***Disclaimer**: This abstract was accepted for poster presentation after review by the CHEST 2024 Scientific Presentations and Awards Committee at the 2024 CHEST Conference, October 6-9, in Boston, US. Due to the late-breaking nature of the data, this abstract is not available in the 2024 CHEST Supplement. This copy is for health professionals who attended the congress.*

Cite as (adapt as appropriate):

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, Aurélie Olivier, Marie Van der Wielen, Dominique Descamps, on behalf of the AReSVi-006 study group. The Efficacy of a Single Dose of the Respiratory Syncytial Virus Prefusion F Protein Vaccine in Adults ≥60 Years of Age Over 3 RSV Seasons. Poster 3391 presented at CHEST 2024 – (2024 October 6-9), Boston, United States. https://events.rdmobile.com/Lists/Details/2538335

Title:

THE EFFICACY OF A SINGLE DOSE OF THE RESPIRATORY SYNCYTIAL VIRUS PREFUSION F PROTEIN VACCINE IN ADULTS ≥60 YEARS OF AGE OVER 3 RSV SEASONS

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SESSION TITLE: Chest Infections Abstracts Posters (F)

SESSION TYPE: Original Investigation Posters

PRESENTED ON: Tuesday, October 8, 2024, 1:45 PM – 2:30 PM EDT

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Purpose: We report the persistence of vaccine efficacy (VE) of a single dose of respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVPreF3 OA) over 3 RSV seasons.

Methods: In this phase 3, placebo-controlled, double-blind, multi-country study (NCT04886596), adults ≥60 years of age (YOA) were randomized 1:1 to receive RSVPreF3 OA or placebo pre-RSV season 1. RSVPreF3 OA recipients were re-randomized 1:1 pre-season 2 to receive a second RSVPreF3 OA dose (data not shown) or placebo; placebo recipients from pre-season 1 received placebo pre-season 2. VE against RSV-related lower respiratory tract disease (RSV-LRTD) overall and by RSV subtype over 3 RSV seasons were confirmatory secondary objectives. VE against severe RSV-LRTD, RSV-LRTD by age, baseline comorbidity and frailty status, VE against RSV-related acute respiratory illness (ARI) and safety were also assessed. VE was calculated using a Poisson model with season or without (w/o) season (post-hoc analysis) as covariate.

Results: The exposed set (ES) comprised 24,972 participants; 24,966 were included in the modified ES (current VE analyses). The median follow-up over 3 seasons was 30.6 months. The efficacy of a single RSVPreF3 OA dose against RSV-LRTD over 3 RSV seasons was demonstrated, with VE estimates of 62.9% (97.5% CI: 46.7–74.8; with season as covariate) and 69.1% (97.5% CI: 55.8–78.9; w/o season as covariate). VE was demonstrated over 3 seasons against RSV-LRTD caused by RSV-A (69.8%, 97.5% CI: 42.2–85.7 [w/o season: 75.7%, 53.6–88.5]) and RSV-B (58.6%, 97.5% CI: 35.9–74.1 [w/o season: 65.0%, 46.1–78.1]). VE over 3 RSV seasons was 67.4% (95% CI: 42.4–82.7 [w/o season: 72.3%, 51.3–85.2]) against severe RSV-LRTD and 51.1% (95% CI: 40.3–60.2 [w/o season: 57.9%, 48.6–65.6]) against RSV-ARI. VE over 3 seasons was also clinically relevant in participants 60–69 YOA, 70–79 YOA, those with ≥1 baseline comorbidity of interest and pre-frail participants. VE of a single dose of RSVPreF3 OA against RSV-LRTD during season 3 was 48.0% (95% CI: 8.7–72.0). The frequency of serious adverse events and potential immune-mediated diseases remained low and balanced across groups through the study. No cases of Guillain-Barré syndrome or acute disseminated encephalomyelitis were reported up to study end.

Conclusions: A single RSVPreF3 OA dose provides clinically relevant protection against RSV disease over 3 RSV seasons in adults ≥60 YOA, regardless of RSV subtype, disease severity (RSV-LRTD, severe RSV-LRTD and RSV-ARI), baseline comorbidities or age, and in pre-frail

participants, with an acceptable safety profile. This supports a favorable benefit-risk profile of RSVPreF3 OA over 3 RSV seasons.

Clinical Implications: Older adults or those with comorbidities are at increased risk of LRTD, hospitalization and death due to RSV. A single dose of RSVPreF3 OA offers clinically meaningful protection against RSV-LRTD in adults ≥60 YOA with or without comorbidities over 3 RSV seasons.

Funding: GSK

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Acknowledgement: We are grateful to all participants, study team members, investigators, and study site staff for their contributions to the study, to the members of the independent data monitoring committee: Robert B. Belshe, Nadia Tornieporth, Catherine Legrand, and Donald Middleton; to the members of the Adjudication Committee: Carlos Luna, Harish Nair, Yuichiro Shindo, Christian Uggerhoej Woehlk, Jeroen Van der Hilst, Jadwiga Wedzicha, and Carl Heinz Wirsing von Koening; and to all the AReSVi-006 study group members (see Supplementary materials), their staff, and their institutions. We also thank Akkodis Belgium (c/o GSK) for medical writing (by Noemi Sas), design, and coordination support. The GSK team

members dedicate this publication to the memory of their dear colleague Céline Boutry who contributed with passion to the delivery of this study.

Disclosures: 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; 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 and/or 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; participation on a data safety monitoring board or advisory board for Vaxcyte and Seqirus. **ILR** declares grants or research support paid to her institution from GSK, Icosavax, Janssen Vaccines, Curevac, Moderna, Osivax, MSD, and OSE Immunotherapeutics for conducting trials; consulting services and/or payment for participation on a data safety monitoring board or advisory board from Janssen Vaccines and MSD. **FMT** declares grants or research support payments to his institution from GSK, Sanofi, and Pfizer for conducting vaccine trials; and consulting fees or participation on advisory boards for GSK, Sanofi, MSD, Moderna, AstraZeneca, Novavax, and Janssen. **TFS** reports honoraria and/or 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. **RNZS** reports that his institution received support from Boehringer Ingelheim for the ILD (Interstitial Lung Disease) registry and consulting fees from GSK and honoraria for lectures from Glenmark, Boehringer Ingelheim, Cipla, and Novartis; payment for participation on data safety monitoring boards or advisory boards for OnQ SA. **SC, QD, ND, CG, LF, SX, AO, MVdW,** and **DD** are employed by GSK; **SC, QD, ND, CG, LF, 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 eliciting immune response to RSV and S. pneumoniae infections. **MVdW** has stock options from Haleon. **LF, AO,** and **MVdW** are part of vaccine patents filed by GSK. The authors declare no other financial or non-financial relationships. **EA** and **DGL** declare no conflicts of interest.