Respiratory syncytial virus vaccine in older adults side-by-side comparison

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Executive Summary

Introduction

Respiratory syncytial virus (RSV) is a highly contagious human pathogen that is responsible for yearly epidemics during the winter season in the Northern hemisphere. RSV strains are separated into 2 major phylogenetic lineages, RSV subtypes A and B. Both subtypes typically co-circulate each season; however, the prevalence of the dominating RSV subtype varies across seasons. Symptoms of upper respiratory tract infection due to RSV include cough, headache, rhinorrhea, pharyngitis, fatigue, and fever. RSV is a common cause of lower respiratory tract disease in older adults and can lead to severe disease, which may require oxygen, intubation, and mechanical ventilation. The risk of severe RSV disease increases with age and comorbidities, such as chronic obstructive pulmonary disease, congestive heart failure, and asthma. Each year between 60,000 and 120,000 adults ≥ 65 years of age in the US are hospitalized and 6,000 to 10,000 die due to RSV infection. For comparison, during the 2019-2020 influenza season, there were approximately 171,000 hospitalizations and 16,000 deaths related to influenza in adults ≥ 65 years of age. Development of an RSV vaccine that can protect against RSV illness addresses an unmet medical need due to the lack of preventive therapies and limited treatment options.

On May 3, 2023, FDA approved Arexvy (GlaxoSmithKline)--the first RSV vaccine for use in the US. Arexvy is indicated to prevent lower respiratory tract disease caused by RSV in adults 60 years and older. A second RSV vaccine, Abrysvo (Pfizer) was approved on May 31, 2023, for the same indication. Pfizer is also seeking approval for the use of Abrysvo for maternal use, with an FDA decision expected in August 2023. Arexvy is an adjuvanted, monovalent vaccine containing the RSVpreF3 subgroup A antigen with $AS01_E$ adjuvant. Abrysvo is a bivalent, non-adjuvanted vaccine, containing the RSVpreF subgroup A antigen and RSVpreF subgroup B antigen.

ACIP recommendations for RSV vaccines in older adults

The Advisory Committee on Immunizations Practices (ACIP) met in June 2023 to vote on the use of RSV vaccines in older adults. The committee approved the recommendation that adults ≥ 60 years of age may receive a single dose of RSV vaccine (without preference), using shared clinical decision making. ACIP's complete recommendations on the use of RSV vaccine in older adults were published in *Morbidity and Mortality Weekly Report* on July 21, 2023.

Efficacy

Arexvy and Abrysvo were each evaluated in a large, multicenter, double-blind, randomized, placebo-controlled, phase 3 trial, AResVi-006 and RENIOR, respectively. Efficacy results are reported for a single RSV season; both trials are ongoing with plans to assess efficacy across subsequent RSV seasons. Each trial evaluated the prevention of lower respiratory disease as the primary endpoint, though the terminology and definition for this endpoint differed slightly between trials. In AResVi-006, the endpoint was referred to as lower respiratory trace disease (LRTD), while the RENOIR trial called this endpoint lower respiratory tract infection (LRTI). Endpoint definitions are provided in the side-by-side comparison table below. Relative vaccine efficacy against LRTD in the AResVi-006 trial was 82.6% (96.95% CI, 57.9-94.1%). In RENIOR, RSV-related LRTI was evaluated in patients who had either ≥ 2 symptoms or ≥ 3 symptoms. Relative vaccine efficacy was 66.7% (96.66% CI, 28.8-85.8%) in patients with ≥ 2 symptoms and 85.7% (96.66% CI, 32-98.7%) in patients with ≥ 3 symptoms. Relative vaccine efficacy against severe LRTD with Arexvy was 94.1% (95% CI, 62.4-99.9%). Efficacy results against severe LRTI with Abrysvo were not reported in the RENIOR trial because the number of events did not meet the prespecified minimum number of cases for the interim analysis. For more general acute respiratory illness (ie, less severe disease), Arexvy had a relative vaccine efficacy of 71.7% (95% CI, 56.2-82.3%) and Abrysvo had a relative vaccine efficacy of 62.1% (95% CI, 37.1-77.9%). Vaccine efficacy across endpoints was demonstrated for subgroups with RSV subtypes A and B for both vaccines. Further study is needed to understand how both vaccines impact clinically important outcomes such as RSV-associated hospitalization and death, as event rates from available data for such outcomes are too low to draw any conclusions. Additionally, given that the currently available data are from a single RSV season with relatively short durations of follow-up, the durability of the efficacy for these vaccines across subsequent RSV seasons is currently unknown.

Safety

Overall, both Arexvy and Abrysvo were well tolerated in clinical studies in older adults. While not compared head-to-head, Arexvy appears to have numerically higher incidence rates of adverse reactions in general than what was observed with Abrysvo. The reason for this is unknown, but vaccines containing adjuvants may cause more local and systemic adverse reactions. The most common adverse reactions with Arexvy are injection-site pain (60.9%), fatigue (33.6%), myalgia (28.9%), headache (27.2%), and arthralgia (18.1%). The most common adverse reactions with Abrysvo are fatigue (15.5%), headache (12.8%), pain at the injection-site (10.5%), and muscle pain (10.1%). Rates of serious adverse reactions were low and similar with placebo groups in studies with both Abrysvo and Arexvy. FDA's VRBPAC voted 10-2 in support of the safety of Arexvy based on concerns around 1 case of Guillain Barré Syndrome (GBS) and 2 cases of acute disseminated encephalomyelitis (ADEM) seen across 2 separate, smaller, phase 3 studies (Study 004; N = 1,653 and Study 007; N = 868). No cases of GBS or ADEM were reported in the AResVi-006 trial (N = 24,966). For Abrysvo, VRBPAC voted 7-4 in support of safety. Two cases of GBS or a variation of GBS were reported following vaccination in the RENIOR study (N = 34,284). Given the relatively low number of patients who have received these vaccines in clinical studies, the occurrence of these events could highlight a potential safety signal that will be important to monitor with the RSV vaccines moving forward. FDA has required postmarketing surveillance studies for both vaccines as a condition of approval. GSK's study is expected to be completed by June 30, 2030 and Pfizer's study is expected to be completed by May 31, 2029.

Summary

Two RSV vaccines, Arexvy and Abrysvo, are approved for use in adults ≥ 60 years of age. For this population, ACIP recommends a single dose of either vaccine without preference, based on shared clinical decision making. Both vaccines have demonstrated efficacy in reducing RSV-related LRTD/LRTI in the first RSV season following vaccination. The pivotal trials for both Arexvy and Abrysvo are both ongoing to evaluate the durability of vaccine efficacy in subsequent RSV seasons. Additionally, further evaluation is needed to better understand the impact of both vaccines on clinically important outcomes such as RSV-associated hospitalization and death. Postmarketing surveillance studies of vaccine safety are planned for both vaccines to further evaluate potential safety signals seen in clinical studies.

Respiratory syncytial virus vaccine in older adults side-by-side comparison

	Generic name (brand name)	
	Respiratory syncytial virus vaccine, adjuvanted (Arexvy)[1]	**Respiratory syncytial virus vaccine (Abrysvo)[2]**
Manufacturer	GlaxoSmithKline	Pfizer
Approval date	May 3, 2023	May 31, 2023
FDA-approved indications		
Approved population	Adults ≥ 60 y of age	Adults ≥ 60 y of age
Indications	Active immunization for the prevention of LRTD caused by RSV in individuals ≥ 60 y	Active immunization for the prevention of LRTD caused by RSV in individuals ≥ 60 y
Pharmacology[3,4]		
Vaccine composition	**Monovalent** - RSVpreF3 subgroup A antigen with $AS01_E$ adjuvant	**Bivalent** – RSVpreF subgroup A antigen and RSVpreF subgroup B antigen
Antigen content	120 micrograms of RSVPreF3 antigen (subgroup A)	120 micrograms total – 60 micrograms preF subgroup A antigen and 60 micrograms preF subgroup B antigen
Adjuvant	$AS01_E$	None
Mechanism of action	Induces immune response against RSVpreF3 that protects against LRTD caused by RSV	Induces immune response against RSVpreF that protects against LRTD caused by RSV
Vaccination schedule		
Dose	Single 0.5 mL dose	Single 0.5 mL dose
Schedule	Once	Once
ACIP recommendations[5,6]	**Recommendation:** Adults ≥ 60 y may receive a single dose of RSV vaccine, using shared clinical decision making (full recommendations available in *MMWR* published on July 21, 2023)	
Preparation and administration		
Reconstitution	Reconstitute with adjuvant suspension (supplied)	Reconstitute with sterile water diluent (supplied)
Preparation	• Supplied as 2 vials, including the lyophilized antigen component and the adjuvant suspension component • Prepare by reconstituting lyophilized antigen component with the **adjuvant suspension** component • Following reconstitution, store under refrigeration, between 2˚C and 8˚C, or at room temperature, up to 25˚C, and use within 4 h.	• Supplied as kit with lyophilized antigen component, a prefilled syringe continuing sterile water diluent, and a vial adapter • Prepare by reconstituting lyophilized antigen component with the **sterile water diluent** component utilizing the included vial adapter • Following reconstitution, store at room temperature, between 15˚C and 30˚C, and use within 4 h. Do not refrigerate or freeze reconstituted vaccine.

	Generic name (brand name)	
	Respiratory syncytial virus vaccine, adjuvanted (Arexvy)[1]	**Respiratory syncytial virus vaccine (Abrysvo)[2]**
Administration	Intramuscular	Intramuscular
Co-administration with other vaccines		
ACIP recommendations[6]	Coadministration of RSV vaccines with other adults vaccines is acceptable. However, data are currently only available for coadministration of RSV vaccines with influenza vaccines. RSV and influenza antibodies were somewhat lower with coadministration; however, the clinical significance of this finding is unknown. Data on immunogenicity with other vaccines is overall limited. Administering RSV vaccine with ≥ 1 other vaccines might increase local or systemic reactogenicity.	
Influenza vaccine	Concomitant administration of Arexvy with quadrivalent IIV (standard-dose used in ≥ 60 y and high-dose or adjuvanted used in ≥ 65 y) was evaluated in a phase 3 study. The GMT ratio in antibody response was similar between coadministration and sequential administration of the vaccines 1 mo following completion of vaccination.[7,8] Noninferiority criteria for immunogenicity was met with the exception of the FluA/Darwin H3N2 strain.[6] Overall, safety was similar between concomitant and sequential administration; numerically higher local and systemic adverse reactions occurred with concomitant administration.[7,8]	Concomitant administration of Abrysvo with quadrivalent IIV (standard-dose only) was evaluated in adults ≥ 65 y in a phase 3 study. Noninferiority was demonstrated for GMT ratio antibody responses between coadministration and sequential administration of the vaccines 1 mo following completion of vaccination. Seroprotection and seroconversion rates were also similar. Overall, safety was similar between concomitant and sequential administration; there were some numerically higher local and systemic adverse reactions that occurred with concomitant administration.[9,10]
Other vaccines	No information available	No information available
Safety		
Contraindications	History of severe allergic reaction (eg, anaphylaxis) to any component of vaccine	
Precautions	• **Preventing and managing allergic vaccine reactions:** appropriate medical supervision and treatment must be available in the event of an anaphylactic reaction following administration • **Syncope:** syncope may occur • **Alter immunocompetence**: immunocompromised individuals may have a diminished immune response to the vaccine	
	--	**Limitations of effectiveness:** vaccination may not protect all vaccine recipients
Adverse reactions	The most common (incidence ≥ 10%) adverse reactions are injection-site pain (60.9%), fatigue (33.6%), myalgia (28.9%), headache (27.2%), and arthralgia (18.1%).	The most common (incidence ≥ 10%) adverse reactions are fatigue (15.5%), headache (12.8%), pain at the injection-site (10.5%), and muscle pain (10.1%).
Drug-drug interactions	Not addressed in product labeling	
Special populations		
Pregnancy or lactation	Not approved for used in individuals < 60 y.	Not approved for used in individuals < 60 y.* **Pfizer has submitted for approval for maternal use with an FDA decision expected in August 2023.*

	Generic name (brand name)	
	Respiratory syncytial virus vaccine, adjuvanted (Arexvy)[1]	**Respiratory syncytial virus vaccine (Abrysvo)[2]**
	Pregnancy • A clinical study evaluated a nonadjuvanted RSV vaccine found an increase in preterm births (6.81%) compared with placebo (4.95%). **Lactation** • Unknown if excretion occurs in human milk.	**Pregnancy** • A clinical study evaluating Abrysvo vs placebo administered at 24 to 36 wks gestation did not find evidence for vaccine-associated increases in risk of congenital anomalies or fetal deaths. A numerically higher incidence of preterm births were found in the Abrysvo group (5.7%) compared with placebo (4.7%). **Lactation** • Unknown if excretion occurs in human milk.
Pediatric	Not approved for used in individuals < 60 y. Evidence from an animal model suggests that vaccination of individuals < 2 y would be unsafe due to increased risk of enhanced respiratory distress. Safety and effectiveness in individuals 2 to 17 y have not been established.	Not approved for used in individuals < 60 y. Safety and effectiveness in individuals < 18 y have not been established.
Efficacy summary (older adults)		
Trial	AResVi-006[3,11]	RENOIR[4,12]
N	24,966	34,284
Design	Multicenter, double-blind, randomized, placebo-controlled phase 3 trial	Multicenter, double-blind, randomized, placebo-controlled phase 3 trial

Population	• Adults ≥ 60 y
	• Healthy or stable chronic medical condition
	  ○ ~40% of patients had a pre-existing condition of interest*
	  ○ ~33% of patients where classified as high risk based on the Charlson comorbidity index
	**Includes COPD, asthma, any chronic respiratory or pulmonary disease, chronic heart failure, diabetes mellitus type 1 or type 2, advanced liver disease, or advanced renal disease*
		• Adults ≥ 60 y
		• Healthy or stable chronic medical condition
		  ○ ~52% of patients had ≥ 1 pre-specified high risk condition*
		  ○ ~15% of patients had ≥ 1 cardiopulmonary condition**
		**Includes tobacco use, diabetes, lung disease, heart disease, liver disease, and renal disease*
		***Includes asthma, COPD, and congestive heart failure*

Intervention	1:1 randomization to Arexvy or placebo	1:1 randomization to Abrysvo or placebo
Endpoint definitions	• **ARI:** ≥ 2 respiratory signs or symptoms OR ≥ 1 respiratory and 1 systemic symptom lasting ≥ 24 h • **LRTD:** ≥ 2 lower respiratory signs or symptoms (including ≥ 1 lower respiratory sign) OR ≥ 3 lower respiratory symptoms lasting ≥ 24 h	• **ARI:** ≥ 1 respiratory symptom • **LRTI:** ARI with ≥ 2 lower respiratory symptoms OR ≥ 3 lower respiratory symptoms, each lasting ≥ 24 h • **Severe LRTI:** LRTI and hospitalization, new or increased oxygen supplementation, or new or increased mechanical ventilation

	Generic name (brand name)	
	Respiratory syncytial virus vaccine, adjuvanted (Arexvy)[1]	**Respiratory syncytial virus vaccine (Abrysvo)[2]**
	• **Severe LRTD:** ≥ 2 lower respiratory signs, assessed as "severe" by investigators, or receipt of additional supportive therapy (eg, oxygen supplementation)	
Signs and symptom definitions	• **Upper respiratory signs or symptoms:** nasal congestion, sore throat • **Lower respiratory symptoms:** sputum, cough, dyspnea • **Lower respiratory signs:** wheezing, crackles/rhonchi, tachypnea, hypoxemia, oxygen supplementation • **Systemic signs or symptoms:** fever, fatigue, body aches, headache, decrease appetite	• **ARI symptoms:** nasal discharge, nasal congestion, sore throat, cough, sputum production, wheezing, shortness of breath • **LRTI symptoms:** cough, sputum production, wheezing, shortness of breath, tachypnea *(No distinction made between signs and symptoms in RENOIR trial)*
Primary endpoint definition	Prevention of RSV-related LRTD confirmed by PCR in first RSV season	Prevention of RSV-related LRTI confirmed by PCR in first RSV season
Primary endpoint results	**rVE:** 82.6% (96.95% CI, 57.9-94.1%) *ARR (calculated):* ~0.26%	**rVE (≥ 2 symptoms):** 66.7% (96.66% CI, 28.8-85.8%) *ARR (calculated):* ~0.13% **rVE (≥ 3 symptoms):** 85.7% (96.66% CI, 32-98.7%) *ARR (calculated):* ~0.08%
Severe LRTD/LRTI results (season 1)	**rVE:** 94.1% (95% CI, 62.4-99.9%) *ARR (calculated):* ~0.13%	**Not reported** – events did not meet prespecified minimum number of cases for the interim analysis
ARI results (season 1)	**rVE:** 71.7% (95% CI, 56.2-82.3%) *ARR (calculated):* ~0.54%	**rVE:** 62.1% (95% CI, 37.1-77.9%) *ARR (calculated):* ~0.23%
How supplied		
Supplied as	2 components • SDV of lyophilized antigen component • SDV of adjuvant suspension component	Kit • SDV of lyophilized antigen component • Prefilled syringe of sterile water diluent • Vial adapter
Syringe included	No	Yes (syringe with diluent is used to withdraw reconstituted vaccine)
Preservatives	No	No
Latex	No	No
Storage prior to use	Store both antigen vial and adjuvant vial at 2˚C to 8˚C. Do not freeze.	Store kit at 2˚C to 8˚C. Do not freeze.
Cost (WAC)[13]	$280	$295

Summary of evidence

Background: RSV is a highly contagious human pathogen that is responsible for yearly epidemics during the winter season in the Northern hemisphere. RSV strains are separated into 2 major phylogenetic lineages, RSV subtypes A and B. Both subtypes typically co-circulate each season; however, the prevalence of the dominating RSV subtype varies across seasons.[3,4] Symptoms of upper respiratory tract infection due to RSV include cough, headache, rhinorrhea, pharyngitis, fatigue, and fever. RSV is a common cause of LRTD in older adults and can lead to severe disease, which may require oxygen, intubation, and mechanical ventilation.[14] The risk of severe RSV disease increases with age and comorbidities, such as chronic obstructive pulmonary disease, congestive heart failure, and asthma. CDC collects data for RSV laboratory results through a voluntary surveillance system called the National Respiratory and Enteric Virus Surveillance System. RSV surveillance reports at the national, regional, and state levels are periodically analyzed and published by CDC. Each year between 60,000 and 120,000 adults ≥ 65 years of age in the US are hospitalized and 6,000 to 10,000 die due to RSV infection.[6,15] For comparison, during the 2019-2020 influenza season, there were approximately 171,000 hospitalizations and 16,000 deaths related to influenza in adults ≥ 65 years of age.[16] Infection with RSV does not confer long-term immunity. Partial protection against homologous strains of RSV following infection does occur, but reliable and durable protection is not achieved, and re-infection throughout life is common. There are also currently limited treatment options for RSV, with treatment primarily being focused on supportive care. Therefore development of an RSV vaccine that can protect against RSV illness addresses an unmet medical need.[17-19]

On May 3, 2023, FDA approved Arexvy (GlaxoSmithKline)--the first RSV vaccine for use in the US. Arexvy is indicated to prevent lower respiratory tract disease caused by RSV in adults 60 years and older.[1] A second RSV vaccine, Abrysvo (Pfizer) was approved on May 31, 2023, for the same indication.[2] Arexvy is an adjuvanted, monovalent vaccine containing the RSVpreF3 subgroup A antigen with $AS01_E$ adjuvant. $AS01_E$ is a proprietary adjuvant component from GSK and is similar to GSK's $AS01_B$ adjuvant that is used in the herpes zoster vaccine, Shingrix. The $AS01_E$ adjuvant suspension contains monophosphoryl lipid A (MPL), a chemically detoxified form of lipopolysaccharide from *Salmonella Minnesota*, and QS-21, a saponin derived from the purified bark of a type of South American tree. $AS01_E$ contains half the amount of MPL and QS-21 contained in $AS01_B$.[14] Abrysvo is a bivalent vaccine, without adjuvant, containing the RSV preF subgroup A antigen and RSV preF subgroup B antigen.[2,4]

ACIP recommendations: ACIP met in June 2023 to vote on the use of RSV vaccines in older adults. The original vote language identified 2 separate patient populations, those 60 to 64 years of age and those ≥ 65 years of age. Originally, the vote language for patients 60 to 64 years of age was based on shared clinical decision making, while the recommendation language for patients ≥ 65 years was a routine recommendation. However, this language was amended to also be based on shared clinical decision making. Ultimately, the RSV recommendation approved in adults was for use of a single dose of either Arexvy or Abrysvo, without preference, in patients ≥ 60 years of age based on shared clinical decision making.[5] ACIP's complete recommendations on the use of RSV vaccine in older adults was published in *Morbidity and Mortality Weekly Report* on July 21, 2023. Recommendations for shared clinical decision making differ from routine and risk-based recommendations, as they do not target all persons in a certain age or risk group. The decision to vaccinate should be based on a discussion between the health care provider and the patient. Factors for consideration include risk for disease; patient's characteristics, values, and preferences; provider's clinical judgement, and vaccine characteristics. ACIP outlined key factors that are known to increase the risk of severe RSV disease, which include lung disease (eg, COPD, asthma), cardiovascular disease (eg, CHF, CAD), moderately to severely immunocompromised, diabetes mellitus, neurologic or neuromuscular conditions, kidney disorders, liver disorders, hematologic disorders, persons who are frail, persons of advanced age (eg, ≥ 75 years), residence in nursing home or other long-term care facility, or other underlying factors determined to increase risk of severe disease by healthcare provider.[6]

Efficacy data: Prior to FDA approval, the vaccine efficacy data for both products was reviewed by VRBPAC. The Committee voted 12-0 in favor of Arexvy's efficacy data and 7-4 in favor of Abrysvo's efficacy data in older adults.[3,4]

Arexvy and Abrysvo were each evaluated in a large, multicenter, double-blind, randomized, placebo-controlled, phase 3 trial, AResVi-006[11] and RENIOR[12], respectively. The results of both trials are summarized individually below. Each trial evaluated the prevention of lower respiratory disease as the primary endpoint, though the terminology and definition for this endpoint differed slightly between trials. In AResVi-006, the endpoint was referred to as lower respiratory trace *disease* (LRTD), while the RENOIR trial called this endpoint lower respiratory tract *infection* (LRTI). Additionally, a distinction between RSV signs and symptoms was made for study endpoint definitions in the AResVi-006 study, while no such distinction was made in the RENOIR study. Therefore, while the endpoints evaluated were similar between trials, the lack of a consistent definition makes indirect comparison of results more difficult. Study endpoint definitions for each trial are provided in the table above for reference.

Both trials also reported the efficacy for preventing ARI (ie, less severe RSV disease), again with differing definitions. For ARI, RENIOR required ≥ 1 respiratory symptom, while AResVI-006 required ≥ 2 respiratory signs or symptoms or ≥ 1 respiratory and ≥ 1 systemic symptom.

While preventing of ARI and LRTD/I are useful outcomes to evaluate, it is also important to assess the efficacy of these vaccines for preventing severe disease, including hospitalization and death. Both trials included endpoint definitions for severe LRTD/I in study protocols; however, results for this outcome were only reported in the AResVI-006 trial.[11,12] Severe LRTI was not included in the analysis for the RENIOR trial because the number of cases of severe disease that had been accrued at the data cut-off date did not meet the prespecified minimum number of cases for the interim analysis.[12] The definition of severe LRTD used in the AresVi-006 trial was LRTD with ≥ 2 lower respiratory signs, LRTD assessed as "severe" by investigators, or LRTD requiring receipt of additional supportive therapy (ie, oxygen supplementation, positive airway pressure, or other types of mechanical ventilation). The event rate for this outcome was low with 1 case in the vaccine group and 17 cases in the placebo group. Across the total study population, 2 participants required hospitalization due to RSV disease, and there were no RSV-related deaths reported.[11] Overall, there is limited information on the effectiveness of these vaccines in preventing key, clinically important outcomes of interest such as hospitalization and death based on the available data.

Both of the pivotal trials for these 2 vaccines are ongoing. Currently, published data are available for a single RSV season with relatively short durations of follow-up; therefore the durability of the efficacy for these vaccines across subsequent RSV seasons is unknown and it remains to be seen if a single dose will provide adequate protection in all patients. However, data from interim analyses for efficacy during the second RSV season for both vaccines are available and presented in the individual study summaries below. The efficacy during the second RSV season appears to be lower compared with the first RSV season for preventing LRTD/I for both vaccines based on initial data.[6] Additionally, the published efficacy data presented thus far for both vaccines were collected during the 2021-22 RSV season. Public health measures in effect due to COVID-19 during this time frame likely had an impact on the RSV season evaluated (eg, baseline immunity could have been altered in the study population). This further illustrates the importance of continuing to gather data on vaccine efficacy in future RSV seasons to ascertain a clearer understanding of the true clinical benefit of these vaccines.

AResVi-006 study[11] (Arexvy; GSK): This is an ongoing, multicenter, double-blind, randomized, placebo-controlled phase 3 trial comparing Arexvy with placebo in 24,966 adults ≥ 60 y. Data collection will continue across 2 to 3 RSV seasons; study results presented here are for vaccine efficacy during the first RSV season. Participants were eligible for the study if they were healthy or had stable chronic medical conditions. The primary efficacy endpoint was the prevention of RSV-related LRTD during 1 RSV season. Additional efficacy endpoints included severe RSV-related LRTD, RSV-related ARI, outcome evaluation by RSV subtype (A or B), age, and presence of risk factors, such as comorbidities. The primary efficacy analysis occurred in the modified exposed population, which included any participants who received either RSV vaccine or placebo and did not report an RSV-related ARI prior to 15 d following vaccination. The *a priori* success criterion for the primary objective required the lower limit of the 96.95% 2-side CI to exceed 20%. Vaccine efficacy was calculated as 1 minus the relative risk. No adjustment for multiplicity was applied to analyses of secondary endpoints. For the primary endpoint, 7 patients (incidence rate: 1 event / 1,000 patient y) in the vaccine group compared with 40 patients (incidence rate: 5.8 events / 1,000 patient y) in the placebo group reported an episode of RSV-related LRTD during a median follow-up of 6.7 mo. The relative vaccine efficacy for the primary endpoint was 82.6% (96.95% CI, 57.9-94.1%); this met the primary objective criteria for efficacy. The ARR for the primary outcome was ~0.26%. In an interim analysis, the relative vaccine efficacy for the primary endpoint during the second RSV season (August 2022 to March 2023) was 56.1% (95% CI, 28.2-74.4%), which is lower compared with the first RSV season.[6] Relative vaccine efficacy against severe LRTD during the first RSV season was 94.1% (95% CI, 62.4-99.9%), with 1 case occurring in the vaccine group and 17 cases occurring in the placebo group. The ARR for severe LRTD was ~0.13%. RSV-related LRTD was further evaluated across various subgroups. Two-thirds of the RSV-related LRTD cases during the first season in this study were attributable to the RSV B subtype. Relative vaccine efficacy for LRTD was 84.6% for RSV subtype A and 80.9% for RSV subtype B, suggesting that protection against both subtypes is provided despite Arexvy containing antigen for subtype A alone. Relative vaccine efficacy tended to increase as age increased across subgroups. Relative vaccine efficacy was 72.5% (ARR ~0.21%) in patients with no coexisting conditions of interest compared with 94.6% (ARR ~0.35%) in patients with ≥ 1 coexisting condition of interest. Given the low event rates and lack of adjustment for multiplicity, no conclusions can be made based on the data presented for these subgroups. For ARI, relative vaccine efficacy was 71.7% (95% CI, 56.2-82.3%) with an ARR of ~0.54%. Efficacy was similar for ARI for both RSV A and B subtypes.

RENIOR study[12] (Abrysvo; Pfizer): This is an ongoing, multicenter, double-blind, randomized, placebo-controlled phase 3 trial comparing Abrysvo with placebo in adults ≥ 60 y. At the interim analysis, 34,284 patients had received RSV vaccine or placebo. Data collection will continue across 2 RSV seasons; study results presented here are for vaccine efficacy during the first RSV season. Participants were eligible for the study if they were healthy or had stable chronic medical conditions. The primary efficacy

endpoint was the prevention of RSV-related LRTI during 1 RSV season. This included an evaluation of patients with ≥ 2 and ≥ 3 signs or symptoms. ARI was the primary secondary efficacy endpoint reported. Severe LRTD was defined in the study protocol, but results for this endpoint were not provided because the number of events did not meet the prespecified minimum number of cases for the interim analysis. The primary efficacy analysis occurred in the evaluable efficacy population, which consisted of participants who received either vaccine or placebo and had a minimum follow-up of 15 d; data collection for efficacy began on day 15 following vaccination. Vaccine efficacy was calculated as 1 minus the relative risk. CIs were calculated using the conditional exact test. For the interim analysis, a 96.66% CI with a 3.34% type 1 error rate was used. The null hypothesis specified a vaccine efficacy against RSV-associated LRTI of less than 20%. Secondary endpoints used a 95% CI and did not include adjustment for multiplicity. For the primary endpoint, RSV-related LRTI with ≥ 2 symptoms occurred in 11 patients (incidence rate: 1.19 cases / 1,000 patient y) in the vaccine group and 33 patients (incidence rate: 3.58 cases per 1,000 patient y) in the placebo group. Relative vaccine efficacy was 66.7% (96.66% CI, 28.8-85.8%) with an ARR of ~0.13%. RSV-related LRTI with ≥ 3 symptoms occurred in 2 patients (incidence rate: 0.22 cases per 1,000 patient y) in the vaccine group compared with 14 patients (incidence rate: 1.52 cases per 1,000 patient y) in the placebo group. Vaccine efficacy was 85.7% (96.66% CI, 32-98.7%) with an ARR of ~0.08%. The lower limit of the confidence interval for LRTI in patients with both ≥ 2 and ≥ 3 symptoms exceeded 20%, meeting the prespecified efficacy criterion. An interim analysis from a partial, second RSV season (July 2022 to January 2023) for the primary outcome based on ≥ 3 symptoms demonstrated a relative vaccine efficacy of 78.6% (95% CI, 23.2-96.1%), which is lower compared with the first RSV season.[6] Efficacy against LRTI during the first RSV season was evaluated in subgroups of patients with subtype A and B infection. The majority of RSV-related LRTI infections during the first season in this study were attributable to the RSV B subtype. For patients with ≥ 2 symptoms, relative vaccine efficacy against LRTI due to RSV subtype A was 88.9% and 56.5% against RSV subtype B. For patients with ≥ 3 symptoms, relative vaccine efficacy against LRTI due to RSV subtype A was 66.7% and 90% against RSV subtype B. Relative vaccine efficacy against LRTI was also evaluated across age and high-risk condition subgroups. Across age groups, relative vaccine efficacy was similar for both ≥ 2 and ≥ 3 symptoms definitions and was generally higher in older populations. For patients with ≥ 2 symptoms, relative vaccine efficacy was 70.6% in patients without high-risk conditions compared with 62.5% in patients with ≥ 1 high-risk condition. For patients with ≥ 3 symptoms, relative vaccine efficacy was 100% in patients without high-risk conditions compared with 75% in patients with ≥ 1 high-risk condition. Denominator sizes of subgroups for age and high-risk condition groups was not specified, so no ARRs estimate were possible. Caution should be used when interpreting these subgroup results given the low event rates, wide confidence intervals, and lack of adjustment for multiplicity. For ARI, vaccine efficacy was 62.1% (95% CI, 37.1-77.9%) with an ARR of ~0.23%. Relative efficacy against ARI for RSV subtypes A and B were similar.

Safety: Overall, both Arexvy and Abrysvo were well tolerated in clinical studies in older adults. While not compared head-to-head, Arexvy appears to have numerically higher incidence rates of adverse reactions in general than what was observed with Abrysvo.[1,2,11,12] The reason for higher adverse reactions with Arexvy is unknown, but it is established that some vaccines containing adjuvants may cause more local and systemic reactions.[20] The most common adverse reactions with Arexvy are injection-site pain (60.9%), fatigue (33.6%), myalgia (28.9%), headache (27.2%), and arthralgia (18.1%).[1] In the AResVi-006 trial[11], solicited adverse reactions were more common in the vaccine group compared with placebo (71.9% vs 37.9%); most reactions were mild to moderate in severity. The most common solicited injection-site reaction was pain (60.9% in the Arexvy group compared with 9.3% in the placebo group). The rate of serious adverse events was approximately 4% in both groups. Rates of potential immune-mediated diseases were rare and similar between both groups. The most common adverse reactions with Abrysvo are fatigue (15.5%), headache (12.8%), pain at the injection-site (10.5%), and muscle pain (10.1%).[2] More local adverse reactions occurred in the vaccine group compared with placebo (12% vs 7%) in the RENOIR trial;[12] injection-site pain was the most common local reaction. Rates of systemic adverse reactions were similar between groups (27% in the Abrysvo group compared with 26% in the placebo group). Most reactions were mild to moderate in severity. The rate of serious adverse reactions was approximately 2.3% in both groups.

Prior to FDA approval, VRBPAC voted 10-2 in support of the safety of Arexvy based on concerns around 1 case of GBS and 2 cases of acute disseminated encephalomyelitis seen across 2 separate, smaller, phase 3 studies (Study 004; N = 1,653 and Study 007; N = 868). No cases of GBS or acute disseminated encephalomyelitis were reported in the AresVi-006 trial (N = 24,966). For Abrysvo, VRBPAC voted 7-4 in support of safety. Two cases of GBS or a variation of GBS were reported following vaccination in the RENIOR study (N = 34,284).[3,4,17,18] Given the relatively low number of patients who have received these vaccines in clinical studies, the occurrence of these events could highlight a potential safety signal that will be important to monitor with the RSV vaccines moving forward. Both vaccines have plans in place for postmarketing surveillance. Events such as GBS and acute disseminated encephalomyelitis must be submitted through the Vaccine Adverse Event Reporting System for 3 years following product licensure for both vaccines.[21,22] Additionally, FDA has required postmarketing surveillance studies for both vaccines as a condition of approval. GSK will conduct a postmarketing active surveillance study to evaluate GBS and acute disseminated encephalomyelitis in adults ≥ 60 years. The study will include 1.9 million individuals following receipt of Arexvy and will be completed by June 30, 2030, with report submission required by the end of 2031.[21] Pfizer will conduct a postmarketing retrospective cohort study using Centers for Medicare and Medicaid Services claims data among 1.5 million individuals vaccinated with Abrysvo. The study has a completion date of May 31, 2029 with report submission required by May 31, 2030.[22]

Conclusion: Two RSV vaccines, Arexvy and Abrysvo, are approved for use in adults ≥ 60 years of age. For this population, ACIP recommends a single dose of either vaccine without preference, based on shared clinical decision making. Both vaccines have demonstrated efficacy in reducing RSV-related LRTD/LRTI in the first RSV season following vaccination. The pivotal trials for both Arexvy and Abrysvo are both ongoing to evaluate the durability of vaccine efficacy in subsequent RSV seasons. Additionally, further evaluation is needed to better understand the impact of both vaccines on clinically important outcomes such as RSV-associated hospitalization and death. Postmarketing surveillance studies of vaccine safety are planned for both vaccines to further evaluate potential safety signals seen in clinical studies.

Abbreviations: ACIP = Advisory Committee on Immunization Practices; ARI = acute respiratory infection; ARR = absolute risk reduction; CAD = coronary artery disease; CDC = Centers for Disease Control and Prevention; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease of 2019; FDA = US Food and Drug Administration; GBS = Guillain-Barré syndrome; IIV = inactivated influenza vaccine; LRTD = lower respiratory tract disease; LRTI = lower respiratory tract infection; MMWR = Morbidity and Mortality Weekly Report; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; RSVpreF = RSV glycoprotein F stabilized in pre-fusion conformation; RSVpreF3 = RSV glycoprotein F stabilized in pre-fusion trimeric conformation; rVE =relative vaccine efficacy; VRBPAC = Vaccines and Related Biological Products Advisory Committee

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