5.13 RESPIRATORY SYNCYTIAL VIRUS VACCINE, Powder and suspension for injection (0.5 mL), Arexvy®, GlaxoSmithKline Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 1 submission requested National Immunisation Program (NIP) listing of a recombinant respiratory syncytial virus (RSV) pre-fusion F protein 3 older adult (RSVPreF3 OA) vaccine for the prevention of RSV-confirmed lower respiratory tract disease (LRTD) according to two alternative NIP schedules (i) among adults aged ≥60 years of age (YOA) (corresponding to the TGA indication) or (ii) ≥75 YOA (corresponding to the Australian Technical Advisory Group on Immunisation [ATAGI] base case).

1.2 Listing was requested on the basis of a cost-utility analysis versus no vaccine. The key components of the clinical issues addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issues addressed by the submission (as stated in the submission)

Component	Description
Population	TGA indication: ≥60 YOA; ATAGI base case: ≥75 YOA
Intervention	RSVPreF3 OA vaccine, single dose
Comparator	Primary comparator: no vaccine Near market vaccines: Pfizer RSVpreF and Moderna mRNA-1345 RSV
Outcomes	Primary efficacy: Single dose during first season – prevention of RSV-confirmed LRTD Secondary safety: Solicited (subset) and unsolicited AEs, all SAEs and pIMDs
Clinical claim	The clinical claim for the RSVPreF3 OA vaccine relative to no vaccine was: • superiority in terms of comparative efficacy for the prevention of RT-PCR confirmed RSV-associated LRTD in people ≥60 YOA, inclusive of those ≥75 YOA. • an acceptable comparative safety profile despite being slightly more reactogenic than placebo (no vaccine).

Source: Table 1-1 of the submission.

AE = adverse event; ATAGI = Australian Technical Advisory Group on Immunisation; LRTD = lower respiratory tract disease; pIMD = potential immune mediated disorder; RSV = respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; YOA = years of age.

2 Background

Registration status

2.1 RSVPreF3 OA was approved for registration by the Therapeutic Goods Administration (TGA) for 'active immunisation of individuals 60 years and older for the prevention of LRTD caused by RSV' on 14 January 2024.

2.2 The submission reported that additional data had been submitted to the TGA for evaluation in April 2024[1].

3 Requested listing

MEDICINAL PRODUCT	Nationally Negotiated Price (requested)	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Available brands
Recombinant Respiratory Syncytial Virus (RSV) pre-fusion F protein 3 older adult vaccine, 120 mcg powder vial and suspension vial	$[redacted]	1	1	0	Arexvy
	National Immunisation Program 1. Adults ≥60 YOA; or 2. Adults ≥75 YOA. Duration of listing: ongoing NIP cohort				

Source: Compiled during the evaluation from Tables 1-4, 1-10 and 3-36 of the submission
NIP = National Immunisation Program; RSV = respiratory syncytial virus; YOA = years of age.
The submission noted that RSVPreF3 OA vaccine will be available in a pack size of 1 vial powder plus 1 vial suspension or in a pack size of 10 vials of powder plus 10 vials of suspension.

3.1 The submission proposed 2 alternative NIP schedules: one dose of RSVpreF3 OA in adults aged ≥60 YOA (corresponding to the TGA indication); or one dose of RSVpreF3 OA in adults aged ≥75 YOA (corresponding to the ATAGI base case). An alternative was also described but not explicitly requested (paragraph 3.8 below): Adults ≥75 YOA, 60-74 YOA at high risk for severe RSV infection, and 60-74 YOA First Nations people (corresponding to the ATAGI's statement on the clinical use of RSVPreF3 OA[2]).

3.2 The price proposed in the submission is shown above. The nationally negotiated price will not be known until after the PBAC has determined the cost-effective price.

3.3 ATAGI's statement on the clinical use of RSVPreF3 OA, which is currently available on the private market for the prevention of RSV disease in older Australian adults, recommends a single dose for (i) adults aged ≥75, (ii) Aboriginal and/or Torres Strait Islander peoples aged 60 to 74 years and (iii) adults aged 60 to 74 years with medical conditions that increase their risk of severe disease due to RSV. Additionally, the ATAGI statement suggested that all other adults aged 60 to 74 years can consider RSV vaccination, while noting that the burden of RSV disease is lower in this age group than in people aged ≥75 years, and therefore the benefits of vaccination may be less.

3.4 ATAGI's statement[1] notes that Arexvy is administered as a single dose of 0.5 mL by intramuscular injection and may be given at any time of the year. The month of

[1] https://www.tga.gov.au/resources/prescription-medicines-under-evaluation/arexvy-glaxosmithkline-australia-pty-ltd

[2] ATAGI statement on the clinical use of Arexvy (RSV PRE-F3) vaccine for RSV (Version 1.0 Issue date: March 2024), available from https://www.health.gov.au/resources/publications/atagi-statement-on-the-clinical-use-of-arexvy-rsv-pre-f3-vaccine-for-rsv?language=en

administration may impact the benefits of vaccination due to seasonality of RSV (see Sensitivity analyses presented in Table 24).

3.5 The ATAGI advice to the PBAC stated that the ATAGI RSV subgroup 'supported a 'base case' program model in which people aged 75+ are vaccinated, and then alternatives where the age group is varied by 5-year intervals (e.g., program for age groups 80+, 75+, 70+, 65+, 60+)'.

3.6 The ATAGI advice to the PBAC recommended presentation of 'cost-effectiveness analyses which consider the inclusion of high risk people aged 60+ years with comorbidities or social factors that are likely to increase the risk of severe RSV or hospitalisation, including: chronic respiratory conditions (e.g. chronic obstructive pulmonary disease, asthma); immunocompromising conditions (e.g. solid malignancy, haematological malignancy); diabetes mellitus; chronic kidney disease; chronic neurological conditions which increase the risk of respiratory infection; and Indigenous status'. The PSCR added, as per clarification received by ATAGI subsequent to the ATAGI pre-PBAC advice, those at risk also include adults aged 60+ YOA with cardiac disease including congenital heart disease, congestive heart failure and coronary heart disease. The PBAC noted that ATAGI's statement on the clinical use of RSVPreF3 OA vaccine provided a table of medical conditions associated with an increased risk of RSV disease complications for which RSV vaccination is recommended in adults ≥60 years (Table 2).

Table 2: Medical conditions associated with an increased risk of RSV disease complications for which RSV vaccination is recommended in adults ≥60 years

Category	Example medical conditions
Cardiac disease	Congenital heart disease, congestive heart failure, coronary artery disease
Chronic respiratory condition	Suppurative lung disease, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, chronic emphysema, severe asthma (requiring frequent medical consultations or the use of multiple medicines)
Immunocompromising condition	HIV infection, malignancy, immunocompromise due to disease or treatment, asplenia or splenic dysfunction, solid organ transplant, haematopoietic stem cell transplant, CAR-T cell therapy
Chronic metabolic disorder	Type 1 or 2 diabetes, amino acid disorders, carbohydrate disorders, cholesterol biosynthesis disorders, fatty acid oxidation defects, mitochondrial disorders, organic acid disorders, urea cycle disorders, vitamin/cofactor disorders, porphyria
Chronic kidney disease Stage 4 or 5	
Chronic neurological condition	Hereditary and degenerative central nervous system diseases, seizure disorders, spinal cord injuries, neuromuscular disorders, conditions that increase respiratory infection risk

Source: . ATAGI statement on the clinical use of Arexvy (RSV PRE-F3) vaccine for RSV (Version 1.0 Issue date: March 2024).

3.7 The submission did not present cost-effectiveness analyses in these high-risk subgroups; however, scenario analyses of the financial impact of listing RSVPreF3 OA for First Nations people 60-74 YOA and high risk persons 60-74 YOA were presented.

3.8 The submission stated that there were evidentiary challenges in presenting cost-effectiveness data for the ATAGI proposed populations, and suggested that 'a pragmatic decision could be made to extend access to at-risk (high risk) populations (60-74 YOA at high risk) and 60-74 YOA indigenous, based on an assumption that

RSVPreF3 OA cost-effectiveness demonstrated in the ATAGI base case (≥75 YOA) would be applicable, given the pre-submission advice has considered these populations are of priority for the NIP'. The evaluation and ESC considered this may not be reasonable noting the submission did not provide cost-effectiveness analyses for these groups.

3.9 The Pre-Sub-Committee Response (PSCR) and pre-PBAC response proposed that at a minimum, protection of adults ≥75 YOA and First Nations Persons 60-74 YOA could be prioritised with a program to commence in time for the 2025 RSV season. The PBAC agreed with the ESC that this may not be appropriate for a national vaccination program, given that it would exclude high risk people aged ≥60 with a clinical need.

3.10 The requested NIP listing was on the basis of a single dose of RSVPreF3 OA. The submission noted that the need for revaccination with RSVPreF3 OA had not been established, and there were currently no data to inform sequential treatment. The TGA Clinical Evaluation Report indicated that the sponsor should be required to submit data to the TGA as soon as available from studies AreSVi-006 and AreSVi-004 regarding persistence of efficacy and potential need for revaccination. The ESC considered that cost-effectiveness may need reconsideration if revaccination is required. The ESC noted that if revaccination is requested in the future, this would impact cost-effectiveness and financial impact.

3.11 The submission proposed NIP listing of a single dose for vaccination with RSVPreF3 OA. The submission stated that the need for and timing of revaccination will be informed by further follow-up data from the pivotal trial AReSVi-006 and immunogenicity trial AReSVi-004. As such, there is the possibility of a future request for NIP listing of a subsequent dose of RSVPreF3 OA as revaccination.

3.12 The PSCR stated that results from studies AreSVi-006 and AreSVi-004 with 36 months follow-up are expected in September 2024 and will provide further information regarding the appropriate timing of revaccination. The PSCR presented new immunogenicity results from AreSVi-004 (see paragraph 6.22). The ESC noted that end of study results for AreSVi-004 are due in mid-2025. The pre-PBAC response stated that results from studies AReSVi-006 (season 3) and AReSVi-004 (36/37 months follow-up) are expected in September 2024 and will provide further information regarding the appropriate timing of revaccination.

3.13 The Product Information states that Arexvy is not recommended during pregnancy, and notes that an increase in preterm births was observed compared to placebo after administration of an investigational unadjuvanted RSVPreF3 vaccine to 3,557 pregnant women based on the results of the RSV MAT-009 trial. The TGA Clinical Evaluation Report noted that the vaccine in the maternal program had a different composition with 120 ug RSVPreF3 antigen not being adjuvanted.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 RSV is highly infectious and spreads via respiratory droplets, generated from coughing or sneezing, coming into direct contact with the mouth, nose, or eyes. Indirect contact may also spread RSV as it remains viable on a hard surface for up to 6 hours.

4.2 The rate of RSV infection varies by season and regional climate. The seasonality of RSV in temperate regions of Australia is predominantly consistent with that observed globally, with a peak coinciding with late autumn or early winter (May/June) and limited activity during summer in most regions[3].

4.3 The clinical presentation of RSV varies from asymptomatic carriage to cold-like symptoms to acute respiratory distress. Most patients develop signs of upper respiratory tract disease (URTD) such as nasal congestion and rhinorrhoea or a sore throat 3-5 days after exposure. Other non-specific symptoms such as asthenia (physical weakness or lack of energy), anorexia, and fever can also occur with varying severity.

4.4 Progression of the virus to the lower respiratory tract leads to development of symptoms such as cough, wheezing, and dyspnoea. Severe RSV in the lower respiratory tract can lead to the development of acute bronchitis, pneumonia, or exacerbation of pre-existing conditions including asthma, chronic obstructive pulmonary disease and congestive heart failure[4, 5] .

4.5 The submission used overseas data to estimate the incidence of RSV disease as 5.72 per 100 person years. There are uncertainties associated with the methodological approach used in estimating the incidence rate (see paragraph 6.54).

4.6 Sequelae of RSV infection are associated with significant morbidity and mortality, particularly in older or vulnerable adults[6]. Severe RSV cases may require hospitalisation, including admission into intensive care units (ICU), and/or mechanical ventilation. RSV can also lead to the development of pneumonia in older adults.

---

[3] Moore, H. C., Jacoby, P., Hogan, A. B., Blyth, C. C., & Mercer, G. N. (2014). Modelling the seasonal epidemics of respiratory syncytial virus in young children. *PLoS One*, *9*(6). https://doi.org/10.1371/journal.pone.0100422

[4] Ackerson, B., Tseng, H. F., Sy, L. S., Solano, Z., Slezak, J., Luo, Y., Fischetti, C. A., & Shinde, V. (2019). Severe Morbidity and Mortality Associated With Respiratory Syncytial Virus Versus Influenza Infection in Hospitalized Older Adults. *Clin Infect Dis*, *69*(2), 197–203. https://doi.org/10.1093/cid/ciy991

[5] Tseng, H. F., Sy, L. S., Ackerson, B., Solano, Z., Slezak, J., Luo, Y., Fischetti, C. A., & Shinde, V. (2020). Severe Morbidity and Short- and Mid- to Long-term Mortality in Older Adults Hospitalized with Respiratory Syncytial Virus Infection. *J Infect Dis*, *222*(8), 1298–1310. https://doi.org/10.1093/infdis/jiaa361

[6] Nguyen-Van-Tam, J. S., O'Leary, M., Martin, E. T., Heijnen, E., Callendret, B., Fleischhackl, R., Comeaux, C., Tran, T. M. P., Weber, K., O'leary, M., Martin, E. T., Heijnen, E., Callendret, B., Fleischhackl, R., Comeaux, C., Tran, T. M. P., & Weber, K. (2022). Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries. *European Respiratory Review*, *31*(166). https://doi.org/10.1183/16000617.0105-2022

4.7 First Nations people have a greater risk of RSV hospitalisation compared with non-Indigenous Australians[7], with an overall incidence rate ratio for RSV-related hospitalisation of 3.3 (95% CI: 3.2, 3.5) times higher among First Nations people[8].

4.8 RSVPreF3 OA is a combination of the RSVPreF3 antigen and the $AS01_E$ adjuvant system. RSVPreF3 antigen is derived from the laboratory-adapted RSV-A A2 strain, stabilised in the pre-fusion conformation of the naturally occurring F protein for which both RSV-A and B subtypes share high amino acid sequence homology. RSVPreF3 OA is designed to induce a functional humoral immune response against the RSV-A and RSV-B subtypes and the antigen-specific cellular immune responses which contribute to protection against RSV-associated LRTD (RSVPreF3 Product Information).

4.9 The RSV chapter of the Australian Immunisation Handbook (AIH) was recently updated, and includes recommendations for use of vaccines and monoclonal antibodies for prophylaxis of RSV disease[9].

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated 'no vaccine' as the main comparator. The main arguments provided in support of this nomination were that there are no other RSV vaccines currently TGA registered or available on the NIP for older adults. The evaluation considered this was reasonable and consistent with the ATAGI advice to the PBAC.

5.2 The submission noted that there were two other RSV vaccines in advanced clinical development or registered overseas which are expected to be TGA-registered in similar timelines to RSVPreF3 OA. Based on this, the submission considered RSVpreF vaccine (Pfizer) and mRNA-1345 RSV vaccine (Moderna) as near market comparators. The evaluation considered that the proposed near market comparators were appropriate.

5.3 The submission presented a comparative analysis of the general characteristics of trials AreSvi-006, RENOIR (RSVpreF vaccine) and ConquerRSV (mRNA-1345 RSV vaccine). The submission concluded that there was a high degree of heterogeneity amongst the trials, with insufficient exchangeability of the trial populations, outcome measurements/statistical analyses and follow-up time and therefore did not conduct

[7] Fagan, P., McLeod, C., & Baird, R. W. (2017). Seasonal variability of respiratory syncytial virus infection in the Top End of the Northern Territory (2012-2014). *J. Paediatr. Child Health*, *53*(1), 43–46. https://doi.org/10.1111/jpc.13303

[8] Saravanos, G. L., Sheel, M., Homaira, N., Dey, A., Brown, E., Wang, H., Macartney, K., & Wood, N. J. (2019). Respiratory syncytial virus-associated hospitalisations in Australia, 2006-2015. *Med. J. Aust.*, *210*(10), 447–453. https://doi.org/10.5694/mja2.50159

[9] Australian Government Department of Health and Aged Care. Australian Immunisation Handbook, Respiratory syncytial virus (RSV) chapter, updated 27 June 2024, available at https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/respiratory-syncytial-virus-rsv.

an indirect comparison of the trials and their results. The submission presented a naïve comparison of results of the 3 trials. The results from these comparisons are not discussed further.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 A written clinician statement was provided for this item. The statement which was co-authored by two Australian clinicians with expertise in areas of immunisation, public health and geriatric medicine supported the NIP listing for RSVPreF3 OA for all persons aged 65 years and above, noting the high incidence of risk factors for more severe RSV infection above 65 years. The statement discussed the incidence of RSV in Australia, the burden of disease for older adults, and key results for the two RSV vaccines that are currently registered for older adults in Australia based on the pivotal trial publications. The PBAC considered that the statement was informative as it provided a clinical perspective on RSV disease and public health rationale for supporting the listing. The PBAC noted that the statement supported an age threshold of 65 years for the NIP listing for RSVPreF3 OA, which differed from the submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (9), health care professionals (13) and organisations (6) via the Consumer Comments facility on the PBS website.

6.3 The comments from individuals described concerns associated with contracting RSV, especially in those people living with pre-existing medical conditions, and noted the need for access to an effective RSV vaccine for themselves and other family members. Several comments referred to the high cost of the RSV vaccine without a listing on the NIP.

6.4 In addition to the comments from individuals, health care professionals described the RSV vaccine as effective in preventing RSV infection, reducing rates of morbidity and mortality, as well as reducing exacerbations of underlying medical conditions. The comments outlined the limited effective treatment options for RSV infection, and noted the importance prevention plays in disease control for older Australians, including a reduction in hospital admissions.

6.5 The organisations that provided comments are listed below, along with comments not covered above:

- Immunisation Foundation of Australia – noted the extensive health, work, financial, family/social, and mental/emotional impacts of contracting RSV, focusing on the burden of severe infection;

- Lung Foundation Australia – quoted substantial RSV infection rates from the Department of Health and Aged Care, National Communicable Disease Surveillance Dashboard (2024);
- Asthma Australia – stated that preventing complications from RSV in susceptible populations should be included in good asthma management practice;
- National Asthma Council Australia – discussed that in addition to the specific complications of RSV infection, older adults experience wider societal and physical effects of RSV infection such as decline in socialisation, feelings of loneliness and isolation, inadequate nutrition, higher incidence of depression, sleep difficulties and loss of involvement in the community, leading to cognitive decline and further illnesses;
- National Aboriginal Community Controlled Health Organisation (NACCHO) – stated that risk factors for severe RSV in First Nations adults include chronic respiratory cardiovascular and kidney disease, contributing to a disproportionate burden of RSV disease in this population.
- Australasian Society of Clinical Immunology and Allergy (ASCIA) – stated that older adults who are immunocompromised and/or have chronic medical conditions such as asthma, diabetes, chronic obstructive pulmonary disease and congestive heart failure have a greater risk of being hospitalised from RSV compared to those without these conditions.

6.6 The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.7 The submission was based on one randomised, placebo-controlled head-to-head trial (AreSVi-006) comparing the efficacy and safety of RSVPreF3 OA to placebo vaccine (saline solution) in adults ≥60 YOA.

6.8 Given the difference in reconstitution and visual appearance of the RSVPreF3 OA investigational vaccine and the saline solution used as placebo, double blinding was not possible, and the study was conducted in an observer-blind manner. The participants, study site and sponsor personnel involved in clinical evaluation of participants were blinded while other study personnel were not required to be blinded with respect to the intervention assignment.

6.9 A claim of superiority was made with respect to VE in terms of prevention of RT-PCR confirmed RSV-associated LRTD in adults ≥60 YOA, inclusive of those ≥75 YOA, with an acceptable safety profile relative to placebo. The submission presented post hoc subgroup analyses to support the efficacy claim in adults ≥75 YOA.

6.10 The submission presented one supportive trial, the pivotal immunogenicity randomised controlled trial (RCT), AreSVi-004, as supportive evidence for the efficacy claim of RSVPreF3 OA in adults ≥75 YOA.

6.11 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Pivotal efficacy trial		
AreSVi-006 (NCT04886596)	A phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above. VE Analysis 1 (Interim Season 1 Analysis)	Clinical Study Report
	Papi A, Ison, MG, Langley, JM et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults	NEJM 2023, 388: 595-608. DOI: 10.1056/NEJMoa2209604
	A phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above: VE Analysis 3 (End of Season Analysis)	Clinical Study Report
	Ison MG, Papi A, Athan, E et al. Efficacy and safety of respiratory syncytial virus prefusion F protein vaccine (REVPreF3 OA) in older adults over 2 RSV seasons.	Clinical Infectious Diseases 2024, ciae010. Doi: 10.1093/cid/ciae010.
	Feldman, RG, Antonelli-Incalzi, R, Steenackers, K. et al. Respiratory syncytial virus prefusion F protein vaccine is efficacious in older adults with underlying medical conditions.	Clinical Infectious Disease 2023; ciad471. DOI: 10.1093/cid/ciad471
	Curran D., Matthews S., Cabrera E.S. et al. The respiratory syncytial virus prefusion F protein vaccine attenuates the severity of respiratory syncytial virus-associated disease in breakthrough infections in adults ≥60 years of age.	Influenza and Other Respiratory Viruses 18.2 (2024): e13236. DOI: 10.1111/irv.13236
Immunogenicity trial		
AreSVi-004 (NCT04732871)	A phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above. Month 13 analysis (1 month post first revaccination).	Clinical Study Report
	Schwarz, TF, Hwang, SJ, Ylisastigui, P. et al. Immunogenicity and safety following one dose of $AS01_E$-adjuvanted respiratory syncytial virus prefusion F protein vaccine in older adults: a phase 3 trial.	JID 2023; jiad546. DOI: 10.1093/infdis/jiad546
	Schwarz, TF, Hwang, SJ, Ylisastigui, P. et al. Immunogenicity and safety of a second dose of the respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVPreF3 OA), 12 months after the first dose in adults ≥60 years.	The Ninth ESWI Influenza Conference Valencia. Page 285-286.

Source: Table 2-5of the submission.
RSVPreF3 OA = Recombinant Respiratory Syncytial Virus (RSV) pre-fusion F protein 3 older adult.

6.12 The key features of the included evidence are summarised in Table 4.

6.13 AreSVi-006 was initially designed to assess the efficacy of RSVPreF3 OA against RSV related LRTD according to two dosing schedules; a single dose of vaccine up to the end of Season 3 in the NH, or following an annual revaccination schedule at 12- and 24-months post Dose 1 administration. The trial protocol was amended on 31 October 2023 to remove the Month 24 revaccination because initial analysis of

efficacy for the 12-month revaccination demonstrated no additional efficacy benefit for the trial population. The PSCR acknowledged that the analysis of re-vaccination at Month 12 showed no additional benefit of vaccination with a 12-month interval (therefore no benefit to administer second re-vaccination dose at Month 24, an interval 12 months after the Month 12 re-vaccination dose). It was noted that AreSVi-006 was ongoing and would continue to follow-up participants over 2.5 Southern Hemisphere (SH) seasons and 3 NH RSV seasons. The submission presented results from 3 data analysis points:

- VE analysis 1 (Season 1): interim results from RSV Season 1 NH (median follow-up of 6.7 months). Based on the trial protocol, this was the primary analysis.
- VE analysis 2 (Season 1): end of Season 1 NH & SH (median follow-up of 11.5 months).
- VE analysis 3 (Season 2): Seasons 1 and 2 (to the end of Season 2 NH) (median follow-up of 17.8 months).

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Population	Outcomes	Use in modelled evaluation
RSVPreF3 OA versus placebo						
AreSVi-006	24,966	Phase 3 R, OB, PC, MC Ongoing	Low	Adults ≥60 YOA	Primary outcome: Risk of the first occurrence of RT-PCR confirmed RSV-LRTD Key secondary outcomes: safety, PROs	Reduction of the risk of the first occurrence of RT-PCR confirmed RSV-LRTD, safety

Source: compiled during the evaluation from Table 2-7, and Table 2-10 of the submission.
MC = multi-centre; OB = observer blinded; PC = placebo-controlled; PRO = patient reported outcome; R = randomised; RSV-LRTD = lower respiratory tract disease respiratory syncytial virus; RT-PCR = reverse transcription-polymerase chain reaction; YOA = years of age.

Comparative effectiveness

6.14 The primary outcome for AreSVi-006 was VE against first occurrence of RSV-confirmed LRTD during the first season after a single dose vaccination and was analysed based on the modified exposed set (mES). The mES included all participants who received at least the first dose of the study intervention and did not report an RSV-confirmed acute respiratory infection (ARI) prior to Day 15 after vaccination (n = 24,960 in VE analysis 1). A total of six participants were excluded from the mES due to having a confirmed RSV-related ARI prior to Day 15 after the first dose (one participant in the RSVPreF3 OA vaccine group and five participants in the placebo group). Two participants were excluded from the Dose 2-mES (both in the placebo group).

6.15 In evaluating the efficacy of RSVPreF3 OA, the submission stated that the VE against RSV-LRTD was to be considered demonstrated if the lower limit (LL) of the two-sided confidence interval (CI) of VE was above the pre-defined threshold of 20%. The final analysis of the primary outcome was to be performed when at least 56 cases of RSV-LRTD had accrued in the mES. In the event that 56 cases had not accrued at the end of the season, an interim analysis was planned if ≥35 cases had accrued. VE analysis 1 was performed when 47 cases (≥35 and <56 pre-specified cases) of

RSV-LRTD had accrued in the mES. As the number of RSV-LRTD cases accrued was ≥35, and the pre-specified efficacy requirement was demonstrated (LL of the two-sided CI of VE was above the pre-defined threshold of 20%), VE analysis 1 was the final analysis for the primary endpoint. Subsequent analyses, VE analysis 2 and VE analysis 3, which were conducted at different timepoints when 57 and 169 RSV-LRTD cases accrued, respectively, were presented by the submission as supportive evidence.

6.16 A summary of the primary efficacy outcome from VE analysis 1 is presented in Table 5. The lower confidence limit of VE was greater than the pre-defined threshold of 20%, thereby demonstrating efficacy of a single dose of RSVPreF3 OA vaccine against first occurrence of RT-PCR-confirmed RSV-LRTD compared to placebo; VE = 82.58% (96.95% CI: 57.89, 94.08).

Table 5: VE of a single dose of RSVPreF3 OA against first occurrence of RSV-confirmed LRTD, VE analysis 1, mES

Endpoint	RSVPreF3 OA				Placebo				VE% (CI [a]) P-value
	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	
VE analysis 1 – Season 1 NH: median follow-up time in the mES = 6.7 months									
RT-PCR-confirmed RSV-LRTD	12,466	7	6,865.9	1.0	12,494	40	6,857.3	5.8	**82.58 (57.89, 94.08) P <0.0001**

Source: Table 2-19of the submission.
CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified exposed set; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV-LRTD; NH = Northern Hemisphere; n/T (per 1000) = incidence rate of participants reporting at least one event; RSV = respiratory syncytial virus; RSVPreF3 OA= RSV pre-fusion protein 3 older adult; RT-PCR = reverse transcription-polymerase chain reaction; T (year) = sum of follow-up time (from Day 15 post-vaccination until first occurrence of the event or until the efficacy data lock point or until drop-out date) expressed in years; VE = vaccine efficacy.
a VE analysis CI = 96.95% . 96.95% CI – adjustment of alpha level at interim obtained using Wang-Tsiatis method.
Bold indicates statistically significant.

6.17 The submission presented results from subsequent efficacy analyses: VE analysis 2, VE analysis 3 (single dose), and VE analysis 3 (revaccination group) (Table 6). Overall, VE of RSVPreF3 OA reduced (waned) as the median follow-up increased. Revaccination with a second dose of RSVPreF3 OA did not provide additional VE from RT-PCR confirmed LRTD. The VE of one dose of RSVPreF3 OA given preseason 1 in preventing RT-PCR-confirmed RSV-LRTD over 2 full seasons was 67.18% (97.5% CI: 48.19, 80.00), which was very similar to the result for the group that received a second dose (VE: 67.12% (97.5% CI: 48.09, 80.00)). The ESC noted that re-vaccination did not improve VE in the analysis at median follow-up time of 17.8 months (VE analysis 3) (Table 6). The ESC and the PBAC considered it was uncertain whether revaccination impacted the duration of protection, and whether boosting would be required at a later stage.

6.18 The PSCR presented new longer-term VE data (VE analysis 4), based on 23.3 months follow-up. VE against first occurrence of RT-PCR-confirmed RSV-LRTD in the overall trial population was similar to that presented in the submission; 67.7% (CI: 52.3, 78.7) in VE analysis 4 vs 67.2% (CI: 48.2, 80.0) in VE analysis 3 (Table 6). The new evidence in the PSCR could not be verified as the sponsor did not provide source data for VE analysis 4. The ESC considered that longer-term VE of RSVPreF3 OA beyond 23.3 months remained unknown.

Table 6: VE of RSVPreF3 OA against first occurrence of RSV-confirmed LRTD[a], VE analysis 1 compared with VE analysis 2 and VE analysis 3 (single dose and revaccination), and VE analysis 4 (as reported in the PSCR), mES

Endpoint	RSVPreF3 OA				No vaccine				VE% (CI[b]) P-value
	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	
VE analysis 1 – Season 1 NH: median follow-up time in the mES = 6.7 months									
RT-PCR-confirmed RSV-LRTD	12,466	7	6,865.9	1.0	12,494	40	6,857.3	5.8	**82.58 (57.89, 94.08) P <0.0001**
VE analysis 2 – Season 1 NH and SH – median follow-up time in the mES = 11.5 months									
RT-PCR-confirmed RSV-LRTD	12,469	10	11,719.0	0.9	12,498	47	11,687.4	4.0	**78.86 (57.60, 90.47) P <0.0001**
VE analysis 3 (single dose) – up to end of Season 2 NH – median follow-up time in mES = 17.8 months									
RT-PCR-confirmed RSV-LRTD	12,469[c]	30	14,662.6	2.0	12,498	139	17,269.0	8.0	**67.18 (48.19, 80.04) P <0.0001**
VE analysis 3 (revaccination group) – up to end of Season 2 NH – median follow-up time in mES = 17.8 months									
RT-PCR-confirmed RSV-LRTD	12,469[d]	30	14,660.5	2.0	12,498	139	17,269.0	8.0	**67.12 (48.09, 80.00) P <0.0001**
VE analysis 4 (single dose) – up to the end of Season 2 NH and SH, median follow-up time in mES = 23.3 months									
RT-PCR-confirmed RSV-LRTD	12,468	32	n.r.	n.r.	12,498	154	n.r.	n.r.	**67.7 (52.3, 78.7)** P n.r.

Source: Table 2-20,; Table 2-21, 3 of the submission, PSCR Table 2 and text,.

CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified exposed set; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV-LRTD; NH = Northern Hemisphere; n.r. not reported; n/T (per 1000) = incidence rate of participants reporting at least one event; RSV = respiratory syncytial virus; RSVPreF3 OA = RSV pre-fusion protein 3 older adult; RT-PCR = reverse transcription-polymerase chain reaction; SH = southern hemisphere; T (year) = sum of follow-up time (from Day 15 post-vaccination until first occurrence of the event or until the efficacy data lock point or until drop-out date) expressed in years; VE = vaccine efficacy.

a In efficacy analysis over 2 RSV seasons, prespecified secondary efficacy analyses included season as a covariate to account for differences between seasons.

b VE analysis 1 = 96.95%, VE analysis 2 = 95% CI and VE analysis 3 = 97.5% CI; VE analysis 4 = 95% CI.

c For single dose evaluation participants who received RSVPreF3 OA investigational vaccine at Dose 2 (revaccination group) were censored at Dose 2.

d For revaccination dose evaluation participants who received placebo at Dose 2 (single dose group) were censored at Dose 2.

At the time of VE analysis 2, a valid informed consent form had been obtained for 7 out of the 15 participants excluded at VE analysis 1, and therefore the number of participants in the exposed set is higher than VE analysis 1.

Bold indicates statistically significant.

6.19 The submission presented post-hoc VE analyses without season as covariate (prespecified analysis included season as covariate). The VE of a single dose of RSVPreF3 OA against first occurrence of RT-PCR confirmed RSV-LRTD from VE analysis 3 was higher compared to the pre-specified analysis: 74.5% (95% CI: 60.0%, 84.5%) versus 67.2% (95% CI: 48.2%, 80.0%). The submission stated that the efficacy of RSVPreF3 OA was driven by the season with the largest person-years of follow-up (Season 1) and therefore efficacy estimates were higher in the post hoc analysis than the prespecified analysis.

6.20 At VE analysis 3 (single dose), RSVPreF3 OA demonstrated a lower efficacy in protecting participants from RT-PCR confirmed RSV-ARI (Table 7) compared to RT-PCR

confirmed RSV-LRTD (52.74% vs 67.18% for VE analysis 3). RSVPreF3 OA was also more efficacious in protecting participants against severe RSV-confirmed LRTD (Table 7) than all RT-PCR-confirmed RSV-LRTD (78.83% vs 67.18% for VE analysis 3). RSVPreF3 OA demonstrated similar efficacy in protecting participants from complications related to RT-PCR confirmed RSV-ARI (Table 7) compared to RT-PCR confirmed RSV-LRTD (67.37% vs 67.18% for VE analysis 3). The submission concluded that the VE against hospitalisation due to RT-PCR confirmed RSV could not be concluded due to the low number of cases reported (1 in the RSVPReF3 OA arm and 5 in the placebo arm in VE analysis 3).

Table 7: VE of RSVPreF3 OA against first occurrence of RSV-ARI, severe RT-PCR confirmed LRTD, complications related to RT-PCR confirmed ARI and hospitalisations due to RT-PR confirmed RSV [a], VE analysis 3, and VE analysis 4 (as reported in the PSCR), mES

Endpoints	RSVPreF3 OA				No vaccine				VE % (CI [b]) P-value
	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	
VE analysis 3 (single dose) – up to end of Season 2 NH – median follow-up time in mES = 17.8 months									
RT-PCR-confirmed RSV-LRTD	12,469[c]	30	14,662.6	2.0	12,498	139	17,269.0	8.0	**67.18 (48.19, 80.04) P <0.0001**
RSV-confirmed ARI	12,469	94	14,626.4	6.4	12,498	292	17,167.0	17.0	**52.74 (40.01, 63.04) P <0.0001**
Severe RSV-confirmed LRTD	12,469	7	14,672.6	0.5	12,498	48	17,320.6	2.8	**78.83 (52.59, 91.96) P <0.0001**
Complications related to RT-PCR confirmed RSV-ARI	12,469	8	14,672.50	0.5	12,498	34	17,328.10	2	**67.37 (27,51, 87.05) P = 0.0035**
Hospitalisations due to RT-PCR confirmed RSV	12,469	1	14,676.5	0.1	12,498	5	17,346.0	0.3	72.82 (-150.30, 99.44) P = 0.4075
VE analysis 4 (single dose) – up to the end of Season 2 NH and SH, median follow-up time in mES = 23.3 months									
Severe RSV-LRTD	12,468	9	n.r.	n.r.	12,498	54	n.r.	n.r.	74.9 (48.4, 89.2) P n.r.

Source: Table 2-24, Table 2-25,; Table 2-29, of the submission, Table 14.2.1.155 of the VE analysis 3 CSR, PSCR Table 2 and text,..
ARI = acute respiratory infection; CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified exposed set; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV-LRTD; NH = Northern Hemisphere; n/T (per 1000) = incidence rate of participants reporting at least one event; RSVPreF3 OA= RSV pre-fusion protein 3 older adult; RSV = respiratory syncytial virus; RT-PCR = reverse transcription-polymerase chain reaction; T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; VE = vaccine efficacy.
a Prespecified secondary efficacy analyses included season as a covariate.
b VE analysis CI = 95%.
Bold indicates statistically significant.

6.21 A post-hoc subgroup analysis in adults ≥75 YOA showed that compared to adults ≥60 YOA (overall trial population), RSVPreF3 OA was less efficacious in preventing RT-PCR confirmed RSV-LRTD based on VE analysis 1 and 3 (single dose) (Table 8). The submission claimed that conclusions could not be made for the efficacy of RSVPreF3

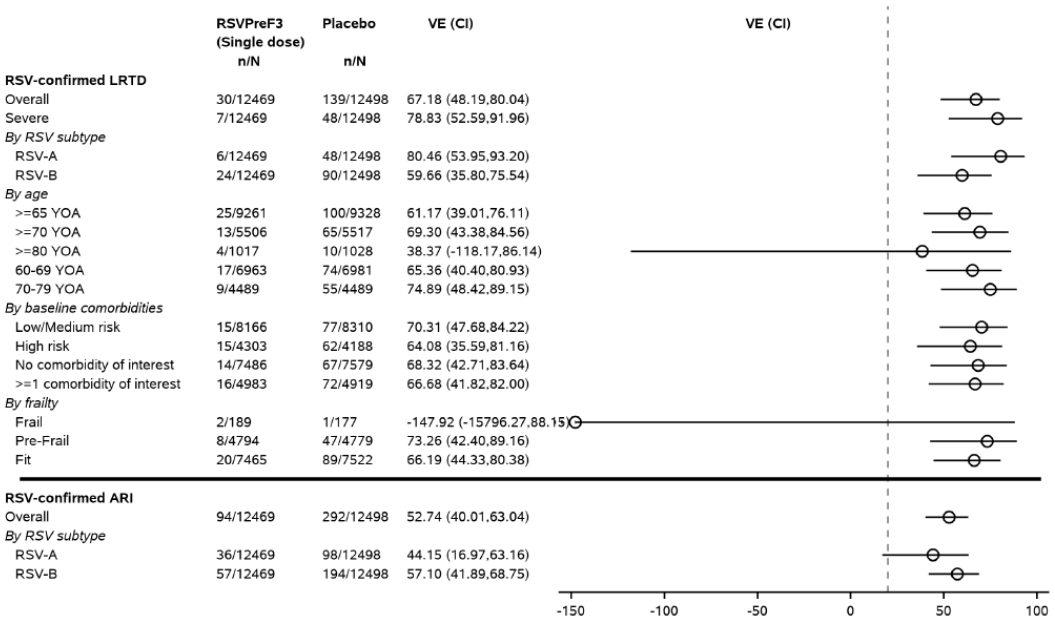
OA against RT-PCR confirmed RSV-LRTD in adults ≥75 YOA due to an insufficient number of accrued RSV-LRTD cases (n=32) and small sample size in this age group. The ability to draw efficacy conclusions based on this analysis are limited by the post hoc nature of the analysis with small numbers of participants. The ESC noted that ATAGI had considered it was reasonable to make an assumption of similar VE for the ≥60 YOA and ≥75 YOA age strata, and agreed with the commentary that this was uncertain due to the post hoc nature of the analysis and the small number of infections observed.

6.22 On the basis of the findings of the immunogenicity study AreSVi-004, the submission claimed that vaccine protection and immune persistence are expected in all adults ≥60 YOA, i.e. regardless of age bracket. The submission supported this claim with evidence from AresVi-004 in which participants who received the vaccine produced measurably higher levels of immunogenic response, irrespective of their age. The immunogenicity results per age subgroup analysis included 60-69 YOA, 70-79 YOA and ≥80 YOA, and did not include adults ≥75 YOA subgroup. That said, the humoral and cellular responses were generally high and consistent across age groups provided. The ATAGI Post-submission Advice to PBAC noted that given the immune response is consistent in older groups it is fair to assume that VE would be maintained, noting that even though VE of many vaccines drops with advancing age, the adjuvant component of RSVPreF3 OA vaccine would help maintain its efficacy in older people. The PSCR presented new immunogenicity results from AreSVi-004 to support the claim of a stronger immune response from revaccination with RSVPreF3 OA at 24 months (compared with revaccination at 12 months and further revaccination at 24 months), and similar reactogenicity and safety profiles (compared to first dose).

6.23 No decline in VE was observed with increasing age when analysed per 10-year strata (60-69 YOA versus 70-79 YOA) (Figure 1). VE was not demonstrated in the ≥80 YOA subgroup (at any time-point), however these results were subject to low numbers of participants and RSV cases in this group. Compared to the overall trial population, RSVPreF3 OA remained efficacious for all the predefined subgroups, except for ≥80 YOA and frail subgroups that showed a low VE compared to the overall trial population (see Figure 1). The submission claimed that the evidence on the efficacy of RSVPreF3 OA in these subgroups was inconclusive due to the low number of RSV confirmed LRTD cases. Given the low number of cases reporting RSV-LRTD in these subgroups this claim was reasonable.

6.24 The ATAGI advice to the PBAC suggested consideration should be given to higher risk individuals aged 60-74 YOA. RSVPreF3 OA demonstrated similar VE in those with ≥1 comorbidity compared to those with no comorbidities(Figure 1). Comorbidities defined by the trial protocol did not include some factors identified by the ATAGI as risk factors for RSV, including immunocompromising conditions (e.g. solid malignancy, haematological malignancy) and chronic neurological conditions which increase respiratory infection risk.

Figure 1: Forest plot summary of vaccine efficacy against first occurrence of RT-PCR-confirmed RSV-LRTD or RSV-ARI up to end of Season 2 in NH, using Poisson method, mES



Source: Figure 2-8of the submission.

ARI = acute respiratory infection; CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified exposed set; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV LRTD or RSV ARI; NH = Northern Hemisphere; RSV = respiratory syncytial virus; RSVPreF3 = participants receiving RSVPreF3 OA investigational vaccine (pooled lots); RT-PCR = reverse transcription-polymerase chain reaction; VE = vaccine efficacy.

For single dose evaluation, participants who received RSVPreF3 OA investigational vaccine at Dose 2 (revaccination group) were censored at Dose 2.

6.25 The ATAGI Pre-submission advice to the PBAC stated that 'the ATAGI RSV subgroup has expressed interest in data for VE in First Nations people, and of any clinical trials underway in adults aged <60 years which may support a lower age of registration for RSV vaccines (and therefore potentially younger age eligibility for First Nations peoples)'. In response, the submission presented a post hoc VE analysis for all adults 60-64 YOA in Season 2 as supportive evidence. The findings (Table 8) demonstrated that VE of RSVPreF3 OA against RT-PCR confirmed RSV-LRTD was higher in adults 60-64 YOA compared to the overall trial population ≥60 YOA in Season 2. VE in the post hoc subgroup 60-64 YOA cannot necessarily be translated to younger First Nations people, given that the subgroup was not pre-specified/stratified. Moreover, data on baseline characteristics for this subgroup, such as co-morbidities and social factors, which are likely to affect the incidence of RSV acquisition and the severity of resulting sequalae, were not provided which means it was not possible to assess the applicability of these results to First Nations people. The PSCR stated that analysis of the 60-69 YOA subgroup was pre-specified, and suggested this age group would be a reasonable proxy for the 60-64 YOA group.

Table 8: VE against first occurrence of RSV-confirmed LRTD in adults ≥75 YOA and 60-64 YOA, post hoc subgroup analysis

Endpoint	RSVPreF3 OA				Placebo				VE % (CI [a]) P-value
	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	
VE analysis 1 – Season 1 NH: median follow-up time in the mES = 6.7 months									
≥60 YOA (overall trial population)	12,466	7	6,865.9	1.0	12,494	40	6,857.3	5.8	**82.58 (57.89, 94.08) P <0.0001**
≥75 YOA	2,671	3	1,473.5	2.0	2,646	6	1,451.1	4.1	52.48 (-122.52, 92.31) P = 0.4591
VE analysis 3 (single dose) – up to end of Season 2 NH – median follow-up time in mES = 17.8 months									
≥60 YOA (overall trial population)	12,469 [b]	30	14,660.5	2.0	12,498	139	17,269.0	8.0	**67.12 (48.09, 80.00) P <0.0001**
60-64 YOA	3,208	5	3,800.3	1.3	3,170	39	4,351.4	9.0	**81.49 (52.62, 94.34) P <0.0001**
≥75 YOA	2,672	8	3,079.0	2.6	2,647	24	3,624.6	6.6	49.33 (-18.24, 80.56) P = 0.1312

Source: Table 2-36 and Table 2-38 of the submission.

CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified exposed set; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV-LRTD; n/T (per 1000) = incidence rate of participants reporting at least one event; RSVPreF3 OA= RSV pre-fusion protein 3 older adult; NH = Northern Hemisphere; RSV = respiratory syncytial virus; RT-PCR = reverse transcription-polymerase chain reaction; T (year) = sum of follow-up time (from Day 15 post-vaccination until first occurrence of the event or until the efficacy data lock point or until drop-out date) expressed in years; VE = vaccine efficacy; YOA = years of age.

a for base case, VE analysis 1 = 96.95% CI and VE analysis 3 = 97.5% CI; for post hoc analysis CI for all VE analysis was 95%.

b for single dose evaluation participants who received RSVPreF3 OA investigational vaccine at Dose 2 (revaccination group) were censored at Dose 2.

Bold indicates statistically significant.

6.26 The PSCR presented results for VE analysis 4 (Table 9) by age group and comorbidity status subgroups. The PSCR did not provide updated results for the >80 YOA subgroup. The pre-PBAC response stated there were too few cases observed in adults >80 YOA, and therefore VE could not be concluded. The new evidence provided could not be verified as the sponsor did not provide source data for VE analysis 4. The ESC noted the results provided in the PSCR, and considered it was reasonable to make assumptions of VE over the period of follow-up data, however, there was uncertainty regarding the pattern of waning immunity over time, and the need for a booster dose.

Table 9: Summary of VE against first occurrence of RT-PCR confirmed RSV-LRTD, subgroup analyses[a]; – VE analysis 3 (single dose), and VE analysis 4 (as reported in the PSCR), mES

Subgroups	RSVPreF3 OA				No vaccine				VE % (CI [b]) P-value
	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	
VE analysis 3 (single dose) – up to end of Season 2 NH – median follow-up time in mES = 17.8 months									
Age category									
≥65 YOA	9,261	25	10,862.3	2.3	9,328	100	12,917.6	7.7	61.17 (39.01, 76.11) <0.0001
≥70 YOA	5,506	13	6,419.5	2.0	5,517	65	7,614.9	8.5	69.30 (43.38, 84.56) <0.0001
≥80 YOA	1,017	4	1,151.2	3.5	1,028	10	1,384.4	7.2	38.37 (-118.17, 86.14) 0.6032
60-69 YOA	6,963	17	8,243.0	2.1	6,981	74	9,654.1	7.7	65.36 (40.40, 80.93) <0.0001
70-79 YOA	4,489	9	5,268.3	1.7	4,489	55	6,230.4	8.8	74.89 (48.42, 89.15) <0.0001
Baseline comorbidity									
≥1 condition	4,983	16	5,882.9	2.7	4,919	72	6,790.9	10.6	66.70 (41.8, 82.0)
≥1 cardiorespiratory condition	2,546	10	2,997.5	3.3	2,479	56	3,411.6	16.4	73.80 (47.9, 88.2)
≥1 endocrine or metabolic condition	3,229	8	3,822.6	2.1	3,255	32	4,509.4	7.1	63.10 (17.4, 85.4)
Low or medium risk of morbidity or mortality (CCI≤3)	8,166	15	9,630.7	1.6	8,310	77	11,485.9	6.7	70.31 (47.68, 84.22) <0.0001
High risk of morbidity or mortality (CCI>3)	4,303	15	5,031.9	3.0	4,188	62	5,783.0	10.7	64.08 (35.59, 81.16) 0.0002
Baseline frailty status									
Pre-Frail	4,794	8	5,537.3	1.4	4,779	47	6,478.5	7.3	73.26 (42.40, 89.16) 0.0002
VE analysis 4 (single dose) – up to the end of Season 2 NH and SH, median follow-up time in mES = 23.3 months									
Age category									
≥65 YOA	9,261	26	n.r.	n.r.	9,328	112	n.r.		63.1 (42.8, 77.0)
≥70 YOA	5,506	12	n.r.	n.r.	5,517	74	n.r.		74.6 (52.6, 87.5)
≥80 YOA	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
60-69 YOA	6,962	20	n.r.	n.r.	6,981	80	n.r.		61.4 (36.0, 77.7)
70-79 YOA	4,489	9	n.r.	n.r.	4,489	63	n.r.		77.5 (54.3, 90.2)
Baseline comorbidity									
≥1 condition [c]	5,000	17	n.r.	n.r.	4,942	79	n.r.		67.1 (43.6, 81.8)
≥1 cardiorespiratory condition	2,567	12	n.r.	n.r.	2,499	61	n.r.		70.5 (44.2, 85.6)
≥1 endocrine or metabolic condition	3,236	8	n.r.	n.r.	3,267	36	n.r.		66.2 (25.4, 86.5)
Low or medium risk of morbidity or mortality (CCI≤3)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	68.5 (46.3, 82.6)[e]
High risk of morbidity or mortality (CCI>3)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	67.2 (41.8, 82.7)[e]
Baseline frailty status									
Pre-Frail [d]	4,794	9	n.r.	n.r.	4,779	50	n.r.		71.3 (40.6, 87.7)

Source: Table 2.6.7: of the commentary, PSCR Table 2 and text,.

CI = confidence interval; CCI = Charleston Co-morbidity index ; mES = modified exposed set; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV-LRTD; LRTD = lower respiratory tract disease; NH = Northern Hemisphere; n.r. not

reported; n/T (per 1000) = incidence rate of participants reporting at least one event; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; RSV: respiratory syncytial virus; RT-PCR: reverse transcription-polymerase chain reaction; T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; VE = vaccine efficacy; YOA = years of age.
For annual revaccination evaluation, participants who received Placebo at Dose 2 (RSV_1 dose group) are censored at Dose 2
a Prespecified secondary efficacy analyses included season as a covariate.
b 96.95% CI for the base case analysis, 95% CI for the subgroup analysis..
c ≥1 pre-existing comorbidities of interest (i.e., COPD, asthma, any chronic respiratory/pulmonary disease, diabetes mellitus, chronic heart failure, advanced liver, or renal disease.
d Frailty assessed using a gait speed test.
e Result for VE analysis 4 reported in pre-PBAC response.

6.27 Patient reported outcomes (PROs) were evaluated in the mES RT-PCR-confirmed RSV-LRTD and mES RT-PCR confirmed RSV-ARI cohorts using FLU PRO version 2.0, SF-12, EQ-5D and PGI-S and PGI-C questionnaires. Using the EQ-5D, the submission claimed a clinically relevant difference in health utility by comparing observed least squares means difference of 0.08 in favour of RSVPreF3 OA compared to placebo to an MCID value range of 0.06 and 0.09 in cancer patients. The submission did not use the results from the PRO questionnaires evaluated in AreSVi-006 in the economic evaluation. The submission argued for the use of utility weights from the literature because there were insufficient data points of the EQ-5D collected from the trial to inform the RSV-URTD and RSV-LRTD health states. The evaluation considered that this was reasonable.

6.28 Based on the FLU-PRO chest score over the first 7 days of the episode in Season 1, the RSVPreF3 OA vaccine significantly reduced the intensity of the LRT symptoms of RSV-ARI (including trouble breathing, chest tightness and frequency and severity of cough) by a clinically meaningful difference of 0.58 (mean scores of 1.32 in RSVPreF3 group and 1.90 in placebo group). The submission did not present evidence to support the claim of 0.58 being a clinically meaningful difference. The FLU-PRO chest score relates to symptoms including trouble breathing, chest tightness and frequency and severity of cough. Based on this result, the submission claimed RSVPreF3 OA vaccine attenuates the severity of RSV-ARI associated symptoms in RSV breakthrough infections and that the findings were in line with the efficacy of RSVPreF3 OA demonstrating higher VE against more severe RSV disease. The evaluation considered that this claim was reasonable.

6.29 A least squares difference of 7 points was observed between RSVPreF3 OA and placebo for the SF-12 physical functioning (PF) domain, suggesting a lower physical functioning impact of RSV-ARI in the RSVPreF3 OA arm. The submission claimed that the observed difference was clinically relevant given it is above a minimum clinically important difference (MCID) of 3.3 in the SF-36 PF domain, estimated for participants with improving symptoms of lower extremities osteoarthritis. The evaluation considered that this claim may not be reasonable considering the difference in the number of items assessed for SF-12 PF and SF-36 PF, and the fact that physical symptoms of lower extremity osteoarthritis are typically more debilitating than physical symptoms of RSV disease.

Comparative harms

Solicited events

6.30 A summary of any grade and Grade 3 solicited events reported within 4 days of vaccination in the solicited safety set (SSS), corresponding to a subset of the overall trial population, is presented in (Table 10). The SSS was defined as all participants who received at least the first dose of the study intervention and had solicited safety data (1,757 participants, 879 in the RSVPreF3 OA group and 878 in the placebo group). Overall, the safety profile was different across the treatment arms, with a higher reactogenicity being reported in the RSVPreF3 OA group compared to placebo. The proportions reported for solicited events were any grade (71.9% vs 27.9%) and Grade 3 (4.1% vs 0.9%). In the RSVPreF3 OA arm, the most frequently reported administrative site event was pain (60.9%; any grade) and for systemic events was fatigue (33.6%; any grade). The most frequently reported Grade 3 systemic event was fatigue (1.7%). The submission stated that the higher reactogenicity rate observed in the RSVPreF3 OA arm was expected given it is an adjuvanted vaccine. The evaluation considered that this was reasonable.

Table 10: Summary of key adverse events (solicited) within 4 days following dose 1 in AreSVi-006, SSS

	RSVPreF3 OA (overall) n with event/N (%)	Placebo n with event/N (%)
Any grade		
Any AE	632/879 (71.9)	245/878 (27.9)
Admin-site AE	548/879 (62.3)	87/878 (9.9)
Systemic AE	435/879 (49.5)	204/878 (23.2)
Grade 3		
Any AE	36/879 (4.1)	8/878 (0.9)
Admin-site AE	13 [a]	13 [a]
Systemic AE	29/879 (3.3)	8/878 (0.9)

Source: Table 2-30 and Table 2-31of the submission

admin = administration; AE = adverse event; n = number of participants reporting data; N = total participants in group; RSVPreF3 OA= RSV pre-fusion protein 3 older adult; SSS = solicited safety set.

a Due to the small number of events, events are represented across all study arms in order to maintain blinding

RSVPreF3OA includes the single dose and the first vaccination of the revaccination arm

6.31 RSVPreF3 OA vaccine had a comparable safety profile in the ≥75 YOA population compared to the ≥60 YOA adult population (data not shown).

Unsolicited AEs

6.32 The submission claimed that unsolicited adverse events (AEs) reported within 30 days post vaccination in the SSS were similar across the RSVPreF3 OA and placebo arms (any AE: 14.9% vs 14.6%, RR = 1.02 [95% CI: 0.80, 1.31]). However this claim was not supported by the summary of unsolicited AEs following vaccination in the exposed set (Table 11). The exposed set included all participants who received at least the first dose of the study intervention (24,973 participants, 12,470 in the RSVPreF3 OA group and 12,503 in the placebo group for data lock point 31 March 2023). As for the SSS described in paragraph 6.30, the incidence of unsolicited AEs within 30 days post-vaccination was higher in the RSVPreF3 OA arm, except for any medically attended

AEs which was similar across both treatment arms. No cases of acute disseminated encephalomyelitis, Guillain-Barré syndrome, or other demyelinating disorders were reported in AreSVi-006.

6.33 The incidence of SAEs and potential immune-mediated disorders (pIMDs) up to 6 months post vaccination were similar across the RSVPreF3 OA and placebo arms (Table 11).

Table 11: Summary of unsolicited adverse events following vaccination in AreSVi-006, exposed set

	RSVPreF3 OA (overall) n with event/N (%)	Placebo n with event/N (%)
Unsolicited AEs within 30 days post vaccination		
Any	4,221/12,470 (33.8)	2,229/12,503 (18.4)
Any Grade 1	3,348/12,470 (26.8)	1,540/12,503 (12.3)
Any Grade 2	1,424/12,470 (11.4)	898/12,503 (7.2)
Any grade 3	251/12,470 (2.0)	158/12,503 (1.3)
Any AE related to the intervention	3,176/12,470 (25.5)	749/12,503 (6.0)
Any grade 3 related to the intervention	110/12,470 (0.9)	23/12,503 (0.2)
Any medically attended	718/12,470 (5.8)	722/12,503 (5.8)
Unsolicited AEs up to 6 months post vaccination		
Any SAE	548/12,470 (4.4)	539/12,503 (4.3)
Any SAE related to the intervention	15/12,470 (0.1)	10/12,503 (0.1)
Any pIMD	46/12,470 (0.4)	38/12,503 (0.3)
Any pIMD related to the intervention	8/12,470 (0.1)	7/12,503 (0.1)
Any fatal SAE	148/12,470 (1.2)	149/12,503 (1.2)

Source: Compiled during the evaluation from evaluation from Table 12.4 of 'RSV OA = Adj-006 Study Report (Blinded End of Season 2) Published 28 Jun 2023' of the Submission.
AE = adverse event; n = number of participants reporting data in at least one event; N = total participants in group; pIMD = potential immune-mediated disorders; RSVPreF3 OA= RSV pre-fusion protein 3 older adult; SAE = serious adverse events.
Events reported up to safety data lock point, 30 April 2022.
RSVPreF3OA includes the single dose and the first vaccination of the revaccination arm.

Solicited and Unsolicited Grade 3 AEs

6.34 A summary of solicited and unsolicited Grade 3 AEs within 30 days following vaccination in the exposed set is provided in Table 12. The intensity of AEs was graded from mild (grade 1) to severe (grade 3); grading was done by the participants for solicited events and by the investigators for unsolicited events.

Table 12: Summary of solicited and unsolicited adverse events within 30 days following vaccination, exposed set

Adverse event	Type	RSVPreF3 OA n with event/N (%)	Placebo n with event/N (%)
Grade 3 AEs	Any AE	283/12,467 (2.3)	166/12,499 (1.3)
	Admin-site AE	57/12,467 (0.5)	4/12,499 (0.0)
	Systemic AE	245/12,467 (2.0)	164/12,499 (1.3)

Source: Compiled during the evaluation from Table 14.3.1.10; Table 14.3.1.12 of RSV OA = Adj-006 Study Report (VE analysis 1) Published 18 August 2022
AE = adverse event; n = number of participants reporting data; N = total participants in group; RSVPreF3 OA= RSV pre-fusion protein 3 older adult.

Benefits/harms

6.35 A summary of the comparative benefits and harms for RSVPreF3 OA versus placebo is presented in Table 13.

Table 13: Summary of comparative benefits and harms for RSVpreF3 OA and placebo

Benefits						
RT-PCR confirmed RSV-LRTD						
Event	**RSVPreF3 OA n/N (%)**	**Placebo n/N (%)**	**Absolute Difference n (%)**	**VE% (CI [a])**		
≥60 YOA (all single dose)						
VE analysis 1 MFU 6.7 months	7/12,466 (0.1%)	40/12,494 (0.3%)	33 (0.3%)	**82.58 (57.89, 94.08)**		
VE analysis 2 MFU 11.5 months	10/12,469 (0.1%)	47/12,498 (0.4%)	37 (0.3%)	**78.86 (57.60, 90.47)**		
VE analysis 3 MFU 17.8 months	30/12,469 (0.2%)	139/12,498 (1.1%)	109 (0.9%)	**67.18 (48.19, 80.04)**		
VE analysis 4 MFU 23.3 months	32/12,468 (0.3%)	154/12,498 (1.2%)	122 (1.0%)	**67.7 (52.3, 78.7)**		
≥75 YOA (all single dose)						
VE analysis 1 MFU 6.7 months	3/2,671 (0.1%)	6/2,646 (0.2%)	3 (0.1%)	52.48 (-122.52, 92.31)		
VE analysis 3 MFU 17.8 months	8/2,672 (0.3%)	24/2,647 (0.9%)	16 (0.6%)	49.33 (-18.24, 80.56)		
Harms						
AreSVi-006	**RSVpreF3 OA n/N**	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				RSVpreF3 OA	**Comparator/ Placebo**	
Solicited Grade 3 events within 4 days following dose 1						
Any AE	36/879	8/878	4.49 (2.10, 9.62)	4.10	0.91	0.03 (0.02, 0.05)
Admin-site AE	13 [b]	13 [b]	NA	NA	NA	NA
Systemic AE	29/879	8/878	3.62 (1.67, 7.88)	3.30	0.91	0.02 (0.01, 0.04)
Unsolicited AEs within 30 days post vaccination						
Any Grade 3	251/12,470	158/12,503	1.59 (1.31, 1.94)	2.01	1.26	0.01 (0.00, 0.01)
Any Grade 3 related to the intervention	110/12,470	23/12,503	4.79 (3.06, 7.51)	0.88	0.18	0.01 (0.01, 0.01)
Any medically attended	718/12,470	722/12,503	1.00 (0.90, 1.10)	5.76	5.77	0.00 (-0.01, 0.01)
Unsolicited AEs within 6 months post vaccination						
Any SAE	548/12,470	539/12,503	1.02 (0.91, 1.15)	4.39	4.31	0.00 (-0.00, 0.01)
Any SAE related to the intervention	15/12,470	10/12,503	1.50 (0.68, 3.35)	0.12	0.08	0.00 (0.00,0.00)
Any pIMD	46/12,470	38/12,503	1.21 (0.79, 1.86)	0.37	0.30	0.00 (-0.00, 0.00)
Any pIMD related to the intervention	8/12,470	7/12,503	1.15 (0.42, 3.16)	0.03	0.06	0.00 (-0.00, 0.00)
Any fatal SAE	148/12,470	149/12,503	1.00 (0.79, 1.25)	1.19	1.19	-0.00 (-0.00, 0.00)

Source: Table 2-19,; Table 22-20Table 2-21, Table 2-31of the submission, and PSCR Table 2 and text, p2. Compiled during the evaluation from evaluation from Table 12.4, p296 of 'RSV OA = Adj-006 Study Report (Blinded End of Season 2) Published 28 Jun 2023' of the Submission.

admin = administration; AE = adverse event; CI = confidence interval; ES = exposed set; mES = modified exposed set; MFU = median follow up; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV-LRTD; LRTD = lower respiratory tract disease; n/T (per 1000) = incidence rate of participants reporting at least one event; RD = risk difference; RR = relative risk; RSV = respiratory syncytial virus; RSVPreF3 OA= RSV pre-fusion protein 3 older adult; RT-PCR = reverse transcription-polymerase chain reaction; T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; VE = vaccine efficacy.

a ≥60 YOA: VE analysis 1 = 96.95% CI; VE analysis 2 = 95% CI and VE analysis 3 = 97.5% CI. ≥60 YOA: VE analysis 1, 2 and 3 = 95% CI.
b Due to the small number of events, events are represented across all study arms in order to maintain blinding.
VE analysis 1: median duration of follow up = 6.7 months. VE analysis 1: median duration of follow up = 11.5 months. VE analysis 3: median duration of follow up = 17.8 months
Bold indicates statistically significant results.

6.36 On the basis of direct evidence presented by the submission, for every 1,000 adults vaccinated with RSVPreF3 OA in comparison with placebo (no vaccine):

- Approximately 3-4.5 fewer adults ≥60 YOA will have RT-PCR confirmed RSV-LRTD per RSV infection season.
- Approximately 30 additional adults ≥60 YOA would experience any Grade 3 solicited events within 4 days following a single dose of RSVPreF3 OA vaccination.
- Approximately 20 additional adults ≥60 YOA would experience grade 3 systemic solicited events within 4 days following a single dose of RSVPreF3 OA vaccination.
- Approximately 7 additional adults ≥60 YOA would experience any Grade 3 unsolicited AEs within 30 days following a single dose of RSVPreF3 OA vaccination.
- Approximately 7 additional adults ≥60 YOA would experience any Grade 3 unsolicited AEs related to RSVPreF3 OA within 30 days following a single dose of RSVPreF3 OA vaccination.

Clinical claim

6.37 The submission described RSVPreF3 OA vaccine as superior in terms of effectiveness in the prevention of RT-PCR confirmed RSV-LRTD compared with placebo (no vaccine) in adults ≥60 YOA, inclusive of those ≥75 YOA and having an acceptable safety profile despite being slightly more reactogenic compared to placebo (no vaccine).

6.38 The evaluation considered that the therapeutic conclusion presented in the submission was adequately supported by the evidence presented for the efficacy of RSVPreF3 OA vaccine in preventing RT-PCR confirmed RSV-LRTD compared with placebo in adults ≥60 YOA and adults ≥75 YOA. This was supported by the evidence presented for the VE of RSVPreF3 OA against first occurrence of RSV-ARI, severe RT-PCR confirmed LRTD and complications related to RT-PCR confirmed ARI (Table 7).

6.39 Based on the evidence presented (Table 8), RSVPreF3 OA was less efficacious in preventing RT-PCR confirmed RSV-LRTD in adults ≥75 YOA than adults ≥60 YOA;

- VE analysis 1 (median follow up 6.7 months): 52.48% vs 82.58% for ≥75 YOA vs ≥60 YOA, respectively;
- VE analysis 3 (median follow up 17.8 months): 49.33% vs 67.12% for ≥75 YOA vs ≥60 YOA, respectively (single dose analysis).

The latter comparison was based on a post hoc analysis with small numbers of accrued RSV-LRTD cases (RSVPreF3 OA n = 8 and placebo n = 24; VE analysis 3). The evaluation

considered that the estimated efficacy of RSVPreF3 OA in the ≥75 YOA subgroup was uncertain.

6.40 The ESC considered that the claim of superior effectiveness of RSVPreF3 OA vaccine compared with placebo was supported for the ≥60 YOA population (overall study population). The ESC noted that ATAGI had considered it was reasonable to make an assumption of similar VE for the ≥60 YOA and ≥75 YOA age strata, and agreed with the commentary that this was uncertain due to the post hoc nature of the analysis and the small number of infections observed.

6.41 The pre-PBAC response stated that results from observational studies provided further confidence of the applicability of outcomes from AReSVi-006 to real world populations, including older adults with underlying comorbidities and immunocompromising conditions, based on an analysis by D. Surie (2024)[10].

6.42 The PBAC agreed with the ESC that the claim of superior comparative effectiveness of RSVPreF3 OA vaccine compared to placebo was reasonable in adults ≥60 YOA, inclusive of those ≥75 YOA. However, it noted uncertainty around the magnitude and duration of benefit given that VE waned as the duration of follow up increased, and also that re-vaccination did not improve VE. Further, the PBAC noted the limitations of the evidence for adults ≥75 YOA based on the post hoc subgroup analysis, with small numbers of participants and infection cases observed, however overall it considered it was reasonable to make assumptions of similar VE in the ≥60 and ≥75 age strata, in line with the ATAGI advice.

6.43 The submission claimed that RSVPreF3 OA vaccine had an acceptable safety profile despite being slightly more reactogenic compared to placebo (no vaccine). The evaluation considered that the therapeutic conclusion was adequately supported by the evidence presented for the safety of RSVPreF3 OA in adults ≥60 YOA and adults ≥75 YOA. The ESC and the PBAC considered that the claim that RSVPreF3 OA vaccine had an acceptable safety profile was reasonable, noting there were higher rates of AEs in the solicited safety set, but overall the safety was comparable to other adjuvanted vaccines.

Economic analysis

6.44 The submission presented an economic evaluation comparing a single dose of the RSVPreF3 OA vaccine with no vaccine based on AreSVi-006 and implementing a modelled evaluation for the following populations:

- ≥60 YOA (approved TGA indication).
- ≥75 YOA (base case proposed in the ATAGI Advice to the PBAC).

[10] Surie, D. (2024). Effectiveness of adult respiratory syncytial virus (RSV) vaccines, 2023–2024. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-06-26-28/07-RSV-Adult-Surie-508.pdf

- ≥65 YOA, ≥70 YOA, and ≥80 YOA (scenario analyses requested in the ATAGI Advice to the PBAC).

6.45 The ATAGI Advice to the PBAC also recommended cost-effectiveness analyses which considered the inclusion of higher risk individuals and First Nations people 60-74 YOA. Scenario analyses for these populations were not provided by the submission and were not constructed during the evaluation. Given the increased rate of hospitalisation in First Nations people and increased risk persons, it would be expected that RSVPreF3 OA would be associated with lower incremental costs and higher incremental QALYs and LYs in these populations, however the impact of other population characteristics on the cost-effectiveness evaluation is uncertain (e.g. the impact of comorbidities impacting survival in the population which may lead to increased ICERs). The PSCR stated that the development of cost-effectiveness analyses in high-risk cohorts is challenging, and re-iterated the request from the submission that a pragmatic decision could be made to extend access to at-risk cohorts (60-74 YOA at high risk, and 60-74 YOA First Nations peoples), based on an assumption that cost-effectiveness from the ≥75 YOA cohort would be applicable to these cohorts. The ESC noted the significantly higher ICERs in younger age groups compared with the 75+ age-group. The ESC also noted that substantive model changes may be required to reflect the high risk/First Nations populations. The ESC noted the broad range of medical conditions that may be associated with increased risk of RSV disease complications identified by ATAGI (see paragraph 3.6). The ESC considered a pragmatic decision was unlikely to be appropriate, in particular for the high risk adults, given the estimated financial impact. The submission stated revaccination was not considered in the model as AreSVi-006 did not provide sufficient information for revaccination. This was consistent with the requested NIP listing.

6.46 The pre-PBAC response cited the results of an analysis conducted by the US CDC which reported similar estimates of cost-effectiveness in US adults ≥75 & 60-74 YOA with >1 condition increasing the risk of severe RSV disease ($45,000 to < $55,000 and $55,000 to < $75,000/QALY, respectively) (Hutton, 2024 slide 30), and stated that further clarity was needed from ATAGI regarding the modelling of this cohort. The PBAC considered that the proposed definition of high-risk conditions was sufficiently detailed to have allowed the sponsor to prepare an informative model to examine the cost-effectiveness of RSVPreF3 OA in this group, and noted that this was supported by the ATAGI's post-submission advice to the PBAC (see paragraph 3.6).

6.47 A summary of the model structure, key inputs and rationale is presented in Table 14.

Table 14: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	RSVPreF3 OA vs no vaccine
Time horizon	3 years in the model base case versus 18 months in AreSVi-006. The model accrued Lys and QALYs due to premature RSV-related death over a lifetime (109 YOA). The PSCR presented a revised model informed by VE analysis 4 of AreSVi-006, based on a median follow-up of 23.3 months.
Outcomes	Lys and QALYs

Component	Summary
Methods used to generate results	Static multi-cohort Markov model
Health states	No-RSV, post-RSV (participants that survived at least one RSV episode), and death
Cycle length	1 month
Transition probabilities	Literature • RSV seasonality proportionality factor (Nazareno et al. 2022): 7-month RSV season starting in March (98%), a peak in June (238%) /July (201%), before declining in September (72%). The base case modelled March as the vaccination month. • Unadjusted annual RSV incidence rate (Korsten et al. 2021; Narejos Pérez et al. 2023): 2.61/100 person-years (95% CI: 1.91-3.57). • Under-ascertainment multiplier (Li et al. 2023): 2.19 (95% CI 1.72–2.97). • Under-ascertainment adjusted annual incidence rate (unadjusted annual incidence rate by under-ascertainment multiplier): 5.72/100 person-years. • Proportion of RSV-LRTD cases that are hospitalised (Branche et al. 2021): 60-64 YOA 4%; 65-74 YOA 9%; 75-84 YOA 18%; ≥85 YOA 34%. • RSV-LRTD deaths (Tseng et al. 2020): 60-64 YOA 0.20%; 65-74 YOA 0.43%; 75-84 YOA 2.00%; ≥85 YOA 3.66%. • Proportion of symptomatic RSV infection seeking medical care: 39.2%. AreSVi-006 placebo arm VE analysis 1 • Proportion of RSV-ARI which is RSV-LRTD: 47.6%. • Proportion of RSV-ARI which is RSV-URTD: 52.4%. • MA RSV-LRTD: 60%. • MA RSV-URTD: 25%. • Proportion MA RSV-LRTD within MA RSV-ARI event: 63%. • Proportion MA RSV-URTD within MA RSV-ARI event: 37%.
Vaccine efficacy (VE)	• Peak VE RSV-ARI: 74.17% (95% CI 56.39- 94.01%). • Peak VE RSV-LRTD: 88.02% (95% CI 65.80-99.20%). • Monthly VE waning rate RSV-ARI: 2.26% (95% CI 0.30-4.32%). • Monthly VE waning rate RSV-LRTD: 2.10% (95% CI 0.14-4.30%). VE was extrapolated to estimate peak VE and waning rate using a weighted least squares regression on VE timepoints sourced from AreSVi-006, which provided data up to 18 months. Month 1 data from AreSVi-006 represented events between 15- and 45-days post vaccination. The midpoint (30 days post-vaccination) was used for modelling purposes. 50% peak VE was used in the first model cycle to allow for an immune build-up period. The submission estimated RSV-URTD VE from individuals with RSV-ARI but without RSV-LRTD.
Adverse events	Grade 3 (severe) AE: 2.27% (Grade 3 AE from AreSVi-006 vaccinated arm)
Health related quality of life	Literature-based: • No-RSV (McCaffrey et al. 2016): 0.89 for 60-64 YOA; 0.87 for 65-74 YOA; 0.83 ≥75 YOA • Vaccine-related AE (Schmader et al. 2019): -0.000677 US TTO study: • RSV-LRTD: -0.018 • RSV-URTD: -0.013
Hospitalisation costs	Estimated by using the National Efficient Price, LOS, separations and adjusting for ICU and MV costs: • 60-64 YOA: $[redacted] • 65-69 YOA: $[redacted] • 70-74 YOA: $[redacted]

Component	Summary
	• 75-79 YOA: $[redacted] • ≥80 YOA: $[redacted] The submission adjusted NHCDC cost weights by ICU stay and LOS. The evaluation considered this may not be reasonable given observed NHCDC cost weights already account for ICU and LOS, potentially overestimating costs. Using unadjusted NHCDC cost weights hospitalisation costs were $[redacted]. The ESC considered that hospitalisation costs had been overestimated by the submission (see paragraph 6.66).
Other costs	• Vaccine acquisition: $[redacted]. • Disease management RSV-URTD: GP visit, specialist visit, RSV testing, pathology, X-rays, antibiotics, bronchodilators. • Disease management RSV-LRTD: all of RSV-URTD in addition to ED visit, hospitalisations, ICU, post-hospitalisation follow-up, and LTCF. • Vaccine-related AE: GP visit, hospitalisations.

Source: Compiled from Section 3 of the submission.
AE = adverse event; ARI = acute respiratory infection; CI = confidence interval; ED = emergency department; GP = general practitioner; ICU = intensive care unit; LOS = length of stay; LRTD = lower respiratory tract disease; LTCF = long term care facility; LY = life-year; MA = medically attended; MV = mechanical ventilation; NHCDC = National Hospital Cost Data Collection; QALY = quality-adjusted life year; RSV = respiratory syncytial virus; RSVPreF3 OA = RSV prefusion protein 3 older adult; TTO = time trade-off; URTD = upper respiratory disease; US = United States; VE = vaccine efficacy; YOA = years of age.

6.48 The submission used a static multi-cohort Markov model. All individuals started in the 'no-RSV' health state and could transition to the 'post-RSV' state if an RSV infection was present, which could manifest through RSV-URTD or RSV-LRTD. This was reasonable. Patients who transition through RSV-LRTD could die due to RSV or other causes. The model tracked patients that survived at least one RSV event with the 'post-RSV' state. Patients in the 'post-RSV' state were susceptible to infection with the same risk as 'no-RSV'. The evaluation considered this was reasonable.

6.49 The submission used a 3-year time horizon given RSVPreF3 OA showed sustained efficacy at the 18-month follow-up (VE 67.2% CI: 48.1%, 80.0%) against RSV-LRTD in AreSVi-006. Life-years (LYs) and quality-adjusted life years (QALYs) due to premature RSV-related death were extrapolated over a lifetime. A sensitivity analysis conducted during the evaluation accounting for RSV-related deaths QALYs over a 3 and 2-year time horizon is presented in Table 24. The PSCR stated that the sensitivity analyses presented in the commentary assuming no benefits exceeding the time horizon were implausible, noting that life tables report an average Australian life expectancy of 83.2 years (AIHW 2023). Further, it was stated that the submission had used a standard approach for a Markov model to apply a lifetime time horizon, to capture vaccine effects on LYs lost due to premature deaths. The ESC considered the standard approach as described by the PSCR was generally reasonable. In addition, with respect to the current submission, the ESC noted that significant uncertainty remained due to limited duration of clinical evidence, and therefore it was informative to consider the impact of long term benefits that were assumed in the submission's economic model.

6.50 The submission claimed that trial-based RSV-ARI or RSV-LRTD incidences (from AresVi-006) did not represent the Australian setting due to limited transmission during the trial period which was over the COVID-19 pandemic. The evaluation considered this was reasonable. The ATAGI Advice to the PBAC stated that using overseas data was

likely reasonable given the lack of Australian-specific data. The submission also stated that RSV recently became a notifiable disease in Australia, making prior estimates unreliable. The submission conducted a systematic literature review to identify studies reporting on the burden of RSV in older adults. Based on this, the modelled RSV incidence rate was based on a meta-analysis based on 2 observational studies selected: Korsten et al. 2021, and Narejos Pérez et al. 2023.

6.51 The submission used a seasonality proportionality factor to model RSV infection distribution over 1 year. The submission noted that the cohorts commenced in the same vaccination month. The submission estimated RSV seasonality using Nazareno et al. 2022, a retrospective modelling study that used a time series analysis of influenza, and RSV-coded hospitalisations in Australia in children <5 YOA. The ATAGI Advice to the PBAC noted that seasonality should not differ between children and adults. The submission extracted data from Nazareno et al. 2022, finding a 7-month RSV season starting in March, a peak in June/July, before declining in September. The base case modelled March as the vaccination month. The ESC noted this maximised clinical benefit in the model, and may not reflect the likely usage in practice. ATAGI's statement on the clinical use of RSVPreF3 OA notes that Arexvy is administered as a single dose of 0.5 mL by intramuscular injection and may be given at any time of the year (paragraph 3.4). The ESC noted that RSV seasonality may vary from year to year, and in different parts of Australia. The ESC considered that vaccination may not always occur at the optimal time in clinical practice, due to a range of issues, such as receiving the vaccine at unrelated GP appointments, rather than attending the GP specifically for the purposes of vaccination.

6.52 A sensitivity analysis that modelled May as the vaccination month, instead of March, is presented in Table 24. The analysis showed that ICERs were increased for the ≥60 YOA and ≥75 YOA groups, by 7% and 24% respectively. The ESC considered that any move from universal March administration would increase the ICER, noting that the magnitude of the impact reflected the RSV seasonality proportionality factor, derived from Nazareno et al. 2022, as described above. Moving administration to May as shown in the sensitivity analysis, had a modest effect on the ICER, based on the modelled vaccine efficacy and waning curve which extrapolated ongoing effectiveness beyond the initial season (see Figure 2).

6.53 The submission applied an under-ascertainment multiplier to RSV incidence, emergency department visits, and hospitalisation rates to account for false negative tests due to inadequate testing methods or sample specimens. The multiplier was based on the Li et al. 2023 meta-analysis of hospitalisation burden due to RSV in high-income countries, which adjusted for case under-ascertainment. The applicability of the multiplier based on Li et al. 2023 was uncertain given this was estimated for hospitalisation rates rather than incidence rates and was based on international data, which may not be reflective of testing practices in the Australian setting. The multiplier published by Li et al. 2023 was estimated to be 2.19 (95%CI: 1.72 – 2.97). RSV incidence increased from 2.61 per 100 persons/year in the

unadjusted analysis to 5.72 per 100 persons/year using the multiplier by Li et al. 2023. The ESC agreed with the commentary that the multiplier had uncertain applicability as the study was focused on hospitalisation rates rather than incidence rates.

6.54 The submission noted there was limited surveillance for RSV-associated hospitalisations in Australia. The submission conducted a systematic literature review to source RSV-associated hospitalisations finding that hospitalisation rates varied widely between meta-analyses and therefore these estimates were not applied in the economic evaluation. The submission did not justify why hospitalisation rates from the Li et al. 2023 meta-analysis were not applied given this source was used for the under-ascertainment multiplier. However, Li et al. 2023 was a study of adults aged at least 65 years, and as such did not report hospitalisation rates for those aged 60-64 YOA.

6.55 The submission short-listed 2 studies: Kujawski et al. 2022 and Branche et al. 2021 to source RSV-associated hospitalisations. Both studies were based on US data. The applicability of these studies to the Australian setting was uncertain given differences in population and testing practices. Based on the testing rates reported in these 2 studies, the submission excluded Kujawski et al. 2022 (testing rate of 19.2%) and applied data from Branche et al. 2021 (testing rate of 93%) to estimate hospitalisation rates in the economic model. The hospitalisation rates were likely overestimated, given Branche et al. 2021 presented data from a densely populated area with different testing practices to the Australian setting. That said, given other studies such as Li et al. 2023 and Kujawski et al. 2022, did not have the granularity of data for age as provided by Branche et al. 2021 and Kujawski et al. 2022 reported a low testing rate these studies may not provide more reasonable estimates of hospitalisation rates. The ATAGI advice to the PBAC also stated that testing practices for RSV in the US are unlikely to be reflective of testing practices in Australia. The PSCR stated that Branche et al 2021 was considered the most robust source as it was the only population-based study in which >90 % of approximately 10,000 patients meeting the surveillance case definition were tested, thereby improving the accuracy and stability of reported estimates. The study is considered reasonably representative of the Australian setting, as the proportion of people >65 YOA in the total population is similar between Australia (16%) and New York City (15.5%) in 2020 (AIHW, 2023c; US Census Bureau, 2023).

6.56 Australian Institute of Health and Welfare (AIHW) hospitalisation data were presented by the submission as reported by McRae et al. 2023. AIHW hospitalisation rates estimated for non-Indigenous older Australians ranged from 32/100,00 (50-64 YOA) to 330/100,000 (≥80 YOA) in 2019. The accuracy of this data was uncertain, given the source (a conference presentation) was not peer reviewed. The submission argued that the AIHW data showed a substantial increase in hospitalisation rates over time, reflecting an increase in RSV testing, and that testing frequency remained sub-optimal. Given these limitations, the submission claimed that AIHW database estimates were unsuitable for economic model application. Similar to the base case, an adjustment

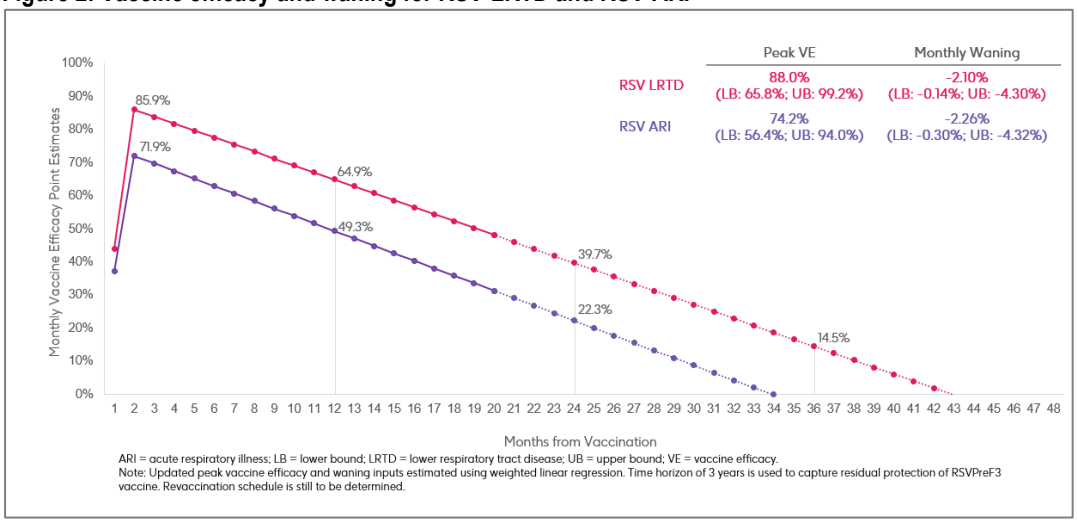
used for under-testing could have been used with AIHW data, however the value of that adjustment factor was not available from the data source.

6.57 The submission used AreSVi-006 data for VE and to derive peak VE and waning rates against RSV-ARI and RSV-LRTD, as well as vaccine-related Grade 3 AE. The submission assumed VE was consistent across all age groups, given the observed humoral and cellular immune response in older adults was consistent with younger subgroups in the key trials. The evaluation considered this was reasonable and supported by the ATAGI Post-submission Advice to PBAC.

6.58 The submission estimated peak VE and VE waning using regression modelling rather than applying the corresponding VE at each time-point. This was because estimated VE at a particular time point was a function of RSV cases observed according to phase of the RSV season and amount of immune level in the body. For example, VE of 67.1% at 18 months did not mean that single 67% VE estimate could be applied consistently from 0 to 18 months in the model. The submission assumed that efficacy began 15 days post-vaccination to give sufficient time for immune build-up. The evaluation considered this was uncertain. Peak VE was modelled between 15 days to 45 days post-vaccination consistent with the timing of peak immune response in AreSVi-004. The submission used the midpoint (30 days post-vaccination) for modelling purposes. The submission considered that a linear trend in VE was appropriate based on the decline in immune response over 12 months post vaccination in AreSVi-004. The evaluation considered this was uncertain. Immunogenicity results from AreSVi-004 showed a sharper decline between months 1 and 6, than in months 6 and 12. The submission assumed 50% of peak VE in the first model cycle to allow for an immune build-up period. This was not supported by evidence and was therefore uncertain. The PSCR claimed that the submission's approach was conservative in the first model cycle, and it was assumed that antibody levels would gradually increase to maximum level from the second cycle onwards. The submission applied peak VE in the second model cycle.

6.59 The submission estimated peak VE and VE waning using regression modelling rather than applying the corresponding VE at each time-point observed in the clinical trial. A graphical representation of peak VE and waning presented by the submission is shown in Figure 2. The analysis predicted that RSVPreF3 OA would have no efficacy against RSV-LRTD by Month 43 and no efficacy against RSV-ARI by Month 34. Revised estimates were provided in the PSCR (see paragraph 6.84).

Figure 2: Vaccine efficacy and waning for RSV-LRTD and RSV-ARI



Source: Figure 3-13 of the submission.
ARI = acute respiratory infection; LB = lower bound; LRTD = lower respiratory tract disease; RSV = respiratory syncytial virus; UB = upper bound; VE = vaccine efficacy.
Month 1 assumes 50% VE.

6.60 Table 15 presents a comparison between VE in AreSVi-006 and estimated VE in the model. Peak VE was modelled between 15 days to 45 days. The submission used the midpoint (30 days post-vaccination) for modelling purposes. Using this method, the peak estimates applied in the model for RSV-LRTD and RSV-ARI were higher than the VE results reported in the trial (between 7 to 18 months). As described above, the submission applied a linear trend to estimate VE waning, which generated VE estimates beyond the trial duration.

Table 15: Trial-based and modelled vaccine efficacy

Time point	AreSVi-006	Economic model
RSV-LRTD		
Peak VE RSV-LRTD (30 days)[b]	n.r.	88.02%
7 months	82.58%	75.42%
12 months	78.86%	64.92%
18 months	67.18% [a]	52.32%
RSV-ARI		
Peak VE RSV-ARI (30 days)[b]	n.r.	74.17%
7 months	71.71%	61.61%
12 months	64.20%	49.31%
18 months	52.74% [a]	35.75%

Source: Table 2-25 of the submission; Table 3-27 of the submission; attachment 'RSV OA static model_v16_PBAC_FINAL' of the submission.
ARI = acute respiratory infection; LRTD = lower respiratory tract disease; n.r. not reported. RSV = respiratory syncytial virus.
[a] Single dose.
[b] Peak VE was modelled between 15 days to 45 days post-vaccination consistent with the timing of peak immune response in AreSVi-004. The submission used the midpoint (30 days post-vaccination) for modelling purposes.

6.61 Despite the model using lower VE than that observed in the clinical trial (other than the peak VE applied at 30 days post-vaccination), the estimated numbers of RSV-LRTD cases avoided in the model were higher than the trial data, because the model applied literature based incidence rates which were higher than the trial data (see paragraph

6.51). The evaluation estimated 18 RSV-LRTD cases (17.8 first occurrences and 0.3 reinfections) avoided over 7 months per 1,000 persons and 32 per 1,000 (31 first occurrences and 1 reinfection) over 18 months in the ≥60 YOA population compared to 3 and 9 first occurrences of RSV-LRTD per 1,000 persons from AreSVi-006 calculated from Table 13.

6.62 The submission claimed that AreSVi-006 EQ-5D quality of life data was unable to inform utility weight calculations due to insufficient data points spent in RSV-LRTD and RSV-URTD. The evaluation considered this was reasonable. The submission sourced baseline utilities from McCaffrey et al. 2016, which provided an EQ-5D-5L data set from South Australia. McCaffrey et al. 2016 estimated utilities using a UK algorithm. Updated utilities using an Australian algorithm have been recently published.[11] The model was not sensitive to these values. The submission used a commissioned TTO study based in the US to source RSV-LRTD and RSV-URTD utility decrements. The utility estimates were uncertain given 21.2% of the sample was ≥60 YOA and it was unclear how many experienced RSV-ARI.

6.63 The submission assumed vaccine administration would incur no additional costs. The ESC has previously suggested a cost for vaccine administration noting 'it was unreasonable to assume no additional cost for administering the vaccine, noting the time taken to record information and marginal increases in consultation times' (paragraph 6.37, diphtheria, tetanus, & acellular pertussis (DTPA) injection Public Summary Document (PSD), July 2016 PBAC meeting). A sensitivity analysis considering administration costs ($9.50) conducted by the submission is presented in Table 24. The ESC noted that the impact of adding administration costs was modest; however agreed with the evaluation that it was appropriate to include a cost for vaccine administration.

6.64 The pre-PBAC response proposed a consultation fee for administration of the vaccine (MBS Item 3: $18.95), and suggested this be applied for approximately one third of cases corresponding to a fee of $6.32.

6.65 The submission stated that it estimated the cost per hospital day using the National Efficient Price (NEP), average length of stay (LOS) of 4.1 days and average cost weight of 1.3, weighted by the number of separations of Australian Refined Diagnosis Related Groups (AR-DRGs) codes E62A and E62B (respiratory infections and inflammations, minor and major complexity). The submission noted it sourced these values from 'Appendix H of the IHACPA National Efficient Price Determination 2023-24'. The values used by the submission were not consistent with the 2023-24 NEP Determination. The values used by the submission for cost weights, separations, and LOS correspond to the 2019-20 National Hospital Cost Data Collection (NHCDC) Public Sector report.[12]

[11] Redwood L et al., (2024), Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics, Qual Life Res. Mar;33(3): pp721-733.
[12] https://www.ihacpa.gov.au/resources/national-hospital-cost-data-collection-nhcdc-public-sector-report-2019-20

The submission used external data on the mean LOS for RSV-related hospitalisations by age sourced from McRae et al. 2023 to derive the total cost of an admission. The evaluation noted that given the NHCDC cost weights have been estimated for the national average LOS, adjusting the cost of hospitalisation for LOS may have overestimated costs. The PSCR stated that applying the average AR-DRG cost weight would under-represent the clinical complexity and associated resource use of RSV-related respiratory infection hospitalisation in older adults. The PSCR defended the submission's approach stating patients hospitalised with RSV disease are more likely to be treated with supplemental oxygen, mechanical ventilation, or ICU admission than Influenza or COVID-19 (Surie et al., 2023[13], 2024[14]. However, the ESC agreed with the commentary that the method applied by the submission had overstated the cost, because it inappropriately scaled up costs proportional to LoS, which did not account for front-ended costs that occurred within the early part of the admission, regardless of LOS. The ESC noted that the adjustment applied by the submission more than doubled the cost inputs for hospitalisation and had a major impact on the ICER, and noted that the PSCR provided revised inputs (Table 16). The pre-PBAC response maintained that it was appropriate to adjust the estimated costs for hospitalisation and proposed new inputs which it considered were conservative (60-74 / ≥75 YOA = $ / $). It was stated that there was insufficient RSV reporting within patient hospital records to reliably inform AR-DRG classifications, to represent LOS, healthcare resource use (ICU admission, MV) or complications associated with the hospitalisation.

6.66 The submission stated for ICU-eligible episodes, an ICU adjustment needed to be calculated separately using the estimated ICU cost per hour and the reported number of whole ICU hours. The submission did not adequately justify the application of a cost adjustment for ICU that is higher than represented in the NHCDC report. Further, the cost weights applied in the model, had already been adjusted for ICU admissions, thus applying an adjustment to observed cost weights double-counted ICU costs.

6.67 The submission noted that a proportion of RSV-ICU patients would require mechanical ventilation (MV). The submission also noted that no costing information about MV was provided by the Independent Health and Aged Care Pricing Authority. The 'National Pricing Model Technical Specifications 2023-24' report included ICUs of 'hospitals that report more than 24,000 ICU hours and have more than 20 per cent of those hours reported with the use of mechanical ventilation'; thus cost weights

[13] Surie, D., Yuengling, K. A., DeCuir, J., Zhu, Y., Gaglani, M., Ginde, A. A., Talbot, H. K., Casey, J. D., Mohr, N. M., Ghamande, S., Gibbs, K. W., Files, D. C., Hager, D. N., Ali, H., Prekker, M. E., Gong, M. N., Mohamed, A., Johnson, N. J., Steingrub, J. S., … Self, W. H. (2023). Disease Severity of Respiratory Syncytial Virus Compared with COVID-19 and Influenza Among Hospitalized Adults Aged ≥60 Years - IVY Network, 20 U.S. States, February 2022-May 2023. *MMWR. Morbidity and Mortality Weekly Report*, *72*(40), 1083–1088. https://doi.org/10.15585/mmwr.mm7240a2

[14] Surie, D., Yuengling, K. A., DeCuir, J., Zhu, Y., Lauring, A. S., Gaglani, M., Ghamande, S., Peltan, I. D., Brown, S. M., Ginde, A. A., Martinez, A., Mohr, N. M., Gibbs, K. W., Hager, D. N., Ali, H., Prekker, M. E., Gong, M. N., Mohamed, A., Johnson, N. J., … Network, I. R. V. in the A. I. (IVY). (2024). Severity of Respiratory Syncytial Virus vs COVID-19 and Influenza Among Hospitalized US Adults. *JAMA Network Open*, *7*(4), e244954–e244954. https://doi.org/10.1001/jamanetworkopen.2024.4954

incorporating ICU use (as described at paragraph 6.67) already reflect MV costs. A sensitivity analysis using observed cost weights from the NHCDC 2019-20 with no adjustments applied for ICU, ICU with MV or LOS is presented in Table 24.

6.68 Hospitalisation costs were updated in the PSCR to reflect the current national efficient price and length of stay for AR-DRG codes E62A and E62B. The PSCR also presented two scenarios with alternative RSV-associated hospitalisation costs (Scenario-A and Scenario-B, Table 16). Scenario B was adjusted based on a study by Falsey et al., 2005, which reported that RSV infections accounted for 10.6% of hospitalisations for pneumonia, 11.4% for COPD, 5.4% for CHF and 7.2% for asthma. The ESC considered that applicability of Falsey et al. 2005 to the Australian setting was uncertain, noting the study was conducted in New York over four consecutive winters, from late 1999 through early 2003. Hospitalisation costs accounting for complications were similar in both scenarios. The ESC noted that NHCDC cost weights already account for more severe cases and LOS, and therefore may be a more reasonable estimate for the base case hospitalisation costs. Applying 2020-21 NHCDC cost weights to the 2024 national efficient price yielded hospitalisation costs of $[redacted][15], lower than all estimates in the PSCR (Table 16).

Table 16: RSV-associated hospitalisation costs

	Submission	**PSCR**	**PSCR Scenario analysis-A**	**PSCR Scenario analysis-B**
Scenario	NEP: 2023, NHCDC cost weights & separations: 2019-20	NEP: 2024, NHCDC cost weights & separations: 2020-21		
AR-DRG	E62A-B	E62A-B	E62A-B	E62A-B, F62A-C, E65A-B, E69A-B
Adjustment	LOS, ICU, MV	LOS, ICU, MV	LOS[a]	LOS[b]
60-64 YOA	$[redacted]	$[redacted]	$[redacted]	$[redacted]
65-69 YOA	$[redacted]	$[redacted]	$[redacted]	$[redacted]
70-74 YOA	$[redacted]	$[redacted]	$[redacted]	$[redacted]
75-79 YOA	$[redacted]	$[redacted]	$[redacted]	$[redacted]
>80 YOA	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: PSCR Table 5.

AR-DRG = Australian Refined Diagnosis Related Groups, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, ICU = intensive care unit; LOS = length of stay; MV = Mechanical ventilation; NHCDC = National Hospital Cost Data Collection, NEP = national efficient price, PSCR = pre-subcommittee response; YOA = years of age.

[a] Calculated by multiplying cost per day ($[redacted]) and age specific length of stay in days.

[b] Calculated by multiplying age specific length of stay in days by cost per day ($[redacted]) adjusted based on cost weight and separations accounting for 10.6% of pneumonia hospitalisations, 11.4% of COPD hospitalisations, 5.4% of CHF hospitalisations, and 7.2% of asthma hospitalisations.

6.69 Key drivers of the model are presented in Table 17.

[15] For comparison, a hospitalisation cost of $[redacted] was proposed during the evaluation that removed adjustment for ICU and LOS. See Table 24.

Table 17: Key drivers of the model

Description	Method/Value	Impact Base case:≥60 YOA [1]/QALY gained ≥75 YOA: [2]/QALY gained
QALYs over a lifetime	QALYs were accrued over a lifetime from deaths avoided	High, favours RSVPreF3 OA Including QALYs only over the model time horizon increased the ICER to • ≥60 YOA = [3]/QALY gained • ≥75 YOA = [4]/QALY gained
RSV-LRTD VE waning rate	Extrapolated using regression modelling	High, favours RSVPreF3 OA Use of upper CI (4.3%) increased the ICER to • ≥60 YOA = [5]/QALY gained • ≥75 YOA = [1]/QALY gained
RSV-LRTD Peak VE	Extrapolated using regression modelling	High, favours RSVPreF3 OA Use of lower CI (65.8%) increased the ICER to • ≥60 YOA = [5]/QALY gained • ≥75 YOA = [1]/QALY gained
% RSV-LRTD hospitalised	Branche et al. 2021	High, favours RSVPreF3 OA Use of lower CI (age dependant) increased the ICER to • ≥60 YOA = [6]/QALY gained • ≥75 YOA = [4]/QALY gained
Under-ascertainment multiplier	Sourced from the literature	Moderate, favours RSVPreF3 OA Use of lower CI (1.72) increased the ICER to • ≥60 YOA = [6]/QALY gained • ≥75 YOA = [4]/QALY gained
Hospital costs	NHCDC cost weights adjusted by ICU, MV and LOS	Moderate, favours RSVPreF3 OA Using NHCDC cost weights not adjusting by ICU, MV, and LOS increased the ICER to • ≥60 YOA = [6]/QALY gained • ≥75 YOA = [4]/QALY gained

Source: Table 3-64 & 3-69, of the submission.

CI = confidence interval; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LOS = length of stay; LRTD = lower respiratory tract disease; MV = mechanical ventilation; NHCDC = National Hospital Cost Data Collection; QALY = quality-adjusted life years; RSV = respiratory syncytial virus; RSVPreF3 OA = RSV prefusion protein 3 older adult; VE = vaccine efficacy; YOA = years of age.

The redacted values correspond to the following ranges:

1 $25,000 to < $35,000
2 $5,000 to < $15,000
3 $75,000 to < $95,000
4 $15,000 to < $25,000
5 $55,000 to < $75,000
6 $45,000 to < $55,000

6.70 The submission did not present a stepped analysis. Stepped economic evaluation results estimated in the evaluation are presented in Table 18 for the ≥60 YOA population.

Table 18: Results of the stepped economic evaluation of RSVPreF3 OA vs no vaccine, ≥60 YOA population

	RSVPreF3 OA	No vaccine	Increment
Population	[redacted][1]	[redacted][1]	**-**
Step 1: Cost-effectiveness analysis (18 months) [a]			
Costs ($)	[redacted]		
RSV-LRTD cases	[redacted][2]	[redacted][3]	-[redacted][4]
Incremental cost per case avoided			[redacted]
Step 2: Data transformed into LY (18 months) [a]			
Costs	[redacted]		
LY lost	635	2,387	-1,753
Incremental cost per life year gained			$[redacted][5]
Step 3: Applied utility values (18 months) [a]			
Cost	[redacted]		
QALYs lost	5,157	11,944	-6,787
Incremental cost per QALY gained			[redacted][6]
Step 4: Extrapolate to 3 year time horizon (submission's base case)			
Cost	[redacted]		
QALYs lost	19,389	42,358	-22,969
Incremental cost per QALY gained			[redacted][7]

Source: Table 3-60 of the submission; attachment 'RSV OA static model_v16_PBAC_FINAL' of the submission.
LRTD = lower respiratory tract disease; LY = life-year; RSV = respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; QALY = quality adjusted life years; YOA = years of age.
[a] Deleted cells D40:NF1125 of tabs 'Age group 1', 'Age group 2', 'Age group 3', 'Age group 4', 'Age group 5', 'Age group 6' and 'Age group 7'.
The redacted values correspond to the following ranges:
[1] *6,000,000 to < 7,000,000*
[2] *100,000 to < 200,000*
[3] *300,000 to < 400,000*
[4] *200,000 to < 300,000*
[5] *$555,000 to < $655,000*
[6] *$135,000 to < $155,000*
[7] *$25,000 to < $35,000*

6.71 Stepped economic evaluation results estimated in the evaluation are presented in Table 19 for the ≥75 YOA population.

Table 19: Results of the stepped economic evaluation of RSVPreF3 OA vs no vaccine, ≥75 YOA population

	RSVPreF3 OA	No vaccine	Increment
Population	[redacted][1]	[redacted][1]	**-**
Step 1: Cost-effectiveness analysis (18 months) [a]			
Costs ($)	[redacted]		
RSV-LRTD cases	[redacted][2]	[redacted][3]	[redacted][4]
Incremental cost case avoided ($)			[redacted]
Step 2: Data transformed into LY (18 months) [a]			
Costs ($)	[redacted]		
LY lost	499	1,877	-1,379
Incremental cost per life year gained			[redacted][5]
Step 3: Applied utility values (18 months) [a]			
Cost ($)	[redacted]		
QALYs lost	2,007	4,989	
Incremental cost per QALY gained			[redacted][6]
Step 4: Extrapolate to 3 year time horizon (submission's base case)			
Cost ($)	[redacted]		
QALYs lost	13,083	28,779	-15,697
Incremental cost per QALY gained			[redacted][7]

Source: Table 3-60, of the submission; attachment 'RSV OA static model_v16_PBAC_FINAL' of the submission.
LRTD = lower respiratory tract disease; LY = life-year; RSV = respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; QALY = quality adjusted life years; YOA = years of age.
[a] Deleted cells D40:NF1125 of tabs 'Age group 4', 'Age group 5', 'Age group 6' and 'Age group 7'.
The redacted values correspond to the following ranges:
[1] *2,000,000 to < 3,000,000*
[2] *30,000 to < 40,000*
[3] *100,000 to < 200,000*
[4] *70,000 to < 80,000*
[5] *$115,000 to < $135,000*
[6] *$55,000 to < $75,000*
[7] *$5,000 to < $15,000*

6.72 Disaggregated discounted costs presented by the submission for the ≥60 YOA population are presented in Table 20.

Table 20: Health care resource items: disaggregated summary of cost impacts adults ≥60 YOA (discounted)

Estimate	RSVPreF3 OA	No vaccine	Incremental costs ($)	%
Population	[redacted][1]	[redacted][1]	-	-
Vaccine				
Vaccine acquisition	[redacted]	$0	[redacted]	[redacted]%
Vaccine administration	$0	$0	$0	0.0%
Disease management				
Disease management	[redacted]		[redacted]	[redacted]%
RSV-URTD cases	[redacted]		[redacted]	[redacted]%
GP visits	[redacted]		[redacted]	[redacted]%
Specialist visits	[redacted]		[redacted]	[redacted]%
Diagnostics	[redacted]		[redacted]	[redacted]%
Medicines	[redacted]		[redacted]	[redacted]%
RSV-LRTD cases	[redacted]		[redacted]	[redacted]%
GP visits	[redacted]		[redacted]	[redacted]%
Specialist visits	[redacted]		[redacted]	[redacted]%
ED visits	[redacted]		[redacted]	[redacted]%
Hospitalisations	[redacted]		[redacted]	[redacted]%
Diagnostics	[redacted]		[redacted]	[redacted]%
Medicines	[redacted]		[redacted]	[redacted]%
Vaccine-related AEs				
Vaccine-related AEs	[redacted]	$0	[redacted]	[redacted]%
GP visits	[redacted]	$0	[redacted]	[redacted]%
Hospitalisations	[redacted]	$0	[redacted]	[redacted]%
Total costs	[redacted]			**[redacted]%**

Table 3-55of the submission.

AE = adverse event; ED =emergency department; GP = general practitioner; LRTD = lower respiratory tract disease; RSV= respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; URTD = upper respiratory tract disease; YOA = years of age.

The redacted values correspond to the following ranges:

1 6,000,000 to < 7,000,000

6.73 Costs in the ≥60 YOA population were mainly driven by RSVPreF3 OA acquisition and hospitalisations due to RSV-LRTD; [redacted]% of vaccine cost was offset by hospitalisations avoided.

6.74 Disaggregated discounted costs presented by the submission for the ≥75 YOA population are presented in Table 21.

Table 21: Health care resource items: disaggregated summary of cost impacts for adults ≥75 YOA (discounted)

Estimate	RSVPreF3 OA	No vaccine	Incremental costs ($)	%
Population	[redacted][1]	[redacted][1]	-	-
Vaccine				
Vaccine acquisition	[redacted]	$0	[redacted]	[redacted]%
Vaccine administration	$0	$0	$0	0.0%
Disease management				
Disease management	[redacted]		-[redacted]	-[redacted]%
RSV-URTD cases	[redacted]		-[redacted]	-[redacted]%
GP visits	[redacted]		-[redacted]	-[redacted]%
Specialist visits	[redacted]		-[redacted]	-[redacted]%
Diagnostics	[redacted]		-[redacted]	-1[redacted]%
Medicines	[redacted]		-[redacted]	-[redacted]%
RSV-LRTD cases	[redacted]		-[redacted]	-[redacted]%
GP visits	[redacted]		-[redacted]	-[redacted]%
Specialist visits	[redacted]		-[redacted]	-[redacted]%
ED visits	[redacted]		-[redacted]	-[redacted]%
Hospitalisations	[redacted]		-[redacted]	-[redacted]%
Diagnostics	[redacted]		-[redacted]	-[redacted]%
Medicines	[redacted]		-[redacted]	-[redacted]%
Vaccine-related AEs				
Vaccine-related AEs	[redacted]	$0	[redacted]	[redacted]%
GP visits	[redacted]	$0	[redacted]	[redacted]%
Hospitalisations	[redacted]	$0	[redacted]	[redacted]%
Total costs	[redacted]			**[redacted]%**

Source: Table 3-56of the submission.

AE = adverse event; ED = emergency department; GP = general practitioner; LRTD = lower respiratory tract disease; RSV= respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; URTD = upper respiratory tract disease; YOA = years of age.

The redacted values correspond to the following ranges:

1 2,000,000 to < 3,000,000

6.75 Costs in the ≥75 YOA population were mainly driven by RSVPreF3 OA acquisition and hospitalisations; [redacted]% of vaccine cost was offset by hospitalisations avoided. Hospitalisation costs had a higher impact on the ≥75 YOA compared to the ≥60 YOA population, with a cost per person vaccinated of $[redacted] and $[redacted], respectively. This was driven by the higher probabilities of hospitalisation in the ≥75 YOA population.

6.76 Disaggregated discounted health outcomes presented by the submission for the ≥60 YOA population are presented in Table 22.

Table 22: Disaggregated summary of health outcomes included in the economic evaluation for adults ≥60 YOA (discounted)

Estimate	RSVPreF3 OA	No vaccine	Incremental outcomes	%
Events				
Population	[1]	[1]	[2]	-
Vaccinated population	[1]	[2]	[1]	-
RSV-ARI cases	[3]	[4]	[5]	%
RSV-URTD cases	[5]	[6]	[7]	%
First infection	[5]	[6]	[7]	%
Reinfection	[8]	[9]	[8]	%
RSV-LRTD cases	[10]	[6]	[10]	%
First infection	[10]	[5]	[10]	%
Reinfection	[8]	[11]	[12]	%
RSV-related deaths	[13]	[14]	[13]	-
Vaccine-related AEs	[7]	[2]	[7]	-
Health outcomes				
Lys lost	19,389	42,358	-22,969	100.0%
QALYs lost	25,830	51,317	-25,486	100.0%
RSV-related deaths	16,223	35,448	-19,225	75.4%
Vaccine-related AEs	100	0	100	-0.4%
RSV-URTD cases	5,441	7,161	-1,720	6.7%
RSV-LRTD cases	4,066	8,707	-4,641	18.2%

Source: Table 3-58of the submission.

AE = adverse event; ARI = acute respiratory infection; LRTD = lower respiratory tract disease; LY = life years; QALY = quality-adjusted life years; RSV= respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; URTD = upper respiratory tract disease; YOA = years of age.

The redacted values correspond to the following ranges:

1 6,000,000 to < 7,000,000
2 < 500
3 600,000 to < 700,000
4 1,000,000 to < 2,000,000
5 400,000 to < 500,000
6 500,000 to < 600,000
7 100,000 to < 200,000
8 20,000 to < 30,000
9 40,000 to < 50,000
10 200,000 to < 300,000
11 30,000 to < 40,000
12 10,000 to < 20,000
13 500 to < 5,000
14 5,000 to < 10,000

6.77 QALYs lost in the ≥60 YOA population were driven by RSV-related deaths (75.4%), which were estimated using baseline utility and extrapolated over a lifetime time horizon.

6.78 Disaggregated discounted health outcomes presented by the submission for the ≥75 YOA population are presented in Table 23.

Table 23: Disaggregated summary of health outcomes included in the economic evaluation for adults ≥75 YOA (discounted)

Estimate	RSVPreF3 OA	No Vaccine	Incremental outcomes	%
Events				
Population	[1]	[1]	[2]	-
Vaccinated population	[1]	[2]	[1]	-
RSV-ARI cases	[3]	[4]	[5]	[redacted]
RSV-URTD cases	[5]	[5]	[6]	[redacted]
First infection	[5]	[5]	[7]	[redacted]
Reinfection	[8]	[5]	[8]	[redacted]
RSV-LRTD cases	[9]	[5]	[10]	[redacted]
First infection	[11]	[5]	[9]	[redacted]
Reinfection	[8]	[12]	[8]	[redacted]
RSV-related deaths	[13]	[13]	[13]	-
Vaccine-related AEs	[14]	[2]	[14]	-
Health outcomes				
Lys lost	13,083	28,779	-15,697	100.0%
QALYs lost	14,107	29,288	-15,182	100.0%
RSV-related deaths	10,859	23,887	-13,028	85.8%
Vaccine-related AEs	35	0	35	-0.2%
RSV-URTD cases	1,841	2,438	-596	3.9%
RSV-LRTD cases	1,372	2,964	-1,592	10.5%

Source: Table 3-59of the submission.

AE = adverse event; ARI = acute respiratory infection; LRTD = lower respiratory tract disease; LY = life years; QALY = quality-adjusted life years; RSV= respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; URTD = upper respiratory tract disease; YOA = years of age.

The redacted values correspond to the following ranges:

1 2,000,000 to < 3,000,000
2 < 500
3 200,000 to < 300,000
4 300,000 to < 400,000
5 100,000 to < 200,000
6 9 40,000 to < 50,000
7 30,000 to < 40,000
8 5,000 to < 10,000
9 80,000 to < 90,000
10 90,000 to < 100,000
11 70,000 to < 80,000
12 10,000 to < 20,000
13 500 to < 5,000
14 50,000 to < 60,000

6.79 QALYs lost in the ≥75 YOA population were driven by RSV-related deaths (85.8%), which were estimated using baseline utility and extrapolated over a lifetime time horizon.

6.80 Based on the base case economic model presented by the submission, for every 1,000 patients vaccinated with RSVPreF3 OA in comparison with no vaccine for the ≥60 YOA population, approximately:

- 42 fewer cases of RSV-LRTD will be acquired.
- 4 Lys will be gained.
- 4 QALYs will be gained.

- $0 to < $10 million will be saved in hospitalisations due to RSV-LRTD.
- 0.4 deaths will be avoided.
- 23 will have a vaccine-related AE.

6.81 Based on the base case economic model presented by the submission, for every 1,000 patients vaccinated with RSVPreF3 OA in comparison with no vaccine for the ≥75 YOA population, approximately:

- 41 fewer cases of RSV-LRTD will be acquired.
- 7 Lys will be gained.
- 7 QALYs will be gained.
- $0 to < $10 million will be saved in hospitalisations due to RSV-LRTD.
- 1 death will be avoided.
- 23 will have a vaccine-related AE.

6.82 The results of key univariate / multivariate sensitivity analyses are summarised in Table 24. Due to the small incremental per person costs and QALYs in the base case evaluation, changes in most parameters had a substantial effect on the ICER when testing alternative inputs.

Table 24: Sensitivity analyses

Model variable	≥60 YOA				≥75 YOA			
	Incr. cost ($)	Incr. QALY	ICER	%	Incr. cost ($)	Incr. QALY	ICER	%
Base case	[redacted]	**25,486**	[redacted][1]	**-**	[redacted]	**15,182**	[redacted][2]	**-**
Discount rate: 5%								
3.5%	[redacted]	27,752	[redacted][1]	[redacted]%	[redacted]	16,456	[redacted][3]	[redacted]%
0%	[redacted]	35,269	[redacted][1]	[redacted]%	[redacted]	20,422	[redacted][3]	[redacted]%
Timing of vaccination: March								
May	[redacted]	24,583	[redacted][1]	[redacted]%	[redacted]	14,645	[redacted][2]	[redacted]%
Probability RSV-LRTD hospitalised [a]								
Lower CI	[redacted]	19,739	[redacted][4]	[redacted]%	[redacted]	11,291	[redacted][5]	[redacted]%
Probability RSV-LRTD hospitalised (based on Branche et al. 2021) [b]								
AIHW data; McRae et al. 2023: 2019 rates	[redacted]	24,583	[redacted][6]	[redacted]%	[redacted]	15,971	[redacted][3]	[redacted]%
RSV-LRTD waning rate (2.1%/month) [c]								
Upper CI = 4.3%	[redacted]	17,203	[redacted][7]	[redacted]%	[redacted]	9,796	[redacted][1]	[redacted]%
Peak % efficacy after first vaccination against RSV-LRTD caused by first RSV infection (88.02%) [c]								
Lower CI = 65.8%	[redacted]	17,613	[redacted][7]	[redacted]%	[redacted]	10,028	[redacted][1]	[redacted]%
Under-ascertainment multiplier (2.19) [c,d]								
Lower CI = 1.720	[redacted]	20,123	[redacted][4]	[redacted]%	[redacted]	11,993	[redacted][5]	[redacted]%
Time horizon: 3 years								
2 years **#1**	[redacted]	21,959	[redacted][6]	[redacted]%	[redacted]	13,067	[redacted][2]	[redacted]%
Benefits over a lifetime time horizon [e]								

Model variable	≥60 YOA				≥75 YOA			
	Incr. cost ($)	Incr. QALY	ICER	%	Incr. cost ($)	Incr. QALY	ICER	%
No benefits exceeding time horizon **#2**	[redacted]	10,537	[redacted][3]	[redacted]%	[redacted]	5,447	[redacted][5]	[redacted]%
Vaccine administration costs: not included								
$9.50 **#3**	[redacted]	25,486	[redacted][1]	[redacted]%	[redacted]	15,182	[redacted][2]	[redacted]%
NHCDC cost weights adjusted by ICU stays and LOS [f, g]								
Not adjusted by ICU and LOS. Hospitalisation cost = $[redacted] **#4**	[redacted]	25,486	[redacted][4]	[redacted]%	[redacted]	15,182	[redacted][5]	[redacted]%
Multivariate sensitivity analyses presented in the commentary								
AND (#1, #2)	[redacted]	7,968	[redacted][9]	[redacted]%	[redacted]	3,765	[redacted][6]	[redacted]%
AND (#1, #2, #3)		7,968	[redacted][9]	[redacted]%		3,765	[redacted][4]	[redacted]%
AND (#1, #2, #3, #4)		7,968	[redacted][10]	[redacted]%		3,765	[redacted][11]	[redacted]%
Revised analyses presented in PSCR								
Revised base case including Updated VE regression and hospitalisation cost	[redacted]	26,713	[redacted][1]	-[redacted]%	[redacted]	15,911	[redacted][3]	-[redacted]%
Scenario-A: PSCR base case and Updated NEP & Cost Weights: LOS only [h]		26,713	[redacted][6]	[redacted]%		15,911	[redacted][2]	[redacted]%
Scenario-A: PSCR base case and Updated NEP & Cost Weights: LOS and comorbidities [i]		26,713	[redacted][6]	[redacted]%		15,911	[redacted][2]	[redacted]%
Revised analyses based on model provided with pre-PBAC response								
(A) Sponsor's revised base case using VE analysis 4 (as for PSCR) and additional changes to hospitalisation costs; assumed dosing in April (rather than March), and administration cost of $6.32.	[redacted]	26,450	[redacted][6]	[redacted]%	[redacted]	15,758	[redacted][2]	[redacted]%
(B) Revised MSA, as described in (A) and assuming VE over 2 years using VE analysis 4, and unadjusted hospitalisation cost based on ESC Advice ($[redacted])		22,078	[redacted][7]	[redacted]%		13,143	[redacted][1]	[redacted]%

Source: Table 3-69 of the submission; Attachment 'RSV OA static model_v16_PBAC_FINAL' of the submission.

CI = confidence interval; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; LOS = length of stay; LRTD = lower respiratory tract disease; NHCDC = National Hospital Cost Data Collection; RSV= respiratory syncytial virus; QALY = quality-adjusted life years; YOA = years of age.

[a] See Table 3.6.8 of the Commentary for CI values.

[b] Replaced cells Y8:12 with 32, 162 (mean of 63, 98, 155, and 330), 81 (mean of 63 and 98), 243 (mean of 155 and 330), and 330 respectively of the tab 'RSV Hospital Burden'.

[c] Sourced from tab 'UDSA', cells AA77:AD111, attachment 'RSV OA static model_v16_PBAC_FINAL' of the submission.

[d] Replaced cells I284 with 1.720 of the 'Sensitivity' tab.

[e] Deleted cells D58:NF1125 of tabs 'Age group 1', 'Age group 2', 'Age group 3', 'Age group 4', 'Age group 5', 'Age group 6' and 'Age group 7'.

[f] Replaced cells L140:146 for $[redacted] ([redacted]*[redacted], i.e., NEP * separation weighted cost weight from the NHCDC 2019-20).

[g] See Table 14 for base case values.

[h] Based on the hospitalisation cost for PSCR Scenario analysis-A shown in column Table 16.

[i] Based on the hospitalisation cost for PSCR Scenario analysis-B shown in column Table 16.

The redacted values correspond to the following ranges:

1 $25,000 to < $35,000
2 $5,000 to < $15,000
3 $0 to < $5,000
4 $45,000 to < $55,000
5 $15,000 to < $25,000
6 $35,000 to < $45,000
7 $55,000 to < $75,000
8 $75,000 to < $95,000
9 $115,000 to < $135,000
10 $155,000 to < $255,000
11 $95,000 to < $115,000

6.83 The PSCR presented a revised base case applying updated VE regression analyses based on follow-up data from VE Analysis 4 (median follow-up: 23.3 months) and hospitalisation costs (NHCDC National Efficient Price for 2024 and public sector cost weights for 2021-22). The PSCR reported that RSV-LRTD and RSV ARI VE and monthly waning estimates decreased compared to VE analysis 3. It was stated that based on VE analysis 4, VE would reach 0% at month 50 for RSV-LRTD, and at month 36 for RSV-ARI (in VE analysis 3 the respective estimates were month 43 and month 34).

6.84 The revised base case yielded an ICER of $0 to < $5,000/QALY and $25,000 to < $35,000/QALY for the ≥75 YOA and ≥60 YOA populations, respectively. The results are presented in Table 24 above. A summary of changes applied in the PSCR is provided in Table 25. The ESC noted that that revised estimates of peak VE and monthly VE waning from VE Analysis 4 were more favourable to RSVPreF3 OA compared with VE Analysis 3. The ESC considered that the analysis with longer duration of follow-up was informative, however the estimates of effect beyond the trial follow-up remained uncertain.

Table 25: Summary of changes applied in the model for revised base case cost-utility analysis in PSCR

Input	Submission		PSCR	
Vaccine efficacy, % (95% CI)	RSV-LRTD	RSV-ARI	RSV-LRTD	RSV-ARI
Peak VE (Efficacy!AH15:AJ16)	88.02 (65.80 - 99.20)	74.17 (56.39 - 94.01)	86.50 (67.70 - 98.70)	73.30 (57.90 - 87.40)
Monthly VE waning (Efficacy!AH19:AJ20)	2.10 (0.14 - 4.30)	2.26 (0.30 - 4.32)	1.80 (0.30 - 3.51)	2.10 (0.67 - 3.69)
Hospitalisation costs (AR-DRG E62A-B)				
National Efficient Price	$		$	
Cost weights ("Direct costs"!F154)	1.34		1.43	
Length of stay (LOS) ("Direct costs"!I154)	4.13		4.40	

Source: Table 8, PSCR.

ARI = acute respiratory infection; AR-DRG = Australian refined diagnosis-related groups; CI = confidence interval; LRTD = lower respiratory tract disease; NHCDC = National Hospital Cost Data Collection; RSV= respiratory syncytial virus; VE = vaccine efficacy.

6.85 The results of the economic evaluation are presented in Table 26 by age cohorts using the submission's base case settings. The ESC noted that the results ranged from $0 to < $5,000/QALY for the ≥80 YOA age group, to $25,000 to < $35,000/QALY for the ≥60 YOA age group. The ESC noted that the ICERs declined with increasing age and that it was appropriate to consider the incremental population when considering the cost-effectiveness for a broader group (see Table 27). The ESC noted that the ICERs presented in Table 24 all included the most cost-effective (oldest age group), and do not consider the incremental impact of including younger age groups.

Table 26: Results of the economic evaluation by age cohorts, ≥60 YOA, ≥65 YOA, ≥70 YOA, ≥75 YOA, ≥80 YOA (submission base case settings)

Estimate	RSVPreF3 OA	No vaccine	Incremental difference
Base-case populations			
TGA indication: ≥60 YOA			
Population	[redacted]		-
Direct costs ($)			[redacted]
LYS lost	19,389	42,358	-22,969
QALYs lost	25,830	51,317	-25,486
Cost per LY gained			[redacted][1]
Cost per QALY gained			[redacted][2]
ATAGI base-case: ≥75 YOA			
Population	[redacted]		-
Direct costs ($)			[redacted]
LYS lost	13,083	28,779	-15,697
QALYs lost	14,107	29,288	-15,182
Cost per LY gained			[redacted][3]
Cost per QALY gained			[redacted][3]
ATAGI alternative populations			
≥65 YOA			
Population	[redacted]		-
Direct costs ($)			[redacted]
LYS lost	17,814	38,980	-21,166
QALYs lost	22,087	44,478	-22,391
Cost per LY gained			[redacted][4]
Cost per QALY gained			[redacted][4]
≥70 YOA			
Population	[redacted]		-
Direct costs ($)			[redacted]
LYS lost	15,090	33,118	-18,028
QALYs lost	17,617	35,944	-18,327
Cost per LY gained			[redacted][4]
Cost per QALY gained			[redacted][3]
≥80 YOA			
Population	[redacted]		-
Direct costs ($)			[redacted]
LYS lost	6,612	14,704	-8,092
QALYs lost	7,223	15,107	-7,884
Cost per LY gained			[redacted][5]
Cost per QALY gained			[redacted][5]

Source: Table 3-61, of the submission.

ATAGI = Australian Technical Advisory Group on Immunisation; LY = life years; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; TGA = Therapeutics Goods Administration; QALY = quality-adjusted life years; YOA = years of age.

The redacted values correspond to the following ranges:

1 $35,000 to < $45,000

2 $25,000 to < $35,000

3 $5,000 to < $15,000

4 $15,000 to < $25,000
5 $0 to < $5,000

6.86 The results of the economic evaluation are presented in Table 27 by age groups in five-year categories using the submission's base case settings. The reported ICERs ranged from dominant for the ≥85 YOA age group, to $95,000 to < $115,000 /QALY for the 60-64 YOA age group, with a noteworthy difference between the reported ICERs above and below 75 YOA. For ease of reference, the assumed baseline rates of RSV-LRTD hospitalisations and RSV-LRTD deaths, which are key drivers of the cost-effectiveness differences between age groups, are shown in Table 27. Further details of data informing the economic model are shown in Table 14 above. The ESC noted that the submission's estimates of the proportion of RSV-LRTD cases that are hospitalised were derived from a US study (Branche 2021), and ranged from 4% in the 60-64 age group, to 34% in the ≥85 age group. The submission's estimates of RSV-LRTD deaths were derived from a second US study (Tseng et al. 2020) multiplied by the proportion of hospitalised RSV-LRTD cases, and ranged from 0.2% in the 60-64 age group, to 3.66% in the ≥85 age group.

6.87 The ESC noted that the reported ICERs for the 65-69 YOA group and 70-74 YOA group in Table 27 did not follow the sequence of decreasing ICER for increasing age. The ESC considered this was difficult to interpret, but noted that the model also applied different utility values and hospitalisation costs by age group (Table 14), as well as all-cause mortality by age which impacted the results.

Table 27: Economic evaluation results of RSVPreF3 OA vs no vaccine per age group in five-year categories (submission base case settings)

Age group (YOA)	Population	RSV-LRTD hospitalisations	30-day mortality within hospital admission	Possibility of death given RSV-LRTD[a]	Incremental costs ($)	Incremental QALYs	ICER
60-64	[redacted][1]	4%	4.67%	0.20%	[redacted]	3,095	[redacted][2]
65-69	[redacted][1]	9%		0.43%		4,064	[redacted][3]
70-74	[redacted][1]					3,146	[redacted][3]
75-79	[redacted][1]	18%	10.87%	2.00%		7,297	[redacted][4]
80-84	[redacted][5]					3,785	[redacted][4]
≥85	[redacted][5]	34%		3.66%		4,099	Dominant

Source: Table 3-24 & 3-43of the submission; attachment 'RSV OA static model_v16_PBAC_FINAL' of the submission.
ICER = incremental cost-effectiveness ratio; LRTD = lower respiratory tract disease; QALY = quality-adjusted life years; RSV = respiratory syncytial virus; RSVPreF3 OA= RSV Pre-fusion protein 3 older adult; YOA = years of age.
a calculated as 30-day mortality within hospital admission multiplied by the proportion of hospitalised RSV-LRTD cases.
The redacted values correspond to the following ranges:
1 1,000,000 to < 2,000,000
2 $95,000 to < $115,000
3 $55,000 to < $75,000
4 $5,000 to < $15,000
5 600,000 to < 700,000

6.88 The ESC considered that significant uncertainty remained regarding the benefit of RSVPreF3 OA in the proposed populations. In addition, the ESC raised the following concerns:

- The submission did not provide cost-effectiveness analyses for use in higher risk individuals and First Nations peoples aged 60-74 YOA (see paragraph 6.46).
- The submission model was based on a single vaccination only, which was consistent with the requested NIP listing (paragraph 6.46), but if revaccination is requested in the future, this would influence both cost-effectiveness and financial impact.
- The submission assumed VE over a 3-year period (paragraph 6.50) but limited data were available to estimate the duration of protection of RSVPreF3 OA, and uncertain relevance of VE analysis 4, which was provided in the PSCR (paragraphs 6.84 to 6.85).
- The submission base case modelled March as the vaccination month which maximised clinical benefit in the model, and was unlikely to reflect use in practice (paragraph 6.52 to 6.53).
- The submission neglected to include administration costs (paragraph 6.64).
- The hospitalisation costs were overestimated (paragraphs 6.66 to 6.69).
- The ESC noted that vaccine cost-effectiveness had a strong age gradient, and presenting the results in age bands (e.g. 60-64 YOA, 65-69 YOA, etc) would be required for decision making, i.e. it was appropriate to consider the incremental population (see paragraph 6.87).

RSVPreF3 OA vaccine cost/patient/course

6.89 The proposed cost per dose of RSVPreF3 OA was $[redacted]. The intervention costs per person are presented in Table 28.

Table 28: RSVPreF3 OA costs per person

	Trial dose and duration	Model	Financial estimates
Mean dose	1 dose	1 dose	1 dose
RSVPreF3 OA price per vaccine	[redacted]		
Mean duration	One-off [a]	One-off	One-off
Cost/person/course ($)	[redacted]		

Source: the submission.
RSVPreF3 OA= RSV Pre-fusion protein 3 older adult.
[a] AReSVi-006 re-randomised participants at Year 2 for a second dose, and a third dose was also planned. However, given no difference was observed between the 1 dose and 2 doses groups, the trial protocol was amended to not administer dose 3.

Estimated PBS usage & financial implications

6.90 This submission was considered by the DUSC.

6.91 The submission presented the financial impact of introducing RSVPreF3 OA to the NIP for adults ≥60 YOA and ≥75 YOA. The submission presented two additional subgroups, noting that the ATAGI pre-submission Advice considered these populations as a priority for the NIP, in addition to the base case program proposed by ATAGI

(≥75 YOA). The two subgroups were: First Nations people aged 60-74 YOA; and individuals considered at increased risk for severe RSV disease aged 60-74 YOA[16].

6.92 The submission did not include revaccination in the base case as this was not proposed in the requested NIP listing. This was reasonable insofar as it reflected the TGA approved Product Information, however there is the possibility of a future request for NIP listing of a subsequent dose of RSVPreF3 OA as revaccination, as discussed in paragraph 3.11.

6.93 The submission used an epidemiological approach. This was reasonable given the comparator was no vaccine.

6.94 The submission based the budget impact model on the economic model, which captured VE, RSV-ARI, RSV-LRTD, RSV-URTD, and vaccine-related AEs, as well as resource utilisation. It was reasonable to base the budget impact model structure on the economic model. However, parameters related to RSV-LRTD costs had the same caveats as in the economic model, particularly hospitalisations costs, which were discussed in paragraphs 6.66, 6.67, and 6.68. Some of these savings may not be realised and it is notable that most of the estimated cost offsets are not PBS/MBS costs.

6.95 Key inputs used by the submission are presented in Table 29.

Table 29: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Commentary on the submission	DUSC comments
Eligible population				
Incident population	≥ 60 YOA Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1] ≥ 75 YOA Yr 1: [redacted][2] Yr 2: [redacted][2] Yr 3: [redacted][2] Yr 4: [redacted][2] Yr 5: [redacted][2] Yr 6: [redacted][2]	Eligible population based on ABS Population Projections, Australia, 2018 (base) (Series 3222.0).	The submission used 2022 values. This was reasonable.	This was reasonable.

[16] The ATAGI advice recommended consideration of those aged ≥60 YOA years with comorbidities or social factors likely to increase the risk of severe RSV or hospitalisation, including: chronic respiratory conditions (e.g. chronic obstructive pulmonary disease, asthma); immunocompromising conditions (e.g. solid malignancy, haematological malignancy); diabetes mellitus; chronic kidney disease; chronic neurological conditions which increase the risk of respiratory infection; and Indigenous status.

Data	Value	Source	Commentary on the submission	DUSC comments
Prevalent population	≥ 60 YOA Yr 1: [redacted][3] ≥ 75 YOA Yr 1: [redacted][4]			
Treatment utilisation				
Uptake rate	60-64 YOA Yr 1: [redacted]% Yr 2-5: increases by [redacted]% per year Yr 6: [redacted]% 65-74 YOA Yr 1: [redacted]% [redacted]Yr 2-5: increases by [redacted]% per year Yr 6: [redacted]% ≥ 75 YOA Yr 1: [redacted]% Yr 2-5: increases by [redacted]% per year Yr 6: [redacted]%	NCIRS Annual Immunisation Coverage report 2022 influenza coverage. Assumed [redacted]% of influenza coverage in Yr 1 of vaccination increasing linearly to [redacted]% of influenza coverage by Yr 6. i.e., for Yr 1 of 60-64 YOA [redacted]% of the cohort was vaccinated. Then from Yr 2-5 [redacted]% was vaccinated per year, so that the full [redacted]% would be vaccinated by Yr 6. The uptake rates were also applied to the 'newly eligible population' regardless of which year they were vaccinated. i.e. in the 'newly eligible population' 60 YOA the first year of vaccination uptake was [redacted]%. However, only the 2025 cohort would add up to [redacted]% as [redacted]% would be vaccinated per year. Whereas the 'newly eligible population' 2030 cohort would only accrue [redacted]% vaccinated.	NIP funded influenza vaccination uptake was available for ≥ 65 YOA. However, the proposed NIP listing for RSVPreF3 OA was ≥ 60 YOA. Therefore, uptake was likely underestimated for the 60-64 YOA cohort. Assuming [redacted]% of influenza uptake in Yr 1 was uncertain. Uptake rates for 60-64, 65-69, and 70-74 YOA were applied to ≥ 75 YOA populations of the 'newly eligible population' 2025, 2026, and 2027, respectively in the financial model underestimating costs.	DUSC noted the PSCR acknowledged the correction made in the commentary and confirmed that the corrected outputs for newly eligible individuals in the ≥75 YOA were appropriate. DUSC considered the uptake rates for those aged 60-64 to be underestimated given the increased awareness of RSV. However, DUSC considered uptake may be impacted by vaccination fatigue.

Data	Value	Source	Commentary on the submission	DUSC comments
Doses dispensed	≥ 60 YOA Yr 1: [redacted][4] Yr 2: [redacted][5] Yr 3: [redacted][6] Yr 4: [redacted][6] Yr 5: [redacted][6] Yr 6: [redacted][6] ≥ 75 YOA Yr 1: [redacted][7] Yr 2: [redacted][2] Yr 3: [redacted][2] Yr 4: [redacted][2] Yr 5: [redacted][2] Yr 6: [redacted][2]	Total population multiplied by uptake rate. Assumed no revaccination	Incorrect uptake rates applied to the ≥ 75 YOA newly eligible population (2025-27) impacted doses dispensed.	DUSC noted the PSCR (acknowledged the correction made in the commentary and confirmed that the corrected outputs for newly eligible individuals in the ≥75 YOA were appropriate.
Costs				
RSVPreF3 OA	$[redacted]	Requested price	The submission did not apply administration costs underestimating costs to the MBS.	
RSV-LRTD	60-64 YOA: $[redacted] 65-69 YOA: $[redacted] 70-74 YOA: $[redacted] 75-79 YOA: $[redacted] 80-84 YOA: $[redacted] ≥ 85 YOA: $[redacted]	Section 3 of the commentary on the submission for details. Included GP visits, specialist visits, RSV testing, pathology, x-rays, bronchodilators, ED visits, ambulance, hospitalisations (considering ICU and MV), LTCF admissions, post-hospital GP, and antibiotics.	Issues with resources used were discussed in Section 3.6 of the Commentary. Likely overestimated as hospitalisation costs were calculated using NHCDC cost weights adjusted for ICU and LOS.	
RSV-URTD	60-64 YOA: $[redacted] ≥ 65 YOA: $[redacted]	Section 3 of the commentary on the submission for details. Included GP visits, specialist visits, RSV testing, pathology, x-rays, bronchodilators.	Issues with resources used were discussed in Section 3.6 of the Commentary.	
Vaccine-related AE	$[redacted]	Section 3 of the commentary on the submission for details. Included GP visits and hospitalisations.	Issues with resources used were discussed in Section 3.6 of the Commentary.	

Source: Table 1, DUSC Advice.

ED = emergency department; GP = general practitioner; ICU = intensive care unit; LTCF = long-term care facilities; LOS = length of stay; MBS = Medicare Benefits Schedule; MV = mechanical ventilation; NCIRS = National Centre for Immunisation Research and Surveillance; NHCDC = National Hospital Cost Data Collection; NIP = National Immunisation Program; RSV = respiratory syncytial virus; RSVPreF3 OA = RSV prefusion protein 3 older adult; YOA = years of age; Yr = year.

The redacted values correspond to the following ranges:

[1] *300,000 to < 400,000*

[2] *200,000 to < 300,000*

[3] *6,000,000 to < 7,000,000*

[4] *2,000,000 to < 3,000,000*

[5] *400,000 to < 500,000*

[6] *500,000 to < 600,000*
[7] *800,000 to < 900,000*

6.96 The submission assumed Year 1 uptake to be [redacted]% of the influenza vaccination rate in the first year of vaccination, reaching [redacted]% of the influenza vaccination rate by Year 6 based on low disease awareness. A sensitivity analysis with [redacted]% less uptake conducted by the evaluation decreased the costs to all health budgets to $400 million to < $500 million (-[redacted]%) over 6 years. The submission underestimated the newly eligible cohort doses of the ≥75 YOA population by applying uptake rates from the 60-64, 65-69, and 70-74 YOA cohorts to newly eligible individuals from 2025, 2026, and 2027, respectively. The PSCR acknowledged this error in the submission and confirmed that the corrected estimates in the ≥75 YOA population provided in the commentary were appropriate.

6.97 The estimated use and financial implications to the Federal Government, and the State and Territory Governments, for the ≥60 YOA population are presented in Table 30.

Table 30: Estimated use and financial implications for ≥60 YOA population

	2025	2026	2027	2028	2029	2030	Total
Estimated extent of use							
Predicted number of people vaccinated with RSVPreF3 OA	[redacted]1	[redacted]2	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]4
Estimated financial implications of listing RSVPreF3 OA in the NIP							
Federal	[redacted]5	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]7
NIP	[redacted]4	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]7
PBS	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8
MBS	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8
Other Federal Budgets	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8
State and Territory Governments	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8
All budgets combined	[redacted]8	[redacted]8	[redacted]10	[redacted]11	[redacted]12	[redacted]12	[redacted]5

Source: Table 4-7, compiled from Section 4.5 of the submission.
; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Schedule; RSVPreF3 OA = RSV prefusion protein 3 older adult; YOA = years of age; Yr = year.
The redacted values correspond to the following ranges:
1 2,000,000 to < 3,000,000
2 400,000 to < 500,000
3 500,000 to < 600,000
4 4,000,000 to < 6,000,000
5 $500 million to < $600 million
6 $100 million to < $200 million
7 > $1 billion
8 net cost saving
9 $300 million to < $400 million
10 $0 to < $10 million
11 $40 million to < $50 million
12 $50 million to < $60 million

6.98 The total cost to the NIP of listing RSVPreF3 OA for adults ≥60 YOA was estimated to be $100 million to < $200 million in Year 6, and a total of $0 to < $10 million in the first

6 years of listing. The total cost to all health budgets was estimated to be $50 million to < $60 million in Year 6 and $500 million to < $600 million over 6 years. Cost offsets to State and Territory Governments decreased after Year 1 as most individuals were assumed to be vaccinated in Year 1 and VE waning was applied as in the economic model but assuming 0% VE after approximately 3 years.

6.99 Estimated use and financial implications to the Federal Government, and the State and Territory Government for the ≥75 YOA population are presented in Table 31.

Table 31: Estimated use and financial implications for ≥75 YOA population

	2025	2026	2027	2028	2029	2030	Total
Estimated extent of use [a]							
Predicted number of people vaccinated with RSVPreF3 OA	[redacted]1 ([redacted]1)	[redacted]2 ([redacted]2)	[redacted]2 ([redacted]2)	[redacted]2 ([redacted]2)	[redacted]2 ([redacted]3)	[redacted]2 ([redacted]3)	[redacted]4 ([redacted]4)
Estimated financial implications of listing RSVPreF3 OA in the NIP [a]							
Federal	[redacted]5 ([redacted]5)	[redacted]6 ([redacted]7)	[redacted]7 ([redacted]8)	[redacted]7 ([redacted]8)	[redacted]8 ([redacted]9)	[redacted]8 ([redacted]9)	[redacted]11 ([redacted]12)
NIP	[redacted]5 ([redacted]5)	[redacted]7 ([redacted]8)	[redacted]7 ([redacted]8)	[redacted]8 ([redacted]9)	[redacted]8 ([redacted]9)	[redacted]8 ([redacted]10)	[redacted]12 ([redacted]12)
PBS	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)
MBS	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)
Other Federal budgets	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)
State and Territory Governments	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)
All budgets combined	[redacted]14 ([redacted]14)	[redacted]13 ([redacted]13)	[redacted]13 ([redacted]13)	[redacted]15 ([redacted]16)	[redacted]16 ([redacted]16)	[redacted]15 ([redacted]16)	[redacted]14 ([redacted]14)

Source: Table 4-8, compiled from Section 4.5 of the submission. Text in brackets was estimated in the Commentary.
; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Schedule; RSVPreF3 OA = RSV prefusion protein 3 older adult; YOA = years of age; Yr = year.
Corrected uptake application for the newly eligible cohort (2025-27) in the ≥75 YOA population are presented in brackets.
The redacted values correspond to the following ranges:
1 800,000 to < 900,000
2 200,000 to < 300,000
3 300,000 to < 400,000
4 2,000,000 to < 3,000,000
5 $200 million to < $300 million
6 $40 million to < $50 million
7 $50 million to < $60 million
8 $60 million to < $70 million
9 $70 million to < $80 million
10 $80 million to < $90 million
11 $400 million to < $500 million
12 $500 million to < $600 million
13 net cost saving
14 $100 million to < $200 million
15 $0 to < $10 million
16 $10 million to < $20 million

6.100 The total cost to the NIP of listing RSVPreF3 OA for adults ≥75 YOA was estimated to be $60 million to < $70 million in Year 6, and a total of $500 million to < $600 million in the first 6 years of listing. The total cost to the NIP of listing RSVPreF3 OA for adults ≥75 YOA calculated by the evaluation applying uptake rates relevant to the ≥75 YOA newly eligible cohort (2025-27) was estimated to be $80 million to < $90 million in Year 6, and a total of $500 million to < $600 million in the first 6 years of listing. The total cost to all health budgets was estimated to be $0 to < $10 million in Year 6 and $100 million to < $200 million over 6 years. Using uptake rates relevant to the ≥75 YOA newly eligible cohort (2025-27) the total cost to all health budgets was estimated to be $10 million to < $20 million in Year 6, and a total of $100 million to < $200 million (37%) in the first 6 years of listing. Cost offsets to State and Territory Governments decreased after Year 1 as most patients were vaccinated in Year 1 and VE waning was applied as in the economic model but assuming 0% VE after approximately 3 years.

6.101 The financial model predicted cost savings in Year 2 of the ≥60 YOA and Years 2 and 3 in the ≥75 YOA populations. This was driven by costs offsets generated by decreasing hospitalisations associated with RSVPreF3OA vaccination. The model assumed all hospitalisations would be to public hospitals overestimating cost offsets to State and Territory Governments. Further, given there is some Federal funding of hospitals, not all cost offsets as a result of hospitalisations would be accrued by State and Territory Governments.

6.102 Cost offsets as a result of hospitalisation costs were derived by using NHCDC cost weights and adjusted for ICU costs and LOS, potentially overestimating hospitalisation unit costs. A sensitivity analysis using unadjusted observed cost weights, i.e., not adjusting for ICU, MV and LOS (see paragraphs 6.66, 6.67, and 6.68 for further details), to calculate hospitalisation costs, increased all health budgets financial impact from $500 million to < $600 million in the base case to $800 million to < $900 million (62.3%) for the ≥60 YOA population and from $100 million to < $200 million in the base case to $300 million to < $400 million (230.2%) for the ≥75 YOA population in the first 6 years of listing.

6.103 Adding administration costs of $9.50 per dose, consistent with a sensitivity analysis presented in the economic evaluation, increased all health budgets combined costs to $500 million to < $600 million (8.1%) in the ≥60 YOA population and to $100 million to < $200 million (19.3%) in the ≥75 population in the first 6 years of listing.

6.104 The submission presented scenario analyses for the ATAGI Advice to the PBAC for special interest groups, i.e., First Nations people 60-74 YOA and individuals considered at high risk for severe RSV infections 60-74 YOA (increased risk persons).

6.105 The submission estimated the eligible First Nations people 60-74 YOA population from the ABS, and uptake based on the coverage from the influenza vaccine reported in the NCRIS Annual Immunisation Coverage Report 2022. Estimated use and financial implications to the Federal Government, and the State and Territory Government for First Nations people are presented in Table 32.

Table 32: Summary of net financial impact to each health budget, First Nations people 60-74 YOA

Health budget	2025	2026	2027	2028	2029	2030	Total
Predicted number of people vaccinated with RSVPreF3 OA	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]3
Federal	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]5
NIP	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]5
PBS	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
MBS	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
Other	[redacted]4	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
State and Territory Governments	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
All budgets combined	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]5

Source: Table 4-56, p304 of the submission.
K = thousands; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Schedule; YOA = years of age
The redacted values correspond to the following ranges:
1 20,000 to < 30,000
2 5,000 to < 10,000
3 60,000 to < 70,000
4 $0 to < $10 million
5 $10 million to < $20 million
6 net cost saving

6.106 Costs to the NIP estimated by the submission for First Nations people aged 60-74 YOA were $10 million to < $20 million over 6 years The submission estimated the impact on all health budgets over 6 years of listing RSVPreF3 OA for First Nations people 60-74 YOA to be $10 million to < $20 million. These estimates were uncertain given all parameters except uptake and population were estimated for the general population.

6.107 The submission estimated the number of increased risk persons 60-74 YOA based on the proportion of individuals in AReSVi-006 who had at least 1 pre-existing comorbidity of interest at baseline. The submission estimated uptake from De Oliveira Bernardo et al. 2019, which used MedicineInsight data of vaccine coverage between 2015 and 2017. Estimated use and financial implications to the Federal Government, and the State and Territory Government for increased risk persons are presented in Table 33.

Table 33: Summary of net financial impact to each health budget, increased risk persons 60-74 YOA

Health budget	2025	2026	2027	2028	2029	2030	Total
Predicted number of people vaccinated with RSVPreF3 OA	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]3
Federal	[redacted]4	[redacted]5	[redacted]5	[redacted]5	[redacted]6	[redacted]6	[redacted]7
NIP	[redacted]4	[redacted]5	[redacted]5	[redacted]6	[redacted]6	[redacted]6	[redacted]7
PBS	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8
MBS	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8
Other	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8
State and Territory Governments	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8	[redacted]8
All budgets combined	[redacted]4	[redacted]9	[redacted]9	[redacted]10	[redacted]10	[redacted]10	[redacted]11

Source: Table 4-62 of the submission.
K = thousands; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Schedule; YOA = years of age.
The redacted values correspond to the following ranges:
1 500,000 to < 600,000
2 100,000 to < 200,000
3 1,000,000 to < 2,000,000
4 $100 million to < $200 million
5 $30 million to < $40 million
6 $40 million to < $50 million
7 $300 million to < $400 million
8 net cost saving
9 $10 million to < $20 million
10 $20 million to < $30 million
11 $200 million to < $300 million

6.108 Costs to the NIP estimated by the submission for increased risk persons 60-74 YOA were $300 million to < $400 million over 6 years. Costs to all health budgets estimated by the submission for increased risk persons 60-74 YOA was $200 million to < $300 million over 6 years. These estimates were uncertain given all parameters except uptake and population were estimated for the general population. Notably, costs to all health budgets for increased risk persons 60-74 YOA were higher than the ≥75 YOA population, despite a lower estimated number of patients receiving RSVPreF3 OA. This was driven by less cost offsets for States and Territory Governments, mainly due to hospitalisations. As the submission applied the same hospitalisation rates to increased risk persons 60-74 YOA than general population 60-74 YOA, cost offsets were reduced yielding higher costs to all health budgets.

6.109 The combined financial impact to the NIP estimated by the submission for adults ≥75 YOA, First Nations people 60-74 YOA, and increased risk persons 60-74 YOA is presented in Table 34.

Table 34: Summary of net financial impact to the NIP combined for the ≥75 YOA population and populations of special interest

	Population	2025	2026	2027	2028	2029	2030	Total
A	Adults ≥75 YOA	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][4] ([redacted][4a])
B	First Nations people 60-74 YOA	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][6]
C	Increased risk persons 60-74 YOA	[redacted][7]	[redacted][8]	[redacted][8]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][10]
D	A + B	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][4] ([redacted][11])
E	A + C	[redacted][10]	[redacted][12]	[redacted][12]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][13] ([redacted][14])
F	A + B + C	[redacted][10]	[redacted][12]	[redacted][12]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][13] ([redacted][14])

Source: Table 4-63of the submission. Text in brackets was estimated in the Commentary.
K = thousands; YOA = years of age.
[a] The submission applied uptake rates from the 60-64, 65-69, and 70-74 YOA cohorts in preparing its estimates for the newly eligible cohort 2025-27, respectively. Corrected uptake application for the newly eligible cohort (2025-27) in the ≥75 YOA population are presented in brackets.
The redacted values correspond to the following ranges:
1 $200 million to < $300 million
2 $50 million to < $60 million
3 $60 million to < $70 million
4 $500 million to < $600 million
5 $0 to < $10 million
6 9 $10 million to < $20 million
7 $100 million to < $200 million
8 $30 million to < $40 million
9 $40 million to < $50 million
10 $300 million to < $400 million
11 $600 million to < $700 million
12 $90 million to < $100 million
13 $800 million to < $900 million
14 $900 million to < $1 billion

6.110 Costs to the NIP considering the ATAGI base case (≥75 YOA) and populations of special interest presented by the submission were $800 million to < $900 million over 6 years. This increased to $900 million to < $1 billion applying uptake rates relevant to the ≥75 YOA newly eligible cohort (2025-27). Inclusion of these two subgroups would increase the size of the eligible population substantially, which may not be reasonable noting the submission did not provide cost-effectiveness analyses for these groups.

6.111 Overall the DUSC considered the submission's estimates to be uncertain as there was a lack of clarity regarding the requested populations, noting that the submission's approach was not consistent with the ATAGI's advice concerning the populations most likely to benefit from the vaccine.

Quality Use of Medicines

6.112 The submission noted that requirements for RSVPreF3 OA will be similar to the administration of influenza vaccines, such as administration through GP practices or community pharmacies or cold chain issues.

6.113 The submission noted the following post-marketing activities:

- Post-marketing pharmacovigilance plan through clinical trials, individual case safety report review, signal detection activities, literature analyses, and surveillance of AEs of special interest.
- A post-marketing active surveillance study to evaluate GBS, ADEM and atrial fibrillation in adults ≥60 YOA in the US.

6.114 The pre-PBAC response provided additional information about QUM activities planned by the sponsor, including collaboration with implementation partners, vaccine providers and consumer groups to help ensure QUM principles are upheld, for example in relation to quality use, safe storage and administration of the vaccine.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend that respiratory syncytial virus vaccine (Arexvy®, RSVpreF3 OA) be a designated vaccine for the purposes of the *National Health Act 1953* for the prevention of lower respiratory tract illness (LRTI) caused by respiratory syncytial virus (RSV). The PBAC noted that the submission had proposed two alternative NIP schedules (i) among adults aged ≥60 years of age (YOA); and (ii) among adults ≥75 YOA. The PBAC noted that ATAGI supported a listing for patients aged 75 years and over; First Nations people aged 60 to 74 years; and people aged 60 to 74 years with conditions that increase their risk of severe disease due to RSV. The PBAC considered that the vaccine was superior to no vaccine in terms of effectiveness with an acceptable safety profile. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was unacceptably high and uncertain for adults aged ≥60 YOA and for adults aged ≥75 YOA. The PBAC noted that the cost-effectiveness RSVpreF3 OA in First Nations and high risk people aged 60-74 years was unknown as this was not addressed by the submission.

7.2 The primary reason for this outcome was due to the economic evaluation presented.

7.3 The PBAC noted that a number of RSV vaccines and monoclonal antibodies are in development globally for prevention of RSV disease, and the clinical algorithm is changing following TGA registration and market launch of the first wave of these products in Australia, including RSVPreF3 OA vaccine.

7.4 The PBAC considered there is a high clinical need for vaccines, such as RSVPreF3 OA vaccine, to reduce the risk of RSV in older adults, especially those aged over 75 years, and those vulnerable due to existing medical conditions and First Nations adults. The PBAC noted that RSV is a common respiratory infection and although symptoms may be mild, some older adults develop severe disease such as acute bronchitis, pneumonia, or exacerbation of pre-existing conditions including asthma, chronic obstructive pulmonary disease and congestive heart failure. The PBAC noted the proposed listing of RSVPreF3 OA vaccine was supported by the consumer comments received for this submission.

7.5 The PBAC noted that RSVpreF3 OA is a combination of the RSVPreF3 antigen and the $AS01_E$ adjuvant system. RSVPreF3 antigen is derived from the RSV-A A2 strain, stabilised in the pre-fusion conformation of the naturally occurring F protein for which both RSV-A and B subtypes share high amino acid sequence homology. RSVPreF3 OA was designed to induce a functional humoral immune response against the RSV-A and RSV-B subtypes and antigen-specific cellular immune responses to protect against RSV-associated LRTD.

7.6 The PBAC noted and welcomed the advice from the ATAGI that was provided to the PBAC to assist with consideration of this submission. The PBAC noted that the ATAGI may update its advice in the future, as further evidence emerges.

7.7 The PBAC noted that ATAGI recommends vaccination of the following groups as outlined in the ATAGI Pre-submission advice to the PBAC, and as noted in the current Australian Immunisation Handbook (AIH): 1) all people aged ≥75 years; 2) people with risk conditions aged ≥60 years (as defined in AIH); and 3) First Nations people aged ≥60 years. It was also noted that ATAGI considers that epidemiologic data on First Nations populations within Australia is adequate for informing economic modelling and policy decisions for this group; and that ATAGI is confident that the proposed definition of high-risk conditions is appropriate and structurally clear for providers to identify eligible individuals aged 60-74 years that meet the ATAGI's recommendation for RSV vaccination. The ATAGI considered the definition to be sufficiently reliable to allow for an informative economic model for this group.

7.8 The PBAC did not accept the clinical place for RSVPreF3 OA as a single dose for all adults ≥60 YOA as proposed by the submission. The PBAC considered that a future resubmission would need to request a NIP listing that corresponds to the populations recommended for vaccination by the ATAGI; or otherwise provide a suitable justification as to why this advice was not followed. The PBAC noted that the Australian Immunisation Handbook (AIH) includes recommendations for use of vaccines for prophylaxis of RSV disease in OA, and that a resubmission should consider these recommendations when specifying proposed NIP populations.

7.9 The PBAC noted that the pre-PBAC response had proposed the initiation of an RSV vaccination program for OAs ≥75 YOA and First Nations Persons 60-74 YOA with a single dose of RSV PreF3 OA. The PBAC considered it was inappropriate to exclude high risk patients aged ≥60 with a clinical need.

7.10 The PBAC noted that listing was requested based on a single dose of RSVPreF3 OA, and the need for revaccination had not been established. The PBAC noted that the ATAGI will make recommendations for subsequent doses when evidence is available from follow-up data from the ongoing pivotal trial AReSVi-006 and immunogenicity trial AReSVi-004. The PBAC noted that results from AReSVi-006 showed that revaccination at Month 12 conferred no additional protection at 17.8 months median follow-up. The PBAC agreed with the ESC that if revaccination is requested in the future, this would impact both cost-effectiveness and financial implications of the

proposed listing. The PBAC noted that the PSCR reported immunogenicity results from AreSVi-004 suggesting an immune response from revaccination with RSVPreF3 OA administered at 24 months (see paragraph 6.22). The PBAC noted that further results from AReSVi006 and AReSVi-004 are expected in September 2024 and will provide further information regarding the appropriate timing- of revaccination (see paragraph 3.12).

7.11 The PBAC considered the submission's nomination of 'no vaccine' was as main comparator was appropriate in the absence of any vaccine for RSV being currently available on the NIP. The PBAC also considered that the proposed near market comparators (RSVpreF vaccine [Pfizer] and mRNA-1345 RSV vaccine [Moderna]) were appropriate.

7.12 The clinical analysis was based on a randomised placebo controlled, head-to-head trial (AreSVi-006) comparing the efficacy and safety of RSVPreF3 OA to placebo vaccine (saline solution) in adults ≥60 YOA, as well as a supportive trial (AreSVi-004) as evidence for the efficacy claim of RSVPreF3 OA in adults ≥75 YOA. Based on evidence from the AreSVi-006 trial, the PBAC considered that RSVPreF3 OA vaccine was an effective prevention for RSV in adults ≥60 YOA, inclusive of those ≥75 YOA.

7.13 The PBAC considered that a claim of superior comparative effectiveness was reasonable for the main comparison between RSVPreF3 and no vaccination, as supported by the estimates of VE in RT-PCR confirmed RSV-LRTD (Table 13). The PBAC noted that estimates of VE in RT-PCR confirmed RSV-LRTD associated with a single dose of RSVPreF3 in the overall population (aged ≥60 YOA) reduced over time from 82.6% in VE analysis 1 (6.7 months), 78.9% in VE analysis 2 (11.5 months), 67.2% in VE analysis 3 (17.8 months). The PBAC noted that the PSCR reported VE of 67.7% for RT-PCR confirmed RSV-LRTD in VE analysis 4 (23.3 months), which was improved in comparison with VE analysis 3 result but could not be verified as the PSCR did not provide source data for VE analysis 4.

7.14 For the subgroup aged ≥75 YOA, the estimates of VE associated with a single dose of RSVPreF3 were considerably lower than the overall population. The subgroup results indicated VE of 52.5% in VE analysis 1 (6.7 months), and 49.3% in VE analysis 3 at 17.8 months in RT-PCR confirmed RSV-LRTD (Table 13). The PBAC noted the small numbers of participants and infection cases observed, and considered it was reasonable to make assumptions of similar VE in the ≥60 and ≥75 age strata, in line with the ATAGI advice. However, it noted uncertainty in regard to the duration of benefit, given that VE waned over time. The PBAC considered that the claim that RSVPreF3 OA vaccine had an acceptable safety profile was reasonable, noting there were higher rates of AEs compared with placebo, but overall the safety was comparable to other adjuvanted vaccines.

7.15 The submission presented a cost-utility analysis based on the AReSVi-006 clinical trial. The PBAC noted that the base case ICER in the submission was $25,000 to < $35,000/QALY and $5,000 to < $15,000 /QALY for the populations aged

≥60 YOA and ≥75 YOA, respectively. The PBAC considered the results of the economic evaluation uncertain due to the concerns described by the ESC (see paragraph 6.89).

7.16 The PBAC noted that the cost-effectiveness of RSVPreF3 OA had a strong age gradient, and this became very clear when the results were presented in age bands (e.g. 60-64 YOA, 65-69 YOA, etc) rather than by age thresholds (60+, 65+ etc) as shown in Table 27. The PBAC noted the results showed significantly higher ICERs for patients aged less than 75 years, compared with those aged 75 years or above. Revised analyses were proposed in the pre-PBAC response which resulted in an ICER of $35,000 to < $45,000 /QALY for adults ≥60 YOA and $5,000 to < $15,000 /QALY for adults ≥75 YOA (Table 24). The PBAC noted that the pre-PBAC response did not address all of the issues described by the ESC in paragraph 6.89.

7.17 The PBAC noted that an exploratory MSA based on the model provided with the pre-PBAC response which also assumed VE over 2 years using VE analysis 4 (corresponding to median follow-up of 23.3 months), and applied a reduced hospitalisation cost (using unadjusted NHCDC cost weights hospitalisation costs), resulted in an ICER over $55,000 to < $75,000 /QALY for ≥60 YOA and over $25,000 to < $35,000/QALY for ≥75 YOA (Table 24). The PBAC considered that the ICER was unacceptably high and uncertain for both populations proposed by the submission at the proposed price. The PBAC considered that a significant price reduction would be required to achieve a satisfactory ICER in a resubmission, noting that specific consideration on this matter would be advised after the concerns with the requested population and economic modelling were addressed.

7.18 The PBAC noted that lowering the age threshold increased the ICER substantially. The PBAC did not agree with the submission's claim that the cost-effectiveness for RSVPreF3 OA demonstrated in adults aged ≥75 years would be applicable to high risk 60-74 year old patients (see paragraph 6.46), and advised that a resubmission would need to assess the cost-effectiveness for each of the proposed populations.

7.19 The PBAC considered there was a high clinical need in high risk patients aged 60-74 as identified by the ATAGI, however the PBAC was unable to assess if RSVPreF3 OA was cost-effective based on the information presented in the submission for First Nations persons aged 60-74 YOA and high risk patients aged 60-74 YOA.

7.20 The PBAC noted the high financial cost of listing RSVPreF3 OA on the NIP. The PBAC considered that a number of updates should be considered in a resubmission in relation to the financial estimates, including updates to the proposed eligible population (paragraphs 7.8 and 7.8). Additionally, the resubmission should take into account the corrections made during the evaluation, and the advice from the DUSC.

7.21 The PBAC considered that a resubmission for RSVPreF3 OA should address the issues raised in this PSD. For each of the populations proposed for listing there should be an economic model to enable the cost-effectiveness to be assessed, and the model should be supported by applicable clinical data. The PBAC further considered that a resubmission should present information available regarding the need for

revaccination, and if relevant include revaccination in the economic model. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.22 The PBAC noted that this submission is not eligible for an Independent Review because it is only relevant to submissions requesting a listing (or change to a listing) on the PBS.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

GSK is disappointed by the decision to not recommend Arexvy in the base program recommended by ATAGI in older adults aged 75+ years of age.

We will continue to work with the PBAC and ATAGI. GSK is committed to ensuring vulnerable older adults, including those that are at severe risk, are protected against lower respiratory tract illness caused by RSV.