapeutics, Genentech/Roche, Janssen, Shionogi, Takeda, Talaris, and Eurofins Viracor; and payment for participation in data safety monitoring boards or advisory boards from Adamis Pharmaceuticals, AlloVir, National Institutes of Health, CSL Behring, Janssen, Merck, Seqirus, Takeda, and Talaris; all of these ended in December, 2022. MGI also receives author royalties from UpToDate, which is ongoing, and serves as Chair of the International Society for Influenza and other Respiratory Virus Diseases Antiviral Group, and was Editor-in-Chief of *Transplant Infectious Disease*. MGI's involvement was separate from his government service, and the comments are his own. MGI was a consultant for Romark but received no consulting fees. AP declares funding from GSK for conducting the trial; grants paid to his institution from GSK, Chiesi, AstraZeneca, Sanofi, and Agenzia Italiana del Farmaco; consulting fees from GSK, Chiesi, AstraZeneca, Sanofi, Novartis, Avillion, ELPEN Pharmaceuticals, Zambon, and Edmond Pharma; payment for participation in advisory boards from GSK, Chiesi, AstraZeneca, Sanofi, Novartis, Avillion, ELPEN Pharmaceuticals, Zambon, Edmond Pharma, and IQVIA; and honoraria from GSK, Chiesi, AstraZeneca, Sanofi, Novartis, Avillion, ELPEN Pharmaceuticals, Menarini, Zambon, Mundipharma, Edmond Pharma, and IQVIA. RGF declares having received payment from GSK for congress and speaking events lectures and support for travel related to these activities. JML reports grants paid to her institution from GSK, Pfizer, Merck, Moderna, Sanofi, Inventprise, and VBI Vaccines for conducting trials; and participation on a data safety monitoring board or advisory board for Vaxcyte, Sanofi, GSK, Merck, and Seqirus. IL-R declares grants or research support paid to her institution from GSK, Icosavax, Janssen Vaccines, Curevac, Moderna, Osivax, MSD, and OSE Immunotherapeutics for conducting trials; and payment for participation on a data safety monitoring board or advisory board from Janssen Vaccines and MSD. FM-T declares grants or research support payments to his institution from GSK, Sanofi, Moderna, MSD, Novavax, and Pfizer for conducting vaccine trials; and consulting fees or participation on advisory boards for GSK, Sanofi, MSD, Moderna, AstraZeneca, Biofabri, CSL-Seqirus, Novavax, and Janssen. TFS reports participation on data safety monitoring boards or advisory boards from AstraZeneca, Bavarian Nordic, Biogen, BioNTech, CSL-Seqirus, CSL-Vifor, Diasorin, GSK, Janssen-Cilag, Merck-Serono, Moderna, MSD, Novavax, Pfizer, Roche, Sanofi-Aventis, Synlab, and Takeda. RNvZ-S reports that his institution received support from Boehringer Ingelheim for the Interstitial Lung Disease registry and consulting fees from GSK and honoraria for lectures from Glenmark, Boehringer Ingelheim, Cipla, and Novartis; and payment for participation on data safety monitoring boards or advisory boards for OnQ SA. SC, QD, ND, CG, LF, SX, M-PD, AO, MVdW, and DD are employed by GSK; SC, QD, ND, CG, LF, M-PD, AO, MVdW, and DD hold financial equities in GSK. ND is co-applicant on a pending patent for vaccination against RSV and a patent regarding methods for eliciting an immune response to RSV and *Streptococcus pneumoniae* infections. MVdW has stock options from Haleon. LF, M-PD, AO, and MVdW are part of vaccine patents filed by GSK. The authors declare no other financial or non-financial relationships. EA and D-GL declare no competing interests.

For the **GSK study register** see https://www.gsk-studyregister.com/en/

Data sharing

Please refer to the GSK Study Register to access GSK's data sharing policies and to request anonymised participant-level data.

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