

## 5.20 RESPIRATORY SYNCYTIAL VIRUS VACCINE, Injection (0.5 mL), Abrysvo<sup>®</sup>, PFIZER AUSTRALIA PTY LTD

### 1 Purpose of submission

- 1.1 The Category 2 submission requested National Immunisation Program (NIP) listing of a bivalent recombinant respiratory syncytial virus (RSV) pre-fusion F protein (RSVpreF) vaccine for the prevention of lower respiratory tract illness (LRTI) caused by RSV in adults aged 75 years and older, Aboriginal and Torres Strait Islander peoples aged 60 to 74 years, and adults aged 60 to 74 years with at least one risk factor for severe RSV disease.
- 1.2 Listing was requested on the basis of a cost utility analysis versus no vaccine. The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	Active immunisation of adults $\geq 75$ years of age, Aboriginal and Torres Strait Islander peoples aged 60-74 years, and adults aged 60-74 years with at least one risk condition for severe RSV disease
Intervention	One dose (120 $\mu\text{g}$ ) of RSVpreF to be administered as a single 0.5 mL injection. RSVpreF is a bivalent, unadjuvanted vaccine composed of stable RSV pre-fusion F antigens representing the two RSV subgroups (RSV-A and RSV-B).
Comparator	Main comparator: Standard of care (no vaccine) Near-market comparators: Arexvy (RSVPreF3 OA), mRNA-1345
Outcomes	Efficacy: RSV-LRTI ( $\geq 2$ signs and symptoms), RSV-LRTI ( $\geq 3$ signs and symptoms), RSV-ARI, severe RSV-LRTI Immunogenicity Safety: adverse events (all, serious, severe, life-threatening, medically attended and vaccine-related), local reactions, systemic events, AESIs
Clinical claim	In the proposed populations of older adults: RSVpreF is more effective than placebo (no vaccine) at preventing LRTI and ARI caused by RSV. RSVpreF has non-inferior safety compared to placebo (no vaccine).

Source: Table 1.1.1, p4 of the submission.

AESIs = adverse events of special interest; ARI = acute respiratory illness; LRTI = lower respiratory tract illness; mRNA = messenger ribonucleic acid, RSV = respiratory syncytial virus; RSV-A = RSV subtype A; RSV-B = RSV subtype B; RSVpreF = recombinant RSV pre-fusion F protein vaccine.

### 2 Background

#### Registration status

- 2.1 RSVpreF was approved for registration by the Therapeutic Goods Administration (TGA) on 20 March 2024 for:

- active immunisation of pregnant women between 24-36 weeks of gestation for prevention of lower respiratory tract disease caused by RSV in infants from birth through 6 months of age.
- active immunisation of individuals 60 years of age (YOA) and above for prevention of lower respiratory tract disease caused by RSV.

### **Previous PBAC consideration**

2.2 RSVpreF for the prevention of LRTI caused by RSV in infants from birth through 6 months of age by active immunisation of pregnant women was recommended for listing on the NIP at the May 2024 intra-cycle meeting of the PBAC.

2.3 An alternative RSV vaccine, RSVPreF3 OA (Arexvy®), was considered by the PBAC in July 2024. RSVPreF3 OA is a combination of the RSVPreF3 antigen and the AS01<sub>E</sub> adjuvant system. The submission proposed two alternative NIP schedules: (i) among adults aged ≥60 YOA; and (ii) among adults ≥75 YOA. In July 2024, the PBAC noted that the Australian Technical Advisory Group on Immunisation (ATAGI) supported a listing for the following populations:

- patients aged 75 years and over;
- Aboriginal and Torres Strait Islander people aged 60 to 74 years;
- 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 Aboriginal and Torres Strait Islander and high risk people aged 60-74 years was unknown as this was not addressed by the submission (paragraph 7.1, RSVPreF3 OA Public Summary Document (PSD), July 2024).

### **ATAGI advice**

2.4 The Australian Technical Advisory Group on Immunisation (ATAGI) provided pre-submission advice for the PBAC to consider for this submission, dated 21 December 2023. The ATAGI also provided post-submission advice for this submission, dated 20 August 2024, including advice on the pivotal RENOIR trial End-of-season 2 (EOS2) data and responses to questions.

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

### 3 Requested listing

MEDICINAL PRODUCT	Nationally Negotiated Price	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Available brands
Recombinant Respiratory Syncytial Virus (RSV) pre-fusion F protein vaccine, pre-filled syringe, 0.5mL containing 120 micrograms (mcg) of stabilised prefusion F proteins (60 mcg RSV-A and 60 mcg RSV-B antigens)	\$■	1	1	0	ABRYSVO®
National Immunisation Program <ul style="list-style-type: none"> <li>Adults 75 years of age and above</li> <li>Aboriginal and Torres Strait Islander peoples aged 60 to 74 years</li> <li>Adults aged 60 to 74 years with a risk condition for severe RSV disease</li> </ul> Duration of listing: ongoing NIP					
Risk conditions: <ul style="list-style-type: none"> <li>Cardiac disease (congenital heart disease, congestive heart failure, coronary artery disease)</li> <li>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))</li> <li>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)</li> <li>Chronic metabolic disorder (Type 1 or 2 diabetes, amino acid disorders, carbohydrate disorders, cholesterol biosynthesis disorders, fatty acid oxidation defects, lactic acidosis, mitochondrial disorders, organic acid disorders, urea cycle disorders, vitamin/cofactor disorders, porphyrias)</li> <li>Chronic kidney disease Stage 4 or 5</li> <li>Chronic neurological condition (Hereditary and degenerative central nervous system diseases, seizure disorders, spinal cord injuries, neuromuscular disorders, conditions that increase respiratory infection risk).</li> </ul>					

Source: Compiled during the evaluation from Tables 1.4.1 and 1.4.2, p36 of the submission

CAR-T = Chimeric Antigen Receptor T; HIV = Human immunodeficiency virus; mL = millilitre; NIP = National Immunisation Program; RSV = respiratory syncytial virus; RSV-A = RSV subtype A; RSV-B = RSV subtype B; RSVpreF = recombinant RSV prefusion F protein vaccine.

#### 3.1 The submission proposed 3 separate NIP populations;

- one dose of RSVpreF for adults 75 years of age and above;
- one dose for Aboriginal and Torres Strait Islander peoples aged 60 to 74 years;
- one dose for adults aged 60 to 74 years with a risk condition for severe RSV disease.

The Economics Sub-Committee (ESC) noted that the proposed populations were consistent with ATAGI recommendations. The ESC considered that while the overall burden of disease for RSV is highly uncertain, these groups are at higher risk for severe disease and associated complications.

#### 3.2 The defined risk conditions for severe RSV disease pertaining to adults 60 to 74 years are shown in the requested listing. The Pre-Sub-Committee Response (PSCR) stated that obesity was recently added to the list of risk factors in the clinical recommendations for RSV vaccines in the Australian Immunisation Handbook (AIH) RSV chapter (27 June 2024) and that the sponsor is willing to work with the Department of Health and Aged Care to finalise the list of risk conditions for severe

- RSV disease as clinical recommendations evolve. The ESC noted that the omission of obesity from the list of risk conditions for the NIP listing would be consistent with influenza, noting that the AIH lists obesity as a risk factor for influenza and severe outcomes, but obesity is not a NIP-funded condition for influenza vaccination.
- 3.3 The price proposed in the submission is shown above. The Nationally Negotiated Price will be informed by the cost-effective analyses considered appropriate by the PBAC (see section 7 PBAC outcome).
- 3.4 The requested NIP listing is for a single dose of RSVpreF. The submission stated that the need for revaccination with RSVpreF for the proposed populations of older adults has not yet been established.
- 3.5 The submission presented evidence from the pivotal RENOIR trial for the primary efficacy analysis of vaccine efficacy (VE) of RSVpreF against the first episode of RSV-LRTI in the first RSV season in healthy adults  $\geq 60$  years (including those with stable pre-existing conditions). The submission noted that analysis of RSVpreF at the EOS2 from the RENOIR trial (data cut off: 18 December 2023) became available after the time of the ATAGI pre-submission advice, which the submission claimed demonstrated durable efficacy over two RSV seasons. The ATAGI post-submission advice stated there is currently uncertainty about the duration of protection, since data are only available across two seasons and there is evidence of some waning in the second season. There are no correlates of protection and there is no evidence, to date, to inform the rate of waning post season two. Therefore, it is unknown whether, or at what point, immunity is likely to decline to a point below a protective threshold.
- 3.6 The submission and the pre-PBAC response stated that there are three ongoing sub-studies of the RENOIR trial, Sub-study A (SSA), Sub-study B (SSB), and Sub-study C (SSC), evaluating the safety and immunogenicity of revaccination at 1 year, 2 years, and 3 or 4 years, respectively. The initial results (1 month safety and immunogenicity results) from studies SSA and SSB are anticipated in quarter 4 of 2024, with 18-month follow-up data available in 2026. The sponsor noted their intent to seek ATAGI advice on the appropriate revaccination timeframe in older adults upon availability of those results. The evaluation noted the possibility of a request for NIP listing of subsequent dose/s of RSVpreF should the results of those sub-studies support the case for revaccination. The evaluation and the ESC considered that monitoring of VE and consideration of future RENOIR follow-up data from the sub-studies will be important in determining the ongoing efficacy, and -cost-effectiveness, of RSVpreF and any requirements for revaccination. The ESC noted that if revaccination is requested in the future, this would impact cost-effectiveness and financial impact of RSVpreF.
- 3.7 The TGA approved Product Information (PI) states that RSVpreF can be administered concomitantly with seasonal influenza vaccine and COVID-19 mRNA vaccines. The AIH RSV chapter states that older adults can receive RSV vaccines at the same time as other vaccines such as COVID-19, influenza, herpes zoster and pneumococcal vaccines. The AIH RSV chapter further noted that co-administration studies on RSV

and influenza vaccines have shown slightly lower immune responses to certain strains contained in the RSV vaccine and influenza vaccines compared with when these vaccines are administered separately, however, the clinical significance of the decreased immune responses is uncertain. The AIH RSV chapter added that there is a likelihood of increase in the incidence of local and systemic adverse events (reactogenicity) with co-administration, however, the benefits of giving the vaccines at the same time may outweigh the concerns of increased reactogenicity of vaccines (AIH RSV Chapter, 2024).

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

## 4 Population and disease

- 4.1 RSV is a highly infectious disease presenting as either RSV-A or RSV-B subtypes in a given season, with the predominant subtype varying from year to year.<sup>1</sup> The clinical presentation varies from asymptomatic carriage to cold-like symptoms and in some cases acute respiratory distress. Infection is associated with significant morbidity and mortality, particularly in older or vulnerable adults. Severe RSV cases can lead to pneumonia, may require hospitalisation, including admission into intensive care units (ICU), and/or mechanical ventilation.
- 4.2 The rate of RSV infection varies by regional climate and season. In Australia, most temperate regions experience seasonal RSV outbreaks during the autumn and winter, often peaking in June to July and usually preceding the influenza season. In the more tropical northern parts of Australia, RSV activity correlates with the rainfall and humidity patterns of the rainy season from December to March,<sup>2</sup> thus RSV seasonality differs between Australian States and territories. The month of administration may impact the benefits of vaccination due to seasonality of RSV. The submission noted that RENOIR was timed to coincide with the Northern Hemisphere RSV season, whereas the proposed NIP listing would allow vaccination year-round with targeted use towards the variable peak in RSV incidence across temperate and tropical regions of Australia. The submission presented sensitivity analyses regarding the seasonal distribution of incident RSV cases in relation to the timing of vaccination.
- 4.3 The clinical manifestations of RSV vary by age groups, with the highest rates of symptomatic diseases reported in infants, young children and the elderly. Amongst the elderly, RSV is one of the leading causes of respiratory illness, especially those with medical conditions that put them at higher risk for severe RSV disease.<sup>3</sup> Risk factors for severe RSV disease in adults include advanced age, frailty and the presence of

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<sup>1</sup> Tabor, D., Fernandes, F., Langedijk, A., Wilkins, D., Lebbink, R., T. A., & ...Abram, M. (2020). Global Molecular Epidemiology of Respiratory Syncytial Virus from the 2017-2018 INFORM-RSV Study. *J Clin Microbiol*, 59(1).

<sup>2</sup> Eden, J., Sikazewe, C., & Xie, R. (2022). Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. *Nature Communications*, 2884, 1-8

<sup>3</sup> Nam, H., & Ison, M. (2019). Respiratory syncytial virus infection in adults. *BMJ*, Sep;366:I5021.

comorbidities (including cardiopulmonary and immunocompromising conditions).<sup>4</sup> First Nations people have a greater risk of RSV hospitalisation compared with non-Indigenous Australians.

- 4.4 The submission used data from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database (NHMD) of data from 2010 to 2019, hereafter referred to as the Australian modelling study, to estimate the incidence and mortality of RSV disease. The evaluation considered that the extent to which these data reflect the current incidence and mortality of RSV disease in the post-COVID period was unclear, as the period in the report excluded the effects of COVID and its associated public health measures on RSV incidence. While the submission acknowledged that the long-term impact of public health measures associated with COVID-19 on the patterns of RSV infections across Australia remained unknown and would require ongoing monitoring, the PSCR stated that results from the modelling study are likely representative of post-COVID-19 RSV incidence as described by Thindwa et al. 2024,<sup>5</sup> whose study shows that “Patterns of RSV activity have largely returned to normal following successive waves in the post-pandemic era.” The ESC considered that the current rate of RSV infections may be at pre-pandemic levels and therefore the Australian modelling study may be considered informative. The ESC also commented that there has been increased testing for RSV, COVID-19 and influenza in the post-pandemic period. Further discussion on the Australian modelling study is provided in paragraphs 6.49 and 6.50.
- 4.5 RSVpreF is an unadjuvanted 120 microgram/0.5 mL bivalent vaccine composed of stable RSV prefusion F antigens representing the 2 major virus subgroups (RSV-A and RSV-B). Prefusion F is the active form of the protein and is capable of mediating fusion of virus and host cell membranes during cell entry. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects against RSV-associated LRTI.

*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 argument provided in support of this nomination was that there is neither a vaccine to protect older adults against RSV currently available on the NIP, nor a specific RSV treatment currently funded for older adults. The evaluation and the ESC considered this to be reasonable and aligned with the ATAGI advice to the PBAC that concluded no vaccine

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<sup>4</sup> Shi, Vennard, S., Jasiewicz, F., Brogden, R., Nair, H., & Investigators, f. R. (2022). Disease burden estimates of respiratory syncytial virus related acute respiratory infections in adults with comorbidity: a systematic review and meta-analysis. *J Infect Dis.*, Aug;226:S17-21.

<sup>5</sup> Thindwa D et al., Global patterns of rebound to normal RSV dynamics following COVID-19 suppression, *BMC Infectious diseases* 2024;24:635-646.

was an appropriate comparator (ATAGI Pre-Submission Advice to the PBAC, December 2023).

- 5.2 The submission noted the existence of two other RSV vaccines:
- RSVPreF3 OA (Arexvy®), which was considered by the PBAC in July 2024 for NIP listing for the prevention of LRTI in patients aged  $\geq 60$  years and  $\geq 75$  years.
  - mRNA-1345, which was accepted for priority review by the TGA on 30 March 2023 for the prevention of RSV-associated LRTI in adults aged  $\geq 60$  years. mRNA-1345 consists of a single mRNA sequence encoding for a stabilised prefusion F glycoprotein.
- 5.3 The submission nominated RSVPreF3 and mRNA-1345 as near market comparators. RSVPreF3 OA was considered but not recommended by the PBAC in July 2024 for the prevention of RSV-confirmed LRTI in patients aged  $\geq 60$  years and  $\geq 75$  years (paragraph 2.3); mRNA-1345 has not been considered by the PBAC. The evaluation and the ESC considered that the proposed near market comparators were appropriate. The PBAC noted that the near market comparators have not been recommended by the PBAC and therefore did not require further consideration.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (2) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals focussed on the benefits of effective RSV vaccination for older adults, and the high cost of the vaccine without a listing on the NIP. The comments from organisations were supportive of the proposed listing of RSV vaccination. Some of the main themes of the input were:
- National Aboriginal Community Controlled Health Organisation (NACCHO) described the disproportionate burden of RSV disease in Aboriginal and Torres Strait Islander people. Increased prevalence of chronic diseases in Aboriginal and Torres Strait Islander people increases the risk of severe RSV, and Aboriginal and Torres Strait Islander adults aged 60-74 years have a similar hospitalisation rate to non-Indigenous adults aged at least 75 years.
  - Lung Foundation Australia described strong consumer support for making the RSV vaccine available on the NIP for people aged 60 and over, and for those with a lung disease or other medical condition, based on a survey of 860 people living or caring for someone with a lung disease or lung cancer in December 2023 –

January 2024. Almost half (45%) of the respondents aged 60 years and older claimed that they would only receive the RSV vaccination if it was free, based on a survey of the broader community (3,300 responses, May 2024).

- Asthma Australia described RSV as having an important impact on people with asthma, including worsening asthma symptoms and increased risk from pneumonia.
- Immunisation Foundation of Australia described current access to RSV vaccine as inequitable (only those who can afford the vaccine can access it) and stated that many consumers do not know about it, do not prioritise it, or cannot afford it.

### ***Clinical trials***

- 6.3 The submission was based on two randomised trials comparing RSVpreF vaccine to placebo (sterile water injection): RENOIR and Study 1006. The submission also presented a supplementary indirect treatment comparison (ITC) of RSVpreF with RSVPreF3 and mRNA-1345, using placebo as the common reference. The 3 trials used to inform the ITC were RENOIR (RSVpreF), AReSVi-006 (RSVPreF3), and ConquerRSV (mRNA-1345).
- 6.4 A claim of superior effectiveness was made on the basis of the prevention of LRTI and acute respiratory illness (ARI) caused by RSV, compared with placebo. The submission claimed non-inferior safety compared with placebo.
- 6.5 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
RENOIR (NCT05035212)	Study C3671013: Efficacy Study RSV Season 1 Primary Analysis A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults.	CSR – Version 1.0 dated 22 September 2022
	Study C3671013: Efficacy Study End of Season 1 A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults.	CSR – Version 1.0 - dated 22 May 2023
	Study C3671013: EOS2 Analysis – Brief Report of Clinical Data A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults.	CSR - dated 13 March 2024
	Walsh EE, Pérez Marc G, Zareba AM, Falsey AR, Jiang Q, Patton M, Polack FP, Llapur C, Doreski PA, Ilangovan K, Rămet M. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults.	New England Journal of Medicine. 2023 Apr 20;388(16):1465-77.
Study 1006 (NCT05301322)	Study C3671006: Final CSR (primary completion date) A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus Prefusion F Subunit Vaccine When Coadministered With Seasonal Inactivated Influenza Vaccine in Adults ≥65 Years of Age.	CSR – Version 1.0, dated 06 June 2023
	Athan E, Baber J, Quan K, Scott RJ, Jaques A, Jiang Q, Li W, Cooper D, Cutler MW, Kalinina EV, Anderson AS. Safety and immunogenicity of bivalent RSVpreF vaccine coadministered with seasonal inactivated influenza vaccine in older adults.	Clinical Infectious Diseases. 2024 May 15;78(5):1360-8.
Near market comparator trials		
AReSVi-006 (NCT04886596)	Papi, A.; Ison, M.G., Langley, D.G. et al (for the AReSVi-006 Study Group). Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults.	<i>N Engl J Med</i> 2023;388:595-608 DOI: 10.1056/NEJMoa2209604
	Ison MG, Papi A, Athan E, Feldman RG, Langley JM, Lee DG, Leroux-Roels I, Martinon-Torres F, Schwarz TF, van Zyl-Smit RN, Verheust C. Efficacy and safety of Respiratory Syncytial Virus (RSV) prefusion F protein vaccine (RSVPreF3 OA) in older adults over 2 RSV seasons.	<i>Clinical Infectious Diseases</i> . 2024 Jun 15;78(6):1732-44. DOI: <a href="https://doi.org/10.1093/cid/ciae010">https://doi.org/10.1093/cid/ciae010</a> .
	Feldman, R.G.; Antonelli-Incalzi, R.; Steenackers, K. et al (for the AReSVi-006 Study Group) Respiratory Syncytial Virus Prefusion F Protein Vaccine Is Efficacious in Older Adults With Underlying Medical Conditions.	<i>Clinical Infectious Diseases</i> 2024; 78(1):202–9.
	Matte, P.; Feldman, R.; Antonelli-Incalzi, R. et al. Efficacy of a respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVPreF3 OA) in older adults with pre-existing medical conditions.	<i>Vascular Abstracts</i> 2023; S195.
ConquerRSV (NCT05127434)	Wilson E, Goswami J, Baqui AH, Doreski PA, Perez-Marc G, Zaman K, Monroy J, Duncan CJ, Ujije M, Rămet M, Pérez-Breva L. Efficacy and safety of an mRNA-based RSV PreF vaccine in older adults.	New England Journal of Medicine. 2023 Dec 14;389(24):2233-44.

Source: Table 2.2.1 p45, Appendix A Table 2.2.1 p8, and Appendix B Table 2.2.1 p8 of the submission

6.6 The key features of the included evidence are summarised in Table 3. The evaluation considered that the overall risk of bias for RENOIR and Study 1006 was low.

**Table 3: Key features of the included evidence**

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
RSVpreF vs. placebo						
RENOIR	34,383 <sup>a</sup>	Phase 3, R, DB, MC, PC.  Single dose of RSVpreF  ARI surveillance: 16.4 months <sup>b, c</sup>	Low	Adults aged ≥ 60 years	Primary outcomes: VE categorised by: <ul style="list-style-type: none"> <li>• RSV-LRTI with ≥ 2 signs or symptoms</li> <li>• RSV-LRTI with ≥ 3 signs or symptoms</li> </ul> Secondary outcomes: <ul style="list-style-type: none"> <li>• VE against RSV-ARI</li> <li>• VE against sRSV-LRTI</li> <li>• Immunogenicity</li> </ul> Exploratory outcomes: VE against medically-attended cases of: <ul style="list-style-type: none"> <li>• RSV-LRTI with ≥ 2 signs or symptoms</li> <li>• RSV-LRTI with ≥ 3 signs or symptoms</li> <li>• RSV-ARI</li> </ul>	Exploratory outcomes for medically-attended cases were used to inform economic modelling.
Study 1006	1,403	Phase 3 R, MC, DB, PC, conducted in Australia  Single doses of RSVpreF and SIIV. Co-administration versus sequential administration.  2 months	Low	Adults aged ≥ 65 years	Immunogenicity and safety	Not used

Source: Compiled during the evaluation.

ARI = acute respiratory illness; DB = double-blind; LRTI = lower respiratory tract illness; MC = multi-centre; PC = placebo-controlled; R = randomised; SIIV = seasonal inactivated influenza vaccine; sRSV-LRTI = severe lower respiratory tract illness; RSV = respiratory syncytial virus; VE = vaccine efficacy.

<sup>a</sup> Number of participants randomised for primary analysis was 34,383; Number of participants randomised for EOS1 was 36,967. The sample size was increased from 30,000 to 45,000 with the implementation of Protocol Amendment 2 (dated 23 March 2022).

<sup>b</sup> Completion of RENOIR is expected by June 2026.

<sup>c</sup> Results from RENOIR were provided for 3 data analysis cut-offs:

- Primary (interim) analysis Season 1: data cut off 08 and 14 July 2022 (average follow-up 6.78 months);
- End of Season 1 (EOS1) analysis: data cut off 07 and 13 October 2022 (average follow-up 7.05 months); and
- End of Season 2 (EOS2) analysis: Data cut off 18 December 2023 (average follow-up 16.4 months).

6.7 RENOIR was designed to investigate the efficacy, immunogenicity and safety of a single dose of RSVpreF 120 µg in adults aged 60 years and over. Randomisation was stratified by age group (60-69 years, 70-79 years, ≥80 years). Both healthy adults and adults with stable chronic conditions were enrolled. Approximately 10% of participants were to be enrolled with stable chronic cardiopulmonary conditions such

- as chronic obstructive pulmonary disease (COPD), asthma or congestive heart failure (CHF).
- 6.8 In RENOIR, VE was defined as the relative risk reduction at first-episode of RSV-LRTI<sup>6</sup> cases with  $\geq 2$  LRTI symptoms and  $\geq 3$  LRTI symptoms for RSVpreF compared to placebo. The primary efficacy objective would be achieved if the lower bound of the VE confidence interval (CI) was  $>20\%$  for RSV-LRTI with  $\geq 2$  symptoms, with Pocock-adjusted CI at the primary analysis<sup>7</sup>.
- 6.9 Clinically relevant outcomes included the incidence of RSV-LRTI, RSV-ARI and associated hospitalisation and mortality. Selected exploratory outcomes from the RENOIR trial were used to inform the economic evaluation: VE against RSV-LRTI with  $\geq 2$  and  $\geq 3$  symptoms prompting a health care visit as proxies for VE against RSV-related emergency visits and hospitalisations, respectively. VE against RSV-ARI prompting a health care visit was used to inform VE against RSV-related outpatient visits. Quality of life outcomes were not collected in RENOIR.
- 6.10 The evaluation noted that RENOIR included participants reflective of some of the populations for the NIP listing being sought. However, participants in RENOIR were younger (mean age 68.3 years) than one of the target populations (adults aged  $\geq 75$  years), and RENOIR did not enrol participants in Australia. ATAGI considered that there were gaps in the evidence for some pre-specified high-risk conditions (e.g., people with neurological conditions or that were immunocompromised were excluded from RENOIR) and for Aboriginal and Torres Strait Islander peoples (ATAGI Pre-Submission Advice December 2023).
- 6.11 Study 1006 compared the safety, tolerability and immunogenicity of vaccine co-administration (RSVpreF with seasonal inactivated influenza vaccine (SIIV) followed by placebo one month later) with sequential dosing (placebo+SIIV followed by RSVpreF one month later) in adults aged 65 years and older. Study 1006 was conducted in Australia and had a trial duration of only 2 months. Only outcomes pertaining to immunogenicity and safety were reported.

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<sup>6</sup> Symptoms for RSV-LRTI and ARI were predefined. RSV-LRTI were defined as ARI with  $\geq 2$  or  $\geq 3$  of the 5 LRTI symptoms lasting more than 1 day during the same illness, and RT-PCR-confirmed RSV infection within 7 days of ARI symptom onset. ARI were defined as an illness involving 1 or more of the following 7 respiratory illness symptoms, lasting more than 1 day (new or increased): sore throat, cough, nasal congestion, nasal discharge, wheezing, sputum production, shortness of breath.

<sup>7</sup> Further detail from the ATAGI advice to the PBAC indicated these criteria were agreed with the Committee for Medicinal Products for Human Use (CHMP) and the Centre for Biologics Evaluation and Research (CBER), who stated that this would support registration.

## **Comparative effectiveness**

### **RENOIR: RSVpreF versus placebo**

6.12 A summary of the primary efficacy outcomes (RSV-LRTI with  $\geq 2$  or  $\geq 3$  symptoms) for RENOIR is presented in Table 4. In Season 1, VE to prevent the first episode of RSV-LRTI with:

- $\geq 2$  symptoms was 65.1% (95% confidence interval [CI]: 35.9 to 82.0)
- $\geq 3$  symptoms was 88.9% (95% CI: 53.6 to 98.7).

Across 2 seasons, VE to prevent the first episode of RSV-LRTI with:

- $\geq 2$  symptoms was 58.8% (95% CI: 43.0 to 70.6)
- $\geq 3$  symptoms was 81.5% (95% CI: 63.3 to 91.6).

The predefined success criteria (lower bound of the 95% CI  $>20\%$ ) were met for both primary endpoints for both Season 1 and across 2 seasons.

6.13 Table 4 also shows a breakdown of results for the RSV-A and RSV-B subtypes. In Season 1, VE to prevent the first episode of RSV-LRTI with  $\geq 2$  symptoms was:

- 81.3% (95% CI: 34.5 to 96.5) for RSV-A
- 53.8% (95% CI: 5.2 to 78.8) for RSV-B.

ATAGI noted that for the end of Season 1 (EOS1) estimates, the predefined success criteria did not apply to the individual RSV subtypes (A and B); the sample sizes were small (and thus confidence intervals were wide) such that it was not possible to determine whether there may be differential protection against each subtype (ATAGI Pre-Submission Advice to the PBAC Dec 2023).

Across the 2-seasons, VE to prevent the first episode of RSV-LRTI with  $\geq 2$  symptoms was:

- 66.3% (95% CI: 47.2 to 79.0) for RSV-A
- 50.0% (95% CI: 18.5 to 70.0) for RSV-B.

The evaluation noted that the lower limit of the 95% CI was  $>20\%$  for RSV-A (above predefined success criteria) but  $<20\%$  for RSV-B for both Season 1 and across 2 seasons. The pre-PBAC response noted that the RENOIR trial was not powered to detect significant differences between RSVpreF and placebo within RSV subtypes, as per the ATAGI Pre-Submission Advice.

Table 4: Results of RSVpreF VE against the first episode of RSV in RENOIR, evaluable efficacy population – primary efficacy outcomes

	Mid-season <sup>a</sup> 6.78 months		Season 1 7.05 months		Season 2 7.59 months		Across 2 seasons 16.36 months	
	RSVpreF	Placebo	RSVpreF	Placebo	RSVpreF	Placebo	RSVpreF	Placebo
N	16,306	16,308	18,050	18,074	16,164	16,059	18,050	18,074
<b>First episode of RSV-LRTI with ≥2 symptoms</b>								
n (%)	11 (0.07)	33 (0.20)	15 (0.08)	43 (0.24)	39 (0.24)	88 (0.55)	54 (0.30)	131 (0.72)
IR per 1,000 person yrs	1.19	3.58	1.41	4.06	3.83	8.63	2.19	5.32
VE (95% CI)	<b>66.7 (28.8, 85.8)*</b>		<b>65.1 (35.9, 82.0)*</b>		<b>55.7 (34.7, 70.4)*</b>		<b>58.8 (43.0, 70.6)*</b>	
RSV-A, n (%)	1 (0.01)	9 (0.06)	3 (0.02)	16 (0.09)	24 (0.15)	64 (0.4)	27 (0.15)	80 (0.44)
IR per 1,000 person yrs	0.11	0.98	0.28	1.51	2.36	6.27	1.1	3.25
VE (95% CI)	<b>88.9 (10.6, 99.8)</b>		<b>81.3 (34.5, 96.5)*</b>		<b>62.5 (39.2, 77.6)*</b>		<b>66.3 (47.2, 79.0)*</b>	
RSV-B, n (%)	10 (0.06)	23 (0.14)	12 (0.07)	26 (0.14)	14 (0.09)	26 (0.16)	26 (0.14)	52 (0.29)
IR per 1,000 person yrs	1.08	2.50	1.13	2.45	1.38	2.55	1.05	2.11
VE (95% CI)	56.5 (-0.7, 82.8)		<b>53.8 (5.2, 78.8)</b>		46.2 (-7.0, 74.0)		<b>50.0 (18.5, 70.0)</b>	
<b>First episode of RSV-LRTI with ≥3 symptoms</b>								
n (%)	2 (0.01)	14 (0.09)	2 (0.01)	18 (0.10)	8 (0.05)	36 (0.22)	10 (0.06)	54 (0.30)
IR per 1,000 person yrs	0.22	1.52	0.19	1.70	0.79	3.53	0.41	2.19
VE (95% CI)	<b>85.7 (32.0, 98.7)*</b>		<b>88.9 (53.6, 98.7)*</b>		<b>77.8 (51.4, 91.1)*</b>		<b>81.5 (63.3, 91.6)*</b>	
RSV-A, n (%)	1 (0.01)	3 (0.02)	1 (0.01)	5 (0.03)	5 (0.03)	26 (0.16)	6 (0.03)	31 (0.17)
IR per 1,000 person yrs	0.11	0.33	0.09	0.47	0.49	2.55	0.24	1.26
VE (95% CI)	66.7 (-393.7, 99.6)		80.0 (-78.7, 99.6)		<b>80.8 (49.1, 94.2)*</b>		<b>80.6 (52.9, 93.4)*</b>	
RSV-B, n (%)	1 (0.01)	10 (0.06)	1 (0.01)	12 (0.07)	2 (0.01)	10 (0.06)	3 (0.02)	22 (0.12)
IR per 1,000 person yrs	0.11	1.09	0.09	1.13	0.2	0.98	0.12	0.89
VE (95% CI)	<b>90.0 (21.9, 99.8)*</b>		<b>91.7 (43.7, 99.8)*</b>		<b>80.0 (6.1, 97.9)</b>		<b>86.4 (54.6, 97.4)*</b>	

Source: RSV-LRTI with ≥ 2 symptoms, Table 2.5.1 p62 and Table 2.5.4 p64 of the submission; Table 4.2-1, p31 of ATAGI advice to the PBAC Dec 2023.; RSV-LRTI with ≥ 3 symptoms, Table 2.5.2 p62 and Table 2.5.5 p66 of the submission; Table 4.2-1, p31 of ATAGI advice to the PBAC Dec 2023.

CI = confidence interval; IR = incidence rate; LRTI = lower respiratory tract illness; n = number of participants with event; N = total participants in group; NP = Not performed due to insufficient numbers; NR = not reported; RSV = respiratory syncytial virus; RSV-A = RSV subtype A; RSV-B = RSV subtype B; VE = vaccine efficacy.

**Bold** indicates statistically significant results.

\* denotes lower limit for 95% CI >20%.

a The submission did not present the results of the mid-season analyses; however, these were presented in the ATAGI Pre-submission Advice and presented in this document for completeness.

6.14 A summary of the key secondary outcomes for RENOIR is presented in Table 5. The outcomes were severe RSV-LRTI (sRSV-LRTI) and RSV-ARI.

**Table 5: Results of RSVpreF VE against the first episode of RSV in RENOIR, evaluable efficacy population - secondary efficacy outcomes**

	Mid-season <sup>a</sup> 6.78 months		Season 1 7.05 months		Season 2 7.59 months		Across 2 seasons 16.36 months	
	RSVpreF	Placebo	RSVpreF	Placebo	RSVpreF	Placebo	RSVpreF	Placebo
N	16,306	16,308	18,050	18,074	16,164	16,059	18,050	18,074
<b>First episode of severe RSV-LRTI</b>								
n (%)	0	0	0	2 (0.01) <sup>a</sup>	1 (0.01)	1 (0.01)	1 (0.01)	3 (0.02) <sup>a</sup>
IR per 1,000 person yrs	0	0	0	0.19	0.1	0.1	0.04	0.12
VE (95% CI)	NP		100.0 (-432.5, 100.0)		0 (-7749.7, 98.7)		66.7 (-315.1, 99.4)	
RSV-A, n (%)	0	0	0	0	0	1 (0.01)	0	1 (0.01)
IR per 1,000 person yrs	0	0	0	0	0	0.1	0	0.04
VE (95% CI)	NP		100.0 (-432.5, 100.0)		100.0 (-3800.0, 100.0)		100.0 (-3800.0, 100.0)	
RSV-B, n (%)	0	0	0	1 (0.01)	0	0	0	1 (0.01)
IR per 1,000 person yrs	0	0	0	0.09	0	0	0	0.04
VE (95% CI)	NP		100.0 (-3800.0, 100.0)		NE		100.0 (-3800.0, 100.0)	
<b>First-episode of RSV-ARI</b>								
n (%)	22 (0.13)	58 (0.36)	37 (0.20)	98 (0.54)	149 (0.92)	236 (1.47)	186 (1.03)	334 (1.85)
IR per 1,000 person yrs	2.38	6.3	3.49	9.25	14.64	23.14	7.55	13.57
VE (95% CI)	<b>62.1 (37.1, 77.9)*</b>		<b>62.2 (44.4, 74.9)*</b>		<b>36.9 (22.2, 48.9)*</b>		<b>44.3 (33.2, 53.7)*</b>	
RSV-A, n (%)	4 (0.02)	12 (0.07)	11 (0.06)	35 (0.19)	106 (0.66)	175 (1.09)	117 (0.65)	210 (1.16)
IR per 1,000 person yrs	0.43	1.3	1.04	3.3	10.42	17.16	4.75	8.53
VE (95% CI)	66.7 (-10.0, 92.2)		<b>68.6 (36.7, 85.6)*</b>		<b>39.4 (22.5, 52.9)*</b>		<b>44.3 (29.8, 55.9)*</b>	
RSV-B, n (%)	18 (0.11)	45 (0.28)	26 (0.14)	63 (0.35)	43 (0.27)	64 (0.40)	69 (0.38)	127 (0.70)
IR per 1,000 person yrs	1.95	4.89	2.45	5.94	4.23	6.27	2.8	5.16
VE (95% CI)	<b>60.0 (29.5, 78.2)*</b>		<b>58.7 (33.9, 74.9)*</b>		32.8 (-0.4, 55.4)		<b>45.7 (36.6, 60.1)*</b>	

Source: Severe RSV-LRTI, Table 2.5.3 p63 of the submission; Table 4.2-2, p33 of ATAGI advice to the PBAC Dec 2023; ARI-RSV, Table 2.5.6 p67 of the submission; Table 4.2-3, p33 of ATAGI advice to the PBAC Dec 2023.

**Bold** indicates statistically significant results.

ARI = acute respiratory illness; CI = confidence interval; IR = incidence rate; LRTI = lower respiratory tract illness; n = number of participants with event; N = total participants in group; NP = Not performed due to insufficient numbers; NR = not reported; RSV = respiratory syncytial virus; VE = vaccine efficacy

<sup>a</sup> The submission did not present the results of the mid-season analyses; however, these were presented in the ATAGI Pre-submission Advice and presented in this document completeness.

\* denotes lower limit for 95% CI >20%.

6.15 Only two cases of sRSV-LRTI were reported in the placebo group at EOS1. ATAGI noted that the small sample meant the efficacy objective was not achieved since the lower bound of the 95% CI was <20%, and there was insufficient evidence to determine the impact of RSVpreF on sRSV-LRTI (ATAGI Pre-Submission Advice to the PBAC Dec 2023). Across the 2 seasons, only 4 cases of sRSV-LRTI were reported (placebo, 3 cases; RSVpreF, 1 case). Similarly, the lower limit of the 95% CI was <20%, and due to the low number of cases, there was insufficient evidence to determine the impact of RSVpreF on sRSV-LRTI.

6.16 VE to prevent the first episode of RSV-ARI in Season 1 was 62.2% (95% CI: 44.4, 74.9). ATAGI noted that although this outcome was not evaluated against the success criteria (lower 95% CI >20%), the lower limit of the 95% CI was >20% (ATAGI Pre-Submission Advice to the PBAC Dec 2023). Across the 2-seasons, VE to prevent the first episode of RSV-ARI was 44.3% (95% CI: 33.2 to 53.7); again, the lower limit of the 95% CI was >20%.

6.17 A summary of the results for VE against the exploratory outcome of medically-attended RSV cases in RENOIR is presented in Table 6. To inform the economic evaluation, the submission categorised the results for medically-attended VE by: RSV-LRTI with  $\geq 2$  symptoms, RSV-LRTI with  $\geq 3$  symptoms, and RSV-ARI, for the evaluable efficacy population. The VE estimates against the first episode of medically-attended RSV from season 1 in the evaluable efficacy population of RENOIR were used in the economic model, including: First-episode of RSV-ARI (65.1%, applied to outpatient visits in the model); First episode of RSV-LRTI with  $\geq 2$  symptoms (70.4%, applied to emergency visits in the model); and First episode of RSV-LRTI with  $\geq 3$  symptoms (84.6%, applied to hospitalisations in the model) as presented in Table 11).

**Table 6: Results of RSVpreF VE against the first episode of medically-attended RSV in RENOIR, evaluable efficacy population - exploratory efficacy outcomes**

	Season 1 7.05 months			Season 2 7.59 months			Across 2 seasons 16.36 months		
	RSV preF	PBO	VE (95% CI)	RSV preF	PBO	VE (95% CI)	RSV preF	PBO	VE (95% CI)
<b>N</b>	<b>18,050</b>	<b>18,074</b>		<b>16,164</b>	<b>16,059</b>		<b>18,050</b>	<b>18,074</b>	
<b>First episode of RSV-LRTI with <math>\geq 2</math> symptoms</b>									
All cases	15	43	<b>65.1</b> (35.9, 82.0)*	39	88	<b>55.7</b> (34.7, 70.4)*	54	131	<b>58.8</b> (43.0, 70.6)*
Any healthcare visit	8	27	<b>70.4</b> (33.0, 88.4)*	20	43	<b>53.5</b> (19.2, 74.1)	28	70	<b>60.0</b> (37.2, 75.2)*
No healthcare visit	7	16	56.3 (-12.4, 84.8)	19	45	<b>57.8</b> (26.3, 76.7)*	26	61	<b>57.4</b> (31.5, 74.2)*
<b>First episode of RSV-LRTI with <math>\geq 3</math> symptoms</b>									
All cases	2	18	<b>88.9</b> (53.6, 98.7)*	8	36	<b>77.8</b> (51.4, 91.1)*	10	54	<b>81.5</b> (63.3, 91.6)*
Any healthcare visit	2	13	<b>84.6</b> (32.0, 98.3)*	7	25	<b>72.0</b> (33.4, 89.8)*	9	38	<b>76.3</b> (50.2, 89.9)*
No healthcare visit	0	5	100.0 (-9.1, 100.0)	1	11	<b>90.9</b> (37.5, 99.8)*	1	16	<b>93.8</b> (59.8, 99.9)*
<b>First-episode of RSV-ARI</b>									
All cases	37	98	<b>62.2</b> (44.4, 74.9)*	149	236	<b>36.9</b> (22.2, 48.9)*	186	334	<b>44.3</b> (33.2, 53.7)*
Any healthcare visit	15	43	<b>65.1</b> (35.9, 82.0)*	44	83	<b>47.0</b> (22.7, 64.1)*	59	126	<b>53.2</b> (35.7, 66.2)*
No healthcare visit	22	55	<b>60.0</b> (33.3, 76.8)*	105	153	<b>31.4</b> (11.4, 47.0)	127	208	<b>38.9</b> (23.5, 51.4)*

Source: Table 2.5.7 p70 of the submission.

ARI = acute respiratory illness; CI = confidence interval; IR = incidence rate; LRTI = lower respiratory tract illness; n = number of participants with event; N = total participants in group; NP = Not performed due to insufficient numbers; NR = not reported; PBO = placebo; RSV = respiratory syncytial virus; RSVpreF = recombinant RSV prefusion F protein vaccine; VE = vaccine efficacy.

**Bold** indicates statistically significant results.

\* denotes lower limit for 95% CI  $> 20\%$ .

6.18 Overall, for the primary and secondary efficacy outcomes, VE decreased over time; VE estimates reported for the season 2 period were consistently lower than those measured at EOS1.

### Immunogenicity results

- 6.19 In RENOIR, immunogenicity was evaluated from approximately 600 participants from a subset of sites in the US and approximately 450 participants from a subset of sites in Japan, with blood samples collected before vaccination, 1 month after vaccination, and prior to the start of the second RSV season. The sample size of participants informing results for neutralising titres in RENOIR was small and reduced over time.
- 6.20 In Study 1006, non-inferiority of co-administration (RSVpreF + SIIV) compared with sequential dosing was based on a 1.5-fold equivalence margin where the geometric mean ratio (GMR) lower limit of the 2-sided 95% CI >0.667. The GMRs ranged from 0.85 to 0.86 for RSVpreF, and 0.77 to 0.90 for SIIV. Non-inferiority was met based on the pre-specified non-inferiority margin for each of the 6 assay strains.
- 6.21 ATAGI considered that the immunogenicity evidence from RENOIR and Study 1006 were only supportive, as success criteria (lower 95% CI >20%) were not applied to these data in RENOIR, and there are no established correlates of protection for RSV (ATAGI Advice to the PBAC Dec 2023).

### Subgroup analyses

#### **RENOIR: RSVpreF versus placebo**

- 6.22 The submission presented subgroup analyses from RENOIR for participants by:
- Age group (60-69 years; 70-79 years; ≥80 years); RENOIR stratified participants by these age groups.
  - Presence of a pre-specified significant condition (≥1 pre-specified conditions vs. no pre-specified condition), including heart disease, lung disease, asthma, diabetes, liver disease and renal disease. Although RENOIR did not stratify participants based on these conditions, these were pre-specified at baseline, and were balanced across the groups.
- 6.23 A summary of the results from the subgroup analyses by age group is provided in Table 7 for EOS1.

**Table 7: Results for subgroup analyses of efficacy endpoints in RENOIR through the EOS1, by age group, evaluable efficacy population**

Population	RSVpreF		Placebo		VE (95% CI)
	N	Cases, n	N	Cases, n	
<b>First episode of RSV-LRTI with ≥2 symptoms</b>					
Whole trial population	18,058	15	18,076	43	<b>65.1 (35.9, 82.0)*</b>
60-69 years	11,311	10	11,352	25	<b>60.0 (13.8, 82.9)</b>
70-79 years	5,751	4	5,744	12	66.7 (-10.0, 92.2)
≥80 years	996	1	980	6	83.3 (-37.4, 99.6)
Test for treatment effect variation <sup>a</sup>					P = 0.7642
<b>First episode of RSV-LRTI with ≥3 symptoms</b>					
Whole trial population	18,058	2	18,076	18	<b>88.9 (53.6, 98.7)*</b>
60-69 years	11,311	2	11,352	11	<b>81.8 (16.7, 98.0)</b>
70-79 years	5,751	0	5,744	4	100.0 (-51.5, 100.0)
≥80 years	996	0	980	3	100.0 (-142.0, 100.0)
Test for treatment effect variation <sup>a</sup>					P = 0.7263
<b>First episode of RSV-ARI</b>					
Whole trial population	18,058	37	18,076	98	<b>62.2 (44.4, 74.9)*</b>
60-69 years	11,311	25	11,352	68	<b>63.2 (41.1, 77.7)*</b>
70-79 years	5,751	9	5,744	22	<b>59.1 (7.6, 83.4)</b>
≥80 years	996	3	980	8	62.5 (-56.2, 93.6)
Test for treatment effect variation <sup>a</sup>					P = 1

Source: Table 2.6.1 p81 of the submission; RENOIR EOS1 Report Table 9; Table 10 & Table 14.22; Table 11 & Table 14.24; Table 13 & Table 14.27.

ARI = acute respiratory illness; CI = confidence interval; EOS1 = End of Season 1; LRTI = lower respiratory tract illness; N = total number of participants; P = P-value; RSV = respiratory syncytial virus; RSVpreF = recombinant RSV prefusion F protein vaccine; VE = vaccine efficacy.

a P-value for test for treatment effect variation among subgroups calculated post-hoc, based on exact likelihood ratio chi-square test (statistical model assumed for each subgroup, the number of cases in the RSVpreF group CV, given the total number of cases (CV+CP) follows a binomial distribution [RENOIR SAP 5.2.3. Analyses for Efficacy Endpoints]). The submission applied this test to efficacy outcomes only. The post-hoc analysis testing for treatment effect variation conducted could not be verified during the evaluation. The test conducted by the submission appeared to compare differences between the subgroups, and it was unclear from the submission's description whether comparisons were made between the subgroup and the total sample, which would be a more informative test. The PSCR clarified (p4) that comparisons in the submission were made between mutually exclusive subgroups, not between subgroups and the full trial population, which would have been inappropriate due to patients appearing on both sides of the comparison.

\* denotes lower limit for 95% CI >20%.

**Bold** indicates statistically significant results.

6.24 A summary of the results from the subgroup analyses for participants with a pre-specified risk condition is provided in Table 8 for EOS1.

**Table 8: Results for subgroup analyses of efficacy endpoints in RENOIR through the EOS1, by prespecified significant condition, evaluable efficacy population**

Population	RSVpreF		Placebo		VE (95% CI)
	N	Cases, n	N	Cases, n	
<b>First episode of RSV-LRTI with ≥2 symptoms</b>					
Whole trial population	18,058	15	18,076	43	<b>65.1 (35.9, 82.0)*</b>
≥1 prespecified sig. condition	9,377	8	9,432	22	<b>63.6 (15.2, 86.0)</b>
No prespecified sig. conditions	8,681	7	8,644	21	<b>66.7 (18.6, 88.0)</b>
Test for treatment effect variation <sup>a</sup>					P = 1
<b>First episode of RSV-LRTI with ≥3 symptoms</b>					
Whole trial population	18,058	2	18,076	18	<b>88.9 (53.6, 98.7)*</b>
≥1 prespecified sig. condition	9,377	2	9,432	11	<b>81.8 (16.7, 98.0)</b>
No prespecified sig. conditions	8,681	0	8,644	7	<b>100.0 (30.6, 100.0)*</b>
Test for treatment effect variation <sup>a</sup>					P = 0.5211
<b>First episode of RSV-ARI</b>					
Whole trial population	18,058	37	18,076	98	<b>62.2 (44.4, 74.9)*</b>
≥1 prespecified sig. condition	9,377	16	9,432	47	<b>66.0 (38.9, 82.0)*</b>
No prespecified sig. conditions	8,681	21	8,644	51	<b>58.8 (30.3, 76.5)*</b>
Test for treatment effect variation <sup>a</sup>					P = 0.7006

Source: Table 2.6.2 p82 of the submission; RENOIR EOS1 Report Table 9; Table 10 & Table 14.22; Table 11 & Table 14.24; Table 13 & Table 14.27

ARI = acute respiratory illness; CI = confidence interval; EOS1 = end of season 1; LRTI = lower respiratory tract illness; n = number of participants with event; N = total participants in group; RSV = respiratory syncytial virus; RSVpreF = recombinant RSVprefusion F protein vaccine; VE = vaccine efficacy

<sup>a</sup> P-value for test for treatment effect variation among subgroups calculated post-hoc, based on exact likelihood ratio chi-square test (statistical model assumed for each subgroup, the number of cases in the RSVpreF group CV, given the total number of cases (CV+CP) follows a binomial distribution [RENOIR SAP 5.2.3. Analyses for Efficacy Endpoints]). The post-hoc analysis testing for treatment effect variation conducted could not be verified during the evaluation.

\* denotes lower limit for 95% CI >20%.

**Bold** indicates statistically significant results.

6.25 Results reported for VE against RSV for the subgroup of adults aged ≥75 years are provided in Table 9. Results were not significant for all data cut-off periods reported (season 1; season 2, and across 2-seasons) for RSV-LRTI with ≥2 symptoms or ≥3 symptoms. VE results in adults aged ≥75 years for RSV-ARI were as follows:

- Season 1: 87.5%, 95% CI 6.8 to 99.7;
- Across 2-seasons: 65.0%, 95% CI 13.8 to 87.5;
- Season 2: 50%, 95% CI -43.9 to 84.6.

VE efficacy results were statistically significant for season 1 and across 2 seasons, but not for season 2. None of the results satisfied the clinical significance threshold of lower limit for 95% CI >20%.

**Table 9: Results of RSVpreF VE against the first episode of medically-attended RSV requiring any healthcare visit(s) in RENOIR - subgroups adults ≥75 years**

	Season 1 7.05 months			Season 2 7.59 months			Across 2 seasons 16.36 months		
	RSV preF	PBO	VE (95% CI)	RSV preF	PBO	VE (95% CI)	RSV preF	PBO	VE (95% CI)
<b>First episode of RSV-LRTI with ≥2 symptoms</b>									
Subgroups (cases that prompted a healthcare visit(s))									
Adults aged ≥ 75y, N	2892	2904	85.7	2486	2477	40	2892	2904	66.7
Cases, n	1	7	(-11.2, 99.7)	3	5	(-208.4, 90.7)	4	12	(-10.0, 92.2)
<b>First episode of RSV-LRTI with ≥3 symptoms</b>									
N	18,050	18,074		16,164	16,059		18,050	18,074	
Subgroups (cases that prompted a healthcare visit(s))									
Adults aged ≥ 75 y, N	2892	2904	100	2486	2477		2892	2904	
Cases, n	0	3	(-142.0, 100.0)	2	3	33.3 (-482.0, 94.4)	2	6	66.7 (-86.4, 96.7)
<b>First-episode of RSV-ARI</b>									
N	18,050	18,074		16,164	16,059		18,050	18,074	
Subgroups (cases that prompted a healthcare visit(s))									
Adults aged ≥ 75 y, N	2892	2904	<b>87.5</b>	2486	2477	50	2892	2904	<b>65.0</b>
Cases, n	1	8	<b>(6.8, 99.7)</b>	6	12	(-43.9, 84.6)	7	20	<b>(13.8, 87.5)</b>

Source: Table 2.5.7 p70 of the submission; RENOIR EOS 2 efficacy tables, Table 18.18, Table 18.28 and Table 18.38.

ARI = Acute respiratory illness; CI = confidence interval; IR = incidence rate; LRTI = lower respiratory tract illness; mL = millilitre; n = number of participants with event; N = total participants in group; NP = Not performed due to insufficient numbers; NR = not reported; PBO = placebo; RSV = respiratory syncytial virus; RSVpreF = recombinant RSV prefusion F protein vaccine; VE = vaccine efficacy; y = years.

**Bold** indicates statistically significant results.

VE = 1 – Risk Ratio. Results were not presented for VE=1-incidence rate, or VE=1-hazard ratio. Risk difference was not presented.

6.26 The submission stated that the results for subgroup analyses should be interpreted with caution, due to the limited number of cases and smaller sample sizes for subgroups, which contribute to the wide CI around point estimates reported. The evaluation noted that due to the smaller sample size of the population included (relative to the overall study sample), there is an increased risk of type II errors (such as would occur if the trials failed to detect an effect for treatment even where one actually existed). The evaluation commented that although these subgroup analyses have a higher risk of bias due to the smaller sample sizes, the results for the subgroup of participants aged ≥75 years and adults with one or more pre-specified condition are informative for decision making.

#### **Study 1006: RSVpreF with SIIV (coadministered or sequential) versus placebo**

6.27 The submission presented further subgroup analyses by age group (65-74 years; ≥75 years) for Study 1006, approximately 20% were aged ≥75 years, and concluded that results for subgroup analyses were similar to the primary analysis. There was no significant difference in the immune response elicited by RSVpreF or SIIV when administered concomitantly versus sequentially, in either age subgroup. The evaluation noted that the results presented for RSVpreF for adults aged ≥75 years did not meet the non-inferiority criterion of the lower limit of the 2-sided 95% CI >0.667. Notwithstanding, in its pre-submission advice, ATAGI noted there is no immediate reason to expect markedly different responses to coadministration of RSV with SIIV across age groups.

### **Comparative harms**

- 6.28 A summary of safety reported for RENOIR is presented in Table 10, with all the safety results of relevance summarised as follows:
- The proportions of participants reporting any AEs, immediate AEs, and severe AEs within 1-month of vaccination were similar between RSVpreF and placebo in RENOIR.
  - Serious Adverse Events (SAEs): The most frequently reported system order classes (SOCs) for RSVpreF and placebo were cardiac disorders (1.4% vs 1.4%), infections and infestations (1.2% vs 1.1%), and neoplasms benign, malignant and unspecified (including cysts and polyps) (1.2% vs 1.1%). By preferred term (PT), the most frequently reported SAEs for RSVpreF were acute myocardial infarction (n=44; 0.2%), pneumonia (n=39; 0.2%), and atrial fibrillation (n=37; 0.2%), which had a similar frequency in the placebo group (39 [0.2%]), 32 [0.2%] and 29 [0.2%], respectively).
  - SAEs were assessed as related to study intervention by the investigator in 3 participants receiving RSVpreF group and none receiving placebo. The 3 cases reported were: Hypersensitivity (allergic reaction; moderate severity, Guillain-Barre syndrome (GBS; life-threatening), and Miller Fisher syndrome (MFS; severe) (a rare form of GBS).
- 6.29 ATAGI considered that whilst there are no immediate safety concerns based on RENOIR, the claim of non-inferiority could not be assessed due to the absence of established non-inferiority criteria in relation to safety. The data supports the claim that the vaccine appears to be safe and well tolerated, however statistical constraints may prevent detection of other rare events (ATAGI Pre-Submission Advice to the PBAC Dec 2023).
- 6.30 ATAGI recommended that, if approved by the PBAC, post-licensure long-term monitoring is implemented with a specific focus on detecting additional instances of GBS and MFS associated with RSVpreF. In addition, ongoing monitoring is essential to detect other rare events which may not be identified with the sample size of RENOIR (ATAGI advice to the PBAC Dec 2023).
- 6.31 In Study 1006, most AEs were mild or moderate in severity. No SAEs or severe AEs were considered to be related to the study intervention. There were 7 participants (1.0%) who reported AEs that led to withdrawal following concomitant administration of RSVpreF and SIIV at Visit 1, but none after Visit 2. Of the 7 reports, 2 were considered to be related to the study intervention.
- 6.32 ATAGI considered that there are no immediate safety concerns following coadministration of RSVpreF with SIIV, however, this was based on a small sample which prevents identification of rare safety events. Furthermore, safety assessments were not subject to statistical analysis, there was no non-inferiority criteria, and comparisons are descriptive only. There are no completed trials assessing

coadministration of RSVpreF with COVID-19 or any other vaccine in older adults (ATAGI advice to the PBAC Dec 2023).

## Benefits/harms

6.33 A summary of the comparative benefits and harms for RSVpreF versus placebo in RENOIR is presented in Table 10.

**Table 10: Summary of comparative benefits and harms for RSVpreF and placebo**

Benefits						
RT-PCR confirmed RSV-LRTI						
Event	RSVpreF	Placebo	Difference <sup>b</sup>	VE (95% CI)		
<b>First episode of RSV-LRTI with ≥ 2 symptoms</b>						
VE analysis, Season 1	15/18,050 (0.08%)	43/18,074 (0.24%)	0.15%	65.1 (35.9, 82.0)		
VE analysis, Season 2	39/16,164 (0.24%)	88/16,059 (0.55%)	0.31%	55.7 (34.7, 70.4)		
VE analysis, Across 2 seasons	54/18,050 (0.30%)	131/18,074 (0.72%)	0.43%	58.8 (43.0, 70.6)		
<b>First episode of RSV-LRTI with ≥ 3 symptoms</b>						
VE analysis, Season 1	2/18,050 (0.01%)	18/18,074 (0.10%)	0.09%	88.9 (53.6, 98.7)		
VE analysis, Season 2	8/16,164 (0.05%)	36/16,059 (0.22%)	0.17%	77.8 (51.4, 91.1)		
VE analysis, Across 2 seasons	10/18,050 (0.06%)	54/18,074 (0.30%)	0.24%	81.5 (63.3, 91.6)		
<b>VE applied in economic model: First episode of medically-attended RSV (any healthcare visit, Season 1)</b>						
First episode of RSV-LRTI with ≥2 symptoms	8/18,050 (0.04%)	27/18,074 (0.15%)	0.11%	70.4 (33.0, 88.4)		
First episode of RSV-LRTI with ≥3 symptoms	2/18,050 (0.01%)	13/18,074 (0.07%)	0.06%	84.6 (32.0, 98.3)		
First-episode of RSV-ARI	15/18,050 (0.08%)	43/18,074 (0.24%)	0.15%	65.1 (35.9, 82.0)		
Harms						
RENOIR	RSVpreF n/N	Placebo n/N	RR (95% CI) <sup>b</sup>	Event rate/100 patients		RD (95% CI) <sup>b</sup>
				RSVpreF	Placebo	
<b>Any AE (from vaccination through 1-month follow up visit)</b>						
Any AE	2,012/18,574	1,917/18,288	1.03 (0.97, 1.10)	10.83	10.48	0.35% (-0.28%, 0.98%)
Immediate AE <sup>a</sup>	39/18,574	35/18,288	1.10 (0.70, 1.73)	0.21	0.19	0.02% (-0.07%, 0.11%)
Severe or life-threatening AE	106/18,574	97/18,288	1.08 (0.82, 1.42)	0.57	0.53	0.04% (-0.11%, 0.19%)
<b>AE related to study intervention (from vaccination through 1-month follow up visit)</b>						
Any AE	264/18,574	179/18,288	1.45 (1.20, 1.75)	1.42	0.98	0.44% (0.22%, 0.66%)
Immediate AE <sup>a</sup>	33/18,574	27/18,288	1.20 (0.72, 2.00)	0.18	0.15	0.03% (-0.05%, 0.11%)
Severe or life-threatening AE	33/18,574	1/18,288	32.49 (4.44, 237.55)	0.18	0.01	0.17% (0.11%, 0.23%)
<b>Tier 1 AEs</b>						
Atrial fibrillation through 1-month after vaccination	11/18,574	3/18,288	3.61 (1.01, 12.94)	0.06	0.02	0.04% (0.00%, 0.08%)
Guillain-Barre Syndrome from day 1 to day 43	2/18,574	0/18,288	NE	0.01	0.00	0.01% (0.00%, 0.03%)

Source: Compiled during the evaluation; Table 2.5.7 p70 and Table 2.5.8 p72 of the submission; RENOIR EOS2 CSR Table 11 p40.

AE = adverse event; CI = confidence interval; EOS=end of season; N = number of participants; n = number of participants with at least one RT-PCR confirmed RSV-LRTI; NE=not estimable; LRTI = lower respiratory tract illness; RD = risk difference; RR = relative risk; RSV = respiratory syncytial virus; RT-PCR = reverse transcription-polymerase chain reaction; SAE = serious adverse event; VE = vaccine efficacy. a Immediate AE refers to an AE reported in the 30 minute post-vaccination period.

b Calculated during the evaluation.

6.34 On the basis of direct evidence presented by the submission (16.4 months ARI surveillance in RENOIR), for every 1,000 persons aged  $\geq 60$  years administered RSVpreF in comparison with placebo (i.e., no vaccine):

- Approximately 1.5 fewer persons would have RSV-LRTI with  $\geq 2$  symptoms in the first season after one vaccination.
- Approximately 4.3 fewer persons would have RSV-LRTI with  $\geq 2$  symptoms over 2 seasons after one vaccination.
- Approximately 4.4 more persons would experience any AE related to RSVpreF up to 1 month after vaccination.

### **Clinical claim**

6.35 Compared to placebo, the submission described RSVpreF as superior in terms of effectiveness for the prevention of RSV-LRTI and ARI in older adults, and non-inferior in terms of safety. The submission stated that in RENOIR, the pre-defined success criteria (lower bound of the 95% CI  $>20\%$ ) was met for the primary efficacy objective VE against RSV-LRTI  $\geq 2$  symptoms and  $\geq 3$  symptoms. The evaluation considered that the clinical claim of superior effectiveness compared with placebo was adequately supported in that the primary efficacy outcomes in RENOIR were met for the population of adults aged 60 years and older for the duration of follow-up in the trial. The ESC agreed with the evaluation that RSVpreF is more effective than placebo at preventing LRTI (for patients with  $\geq 2$  and  $\geq 3$  symptoms; Table 4) and RSV-ARI (Table 5). However, the ESC noted that for the overall trial population, RSVpreF did not demonstrate a significant difference for prevention of severe RSV-LRTI and considered there was insufficient evidence to determine the impact of RSVpreF on this outcome (Table 5). The pre-PBAC response noted that severe RSV-LRTI was a secondary endpoint that was not powered to detect a difference between RSVpreF and placebo, and only two cases of severe RSV-LRTI were reported at EOS1, both in the placebo group. The pre-PBAC response also presented results from an observational retrospective case control study in hospital or ED settings among US adults aged 60 and older, based on a conference abstract. The response stated that the adjusted VE of RSVpreF against severe RSV-ARI hospitalisations or ED visits was 90% (95% CI 24, 99)<sup>8</sup>. The PBAC noted that it was a favourable result for RSVpreF, however considered that the reliability of the estimate was uncertain as it was derived from a non-randomised study, and could not be evaluated in detail as only a conference abstract was available. The applicability of the results to the Australian setting was also uncertain as the study was conducted in the USA.

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<sup>8</sup> Tartof, S.Y. Real-world Abrysvo Vaccine Effectiveness (VE) Against RSV-related Severe Acute Respiratory Infection (ARI) Hospitalizations and Emergency Department (ED) Visits – Kaiser Permanente Southern California (KPSC), November 2023–April 2024. ID Week 2024.

- 6.36 The evaluation considered that superior effectiveness was adequately supported for the duration of the trial in the RENOIR trial population of healthy adults  $\geq 60$  years (including those with stable pre-existing conditions), however the evaluation and the ESC had concerns regarding the duration of protection, and the comparison of RSVpreF and placebo in the specific populations proposed for listing. While there is evidence of VE against RSV compared with placebo in the short-term (16.4 months), the data presented in the submission do not inform that comparison over the long-term, which is particularly relevant to informing duration of protection beyond the EOS2. There is a decline in immunogenicity by the EOS2 for RSVpreF from RENOIR. ATAGI noted that there are no correlates of protection, and no evidence to date, to inform the rate of waning post season two. Therefore, it is unknown whether, or at what point, immunity is likely to decline to a point below a protective threshold. While the PSCR and pre-PBAC response acknowledged that immunogenicity for RSVpreF waned over time, it claimed that the relatively small level of decline between Seasons 1 and 2, especially for the more severe and clinically important outcomes, showed that immunity is expected to extend well beyond the EOS2.
- 6.37 The evaluation and the ESC had concerns regarding the comparison of RSVpreF and placebo in two of the specific populations proposed for listing:

Participants aged  $\geq 75$  years: VE to prevent the first medically-attended episode of RSV-LRTI with  $\geq 2$  symptoms was not statistically significant; 85.7% (95% CI: -11.2%, 99.7%) at the end season 1, reducing to 40% (95% CI: -208.4%, 90.7%) at the EOS2 (Table 9). These results were also consistent for the outcome of VE against medically-attended RSV-LRTI with  $\geq 3$  symptoms. The subgroup of adults aged  $\geq 75$  years represents 16% of the RENOIR population.

Participants with  $\geq 1$  pre-specified condition: the lower limit for the 95% CI did not meet the criterion required to demonstrate superiority ( $>20\%$ ) relative to no vaccination for the outcome of VE to prevent the first episode of RSV-LRTI with  $\geq 2$  symptoms; 63.6% (95% CI: 15.2%, 86.0%) at the EOS1 (Table 8). These results were consistent for the outcome VE against RSV-LRTI with  $\geq 3$  symptoms. The results for this subgroup were not presented for the EOS2. The subgroup of adults aged  $\geq 60$  years with  $\geq 1$  pre-specified condition represents 52% of the RENOIR population.

The PSCR and pre-PBAC response stated that the RENOIR trial was not powered to detect statistically significant differences between the arms for subgroup analyses and that small sample sizes combined with rare events resulted in wide confidence intervals. The PSCR and pre-PBAC response noted that the point estimates for patients  $\geq 75$  years numerically favoured RSVpreF and were exploratory endpoints only. Further, the PSCR noted that the point estimates shown in Table 7 for the pre-specified analyses (60-69 years, 70-79 years and  $\geq 80$  years) showed that there was a numerical (but not statistically significant) increase in the VE point estimate with increasing age. The ESC noted that the subgroups of participants aged  $\geq 75$  years (Table 9) and adults

with one or more pre-specified conditions (Table 8) are the most relevant to the proposed use of RSVpreF.

- 6.38 The PBAC considered the most significant areas of uncertainty were:
- Declining immunogenicity by the EOS2 and no evidence to inform the rate of waning after season 2 (paragraph 6.36);
  - Impact of RSVpreF on prevention of severe RSV-LRTI in overall trial population, noting there were very few events in the trial (paragraph 6.35);
  - Impact of RSVpreF on efficacy outcomes in the populations requested for NIP listing, noting the smaller number of events in the subgroups compared with the overall study sample (16% of the RENOIR population were adults aged  $\geq 75$  years; 52% of the RENOIR population were adults aged  $\geq 60$  years with  $\geq 1$  pre-specified condition; paragraph 6.37). No adults from Australia were included in the RENOIR trial and no information was available regarding differential immune response or safety in Aboriginal and Torres Strait Island adults.
- 6.39 Overall, the PBAC considered that a claim of superior comparative effectiveness was reasonable for the comparison between RSVpreF and no vaccination based on the RENOIR trial (patients 60 years and older) noting that the RENOIR trial was not powered to detect statistically significant differences between the arms for subgroup analyses. The evaluation considered that the therapeutic conclusion presented in the submission for non-inferior safety compared to placebo may not be reasonable, noting that the trials included were not powered for the assessment of safety outcomes. The PBAC previously considered that that RSVpreF had an inferior but acceptable safety profile compared to placebo for active immunisation of pregnant women (paragraphs 6.46 and 7.1, RSVpreF PSD, March 2024). While the ESC agreed with ATAGI that there were no immediate safety concerns with RSVpreF, which appears safe and well tolerated (paragraph 6.29), it noted that statistical constraints may prevent the detection of rare events and therefore post licensing monitoring is recommended with a focus on GBS and MFS. Consistent with its previous consideration of RSVpreF for immunisation of pregnant women, the PBAC considered that RSVpreF had an inferior but acceptable safety profile compared to placebo in adults aged 60 years and older.

### ***Economic analysis***

- 6.40 The submission presented a modelled economic evaluation comparing a single dose of RSVpreF with no vaccine, with evidence drawn from RENOIR. The type of economic evaluation presented was a cost-utility analysis. The evaluation considered that this was reasonable given the clinical claim of RSVpreF being superior in efficacy to no vaccine.

The summary of the model structure, key inputs and rationale is presented in Table 11.

**Table 11: Summary of model structure, key inputs and rationale**

Component	Summary																																		
Treatments	RSVpreF (one dose) versus no vaccine																																		
Time horizon	<p>Varied by population. Commences at average age of cohort entry until participant reaches 100 years of age for each of the following cohorts:</p> <ul style="list-style-type: none"> <li>Adults aged 75 years and over; and</li> <li>Aboriginal and Torres Strait Islander adults aged 60-74 years; and</li> <li>Adults aged 60-74 years with at least one identified risk factor for severe RSV disease.</li> </ul> <p>Varies by population from 16.93 years to 33.27 years in the model base case vs. 16.4 months follow-up in RENOIR.</p> <p>VE was truncated to zero at month 48 (see extrapolation method below).</p>																																		
Outcomes	QALYs																																		
Methods used to generate results	Markov model using cohort expected value analysis.																																		
Health states	<p>Alive and Dead</p> <ul style="list-style-type: none"> <li>Alive: MA-LRTI: RSV: <ul style="list-style-type: none"> <li>hospital</li> <li>emergency</li> <li>outpatient</li> </ul> </li> <li>Death: <ul style="list-style-type: none"> <li>due to RSV (DSM)</li> <li>from other causes (OCM)</li> </ul> </li> </ul> <p>Cases of MA-LRTI: RSV and associated deaths, hospital admissions, emergency department (ED) visits and general practitioner (GP) or outpatient consultations were informed by results from RENOIR.</p>																																		
Cycle length	1 month																																		
Transition probabilities	<p>Baseline incidence, mortality and morbidity are estimated from a specific Australian modelling study.</p> <p>The Australian modelling study estimated a higher rate of RSV hospitalisation per 100,000 population compared with the results presented by Nazareno (2022), which was presented by the sponsor in the request for Advice from ATAGI. Comparisons of the estimates for RSV hospitalisation rate per 100,000 have been assessed by ATAGI. The evaluation noted that estimates used by the submission were not consistent with the Advice from ATAGI, who considered that applying a multiplier of 2 to 2016-2019 AIHW data would be reasonable.</p>																																		
Extrapolation method	<p>VE of RSVpreF used in the model is shown below:</p> <p>VE of RSVpreF against RSV events (requiring any healthcare visit) from RENOIR compared with VE estimated in model</p> <table border="1"> <thead> <tr> <th rowspan="2">Trial Endpoint: Model Outcome, VE against RSV:</th> <th colspan="3">RENOIR, VE (%) (95%CI)</th> <th colspan="3">Modelled base case VE (%)</th> </tr> <tr> <th>Season 1 7.05 mths</th> <th>Season 2 7.59 mths</th> <th>Across 2 seasons 16.4 mths</th> <th>Months 1-6</th> <th>Month 16</th> <th>Abs VE% reduction per month</th> </tr> </thead> <tbody> <tr> <td>RSV-ARI, Outpatient visit</td> <td>65.1 (35.9, 82.0)</td> <td>47.0 (22.7, 64.1)</td> <td>53.2 (35.7, 66.2)</td> <td>65.1 (SA: 50, 100)</td> <td>50.0</td> <td>1.51%</td> </tr> <tr> <td>RSV-LRTI with ≥2 symptoms, Emergency visit</td> <td>70.4 (33.0, 88.4)</td> <td>53.5 (19.2, 74.1)</td> <td>60.0 (37.2, 75.2)</td> <td>70.4 (SA: 50, 100)</td> <td>56.3</td> <td>1.41%</td> </tr> <tr> <td>RSV-LRTI with ≥3 symptoms, Hospital admission</td> <td>84.6 (32.0, 98.3)</td> <td>72.0 (33.4, 89.8)</td> <td>76.3 (50.2, 89.9)</td> <td>84.6 (SA: 50, 100)</td> <td>74.1</td> <td>1.05%</td> </tr> </tbody> </table> <p>Source: Adapted from Table 2.5.7 p70, text pp110-111, and Table 3.4.2 p112 of the submission; Economic evaluation workbook ABRYSV0_Older Adults_CEA_July 2024, sheet 'ABR'</p>	Trial Endpoint: Model Outcome, VE against RSV:	RENOIR, VE (%) (95%CI)			Modelled base case VE (%)			Season 1 7.05 mths	Season 2 7.59 mths	Across 2 seasons 16.4 mths	Months 1-6	Month 16	Abs VE% reduction per month	RSV-ARI, Outpatient visit	65.1 (35.9, 82.0)	47.0 (22.7, 64.1)	53.2 (35.7, 66.2)	65.1 (SA: 50, 100)	50.0	1.51%	RSV-LRTI with ≥2 symptoms, Emergency visit	70.4 (33.0, 88.4)	53.5 (19.2, 74.1)	60.0 (37.2, 75.2)	70.4 (SA: 50, 100)	56.3	1.41%	RSV-LRTI with ≥3 symptoms, Hospital admission	84.6 (32.0, 98.3)	72.0 (33.4, 89.8)	76.3 (50.2, 89.9)	84.6 (SA: 50, 100)	74.1	1.05%
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Component	Summary
	<p>During the evaluation, the applicant provided a revised model where the rate of waning was increased for each outcome presented; 1.26% per month for hospitalisations, 1.69% per month for VE against emergency visits, and 1.81% for outpatient visits. This was not revised during the evaluation.</p> <p>VE was extrapolated by assuming:</p> <ul style="list-style-type: none"> <li>• Month 1: the onset of effect of RSVpreF is not immediate i.e., assumed to be 50% peak efficacy.</li> <li>• Month 1 to 7: VE assumed to peak post-vaccination. VE is maintained at peak efficacy over this time.</li> <li>• Month 8 to 47: VE is reduced at a constant rate each month. The reduction in the rate is varied for each outcome presented: 1.05% per month for hospitalisations, 1.41% per month for VE against emergency visits, and 1.51% for outpatient visits. The evaluation noted that no calculations or sources were provided for the verification of the reduction in VE assumed in the model.</li> <li>• Month 48 and beyond: VE for all outcomes was truncated to zero.</li> </ul>
Health-related quality of life	<p>Literature-based:</p> <ul style="list-style-type: none"> <li>• McCaffrey (2016): EQ-5D-5L with Australian preference weights <ul style="list-style-type: none"> <li>○ Adults aged 60-64 years: 0.89</li> <li>○ Adults aged 65-74 years: 0.87</li> <li>○ Adults aged ≥ 75 years: 0.83</li> </ul> </li> <li>• Banham (2019); SF-6D <ul style="list-style-type: none"> <li>○ Aboriginal and Torres Strait Islander adults aged ≥ 55 years, 0.675</li> </ul> </li> <li>• Disutility values: <ul style="list-style-type: none"> <li>○ Falsey (2022): Hospital: 0.0167</li> <li>○ Mao (2022): Emergency: 0.0054</li> <li>○ Mao (2022): Outpatient: 0.0054</li> </ul> </li> </ul>
Costs	<ul style="list-style-type: none"> <li>• RSVpreF, proposed NIP price: \$ [REDACTED]</li> <li>• Administration cost: \$7</li> <li>• GP visit: Assumed cost is 1.5 times MBS fee (=41.4*1.5=\$62.10)</li> <li>• Emergency visit: AECC items E0450A, E0450B, E0450C: \$1,299.57.</li> <li>• Hospital admission: AR-DRG E62A and E62B, NHCDC 2020/21: \$8,542.43</li> </ul>

Source: Table 2.5.7 p70, text pp110-111, Table 3.1.1 p103; Table 3.3.1 p107, Table 3.4.2 p112, Table 3.5.1 p114 of the submission; Table 3.6.1 p115 of the submission; Economic evaluation workbook ABRYSVO\_Older Adults\_CEA\_July 2024, sheet 'ABR' and sheet 'Variables'. AECC = Australian Emergency Care Classification; AIHW = Australian Institute of Health and Welfare; AR-DRG = Australian Refined Diagnosis Related Groups; ARI = acute respiratory illness; ATAGI = Australian Technical Advisory Group on immunisation; CI = confidence interval; DSM = death due to RSV; ED = emergency department; EOS = End of Season; GP = general practice; LRTI = lower respiratory tract illness; MA = medically attended; MBS = medical benefit scheme; mL=millilitres; NA = not applicable; NIP=National Immunisation Program; NHCDC=National Hospital Cost Data Collection; OCM = death from other cause; QALY = quality adjusted life years; RSV = respiratory syncytial virus; RSVpreF = recombinant RSV prefusion F protein vaccine; SA = sensitivity analysis; VE = vaccine efficacy. a Value has changed to \$42.85 ( $42.85 \times 1.5 = \$64.28$ ); however, this was not updated during the evaluation.

6.41 The model structure was the same for all populations. Cost-effectiveness was modelled separately for each target population, with a weighted ICER presented across the three populations.

6.42 The economic evaluation used a Markov model with two health states: 'Alive' and 'Dead'. The model estimated RSV cases of medically-attended LRTI (MA-LRTI): hospital admissions, ED visits, outpatient consultations, and deaths. The model assumed that all individuals started in the 'Alive' state and received a single dose of 'RSVpreF' or 'no RSV vaccine'. Within each cycle, individuals in the alive health state may have experienced one of the following events:

- Outpatient visit;
- Emergency visit;

- Hospital admission;
- Death (RSV disease-specific mortality (DSM)); or
- Death (other cause mortality (OCM)).

The evaluation and the ESC considered that the model structure was reasonable.

- 6.43 The submission's model structure differed from the 2-year decision analytic structure presented to ATAGI. The submission reasoned that more mature data were available since the Request for Advice from ATAGI was prepared. The submission stated that the underlying clinical logic of the model was unchanged and it was only the estimated effect profile of the intervention over time and the structure of the model which had changed (monthly rather than annual cycles, and with fatal cases captured using a conventional Markov process, in combination with other cause mortality (OCM) estimates from Australian life tables, rather than as a single payoff). The submission's Markov model applied a lifetime time horizon which differed based on the starting age for each cohort in the model. The evaluation noted that the time horizon ranged from 16.93 years (average age of adults over 75 years: 83.07 years) to 33.27 years (average age of Aboriginal and Torres Strait Islander adults: 66.73 years).
- 6.44 The submission assumed VE of RSVpreF did not vary by age and by subgroup (adults with a pre-specified condition). Efficacy estimates for the evaluable efficacy population in RENOIR included participants aged  $\geq 60$  years. The population in RENOIR was younger than one of the target populations of adults aged  $\geq 75$  years (mean age at vaccination: 68 years, paragraph 6.10), and approximately half of participants (51.6%) had a prespecified high-risk condition at baseline. The point estimate results for VE against RSV  $\geq 2$  symptoms for the evaluable efficacy population were similar to those for the population of adults with  $\geq 1$  pre-specified condition (Table 8); however, the confidence interval for adults aged  $\geq 75$  years crosses zero (Table 9).
- 6.45 ATAGI stated (ATAGI response to PBAC post-submission questions, August 2024), that it is expected that older people, or people with a slightly lower mean age who are considered medically at-risk may have lower immune responses and thus a lower VE following an RSV vaccination. A lower VE may also be observed in Aboriginal and Torres Strait Islander peoples, due to higher rates of medical risk factors and comorbidities. The subgroup analysis by age from RENOIR indicated a lower VE point estimate for 60-69 years than 70-79 years and 80+ years (these latter age groups were similar), with wide and overlapping CIs (Table 7). Similarly, point estimates for those with  $\geq 1$  pre-specified condition were slightly lower compared with the evaluable efficacy population (Table 8), and lower still for those with  $\geq 1$  chronic cardiopulmonary conditions. The ATAGI considered that in the absence of detailed evidence, it was appropriate to use the values from the evaluable efficacy population of RENOIR as the base case VE for each of these groups. Sensitivity analyses using CIs would provide a potential range of impact for the vaccine in each population (ATAGI response to PBAC post-submission questions, August 2024). The model results were not sensitive to the assumption for VE against RSV for outpatient and emergency

visits; however, the model results were sensitive to assumptions for VE against RSV hospitalisation.

- 6.46 Three exploratory outcomes from RENOIR were used to inform VE of RSVpreF in the model:
- VE against RSV-outpatients visits was informed by VE against RSV-ARI that prompted a health care visit. ATAGI did not agree that use of this outcome was appropriate (ATAGI Pre-Submission Advice to PBAC, December 2023). This was largely because such use within the trial may reflect practice in the US that may differ from practice in Australia. The RENOIR Clinical Study Report did not provide a breakdown of whether cases prompting a healthcare visit resulted in an inpatient or outpatient visit. ATAGI considered that VE against RSV-LRTI  $\geq 2$  symptoms for VE relating to outpatient visits (VE: 65.1%; based on 58 cases in Season 1) should be used to inform this outcome in the model. VE results for the two outcomes were the same for Season 1, i.e. 65.1% (95% CI, 35.9 to 82.0); however, VE results in Season 2 and across 2 seasons were lower for the outcome 'RSV-ARI that prompted a healthcare visit' compared to 'RSV-LRTI with  $\geq 2$  symptoms for all cases'. The evaluation and the ESC noted that assumptions pertaining to VE against RSV-outpatients visits were not a main driver in the model.
  - VE against RSV-emergency was informed by VE against RSV-LRTI with  $\geq 2$  symptoms that prompted a health care visit. The evaluation and the ESC noted that this was consistent with ATAGI advice; ATAGI considered that medically-attended RSV-LRTI with  $\geq 2$  symptoms could be applied to emergency cases (ATAGI Advice December 2023).
  - VE against RSV-hospitalisation was informed by VE against RSV-LRTI with  $\geq 3$  symptoms that prompted a health care visit. The evaluation and the ESC noted that this was consistent with ATAGI advice; ATAGI considered that the medically-attended RSV-LRTI with  $\geq 3$  symptoms could be applied to hospitalised cases.
- 6.47 The ESC noted that there were no adjustments made for regionality (US mainly), temporality (conducted during COVID), or seasonality (coinciding with the northern hemisphere RSV season). The ESC considered that the magnitude and direction of any bias associated with these factors is unclear.
- 6.48 The estimated VE of RSVpreF against medically-attended events was based on the evaluable efficacy population in RENOIR. The submission used results from the exploratory analyses to inform RSV medically-attended visits for EOS1 and EOS2. The ATAGI Pre-Submission Advice to PBAC (December 2023) stated that whilst the medically attended subgroup may have more severe illness than those that do not seek any medical attention, this may also be influenced by treatment seeking behaviour. Given that only two people met the sRSV-LRTI criteria in RENOIR (EOS1) (requiring hospitalisation, new/increased oxygen supplementation or new/increased mechanical ventilation), ATAGI noted that the remainder of the cases with RSV-LRTI

≥3 symptoms presumably only sought emergency or outpatient care or did not require increased care and may not be 'severe'.

- 6.49 The inputs for incidence of hospitalisation and mortality used in the model were informed by the Australian modelling study, which was a regression analysis of data from 2010 to 2019 from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database (NHMD). This study follows the protocol outlined by Bruyndonckx et al (2024)<sup>9</sup>.
- 6.50 The Australian modelling study was a retrospective database analysis. In this study, data were modelled using a time-series quasi-Poisson regression approach to estimate RSV-attributable cardiorespiratory, respiratory, and cardiovascular events by age group. RSV and influenza proxies, hospitalisation and mortality data from the AIHW NHMD for people aged 18 years and older residing in Australia were used to inform the regression. The manuscript stated that an identity link function was used to reflect the most biologically plausible link between viral circulation and the occurrence of events. Viral proxies for RSV used were the weekly number of RSV hospitalisations in children <2 years (with ICD-10-AM codes B97.4, J21.0, J12.1, J20.5, J21.9) and influenza specific hospitalisations (i.e., with ICD-10-AM codes J09, J10, J11) in adults aged 65 years and older. The study did not report results for other populations relevant for the NIP listings sought, including Aboriginal and Torres Strait Islander or factors relating to risk-status, or consider these as stratifying variables in the analyses conducted, which the authors stated was due to data limitations. Results were presented by age groups: 16-64 years old, 65-74 years old, ≥75 years and ≥65 years. The PSCR stated that the Australian modelling study provides more robust and contemporary estimates of RSV hospitalisation and mortality rates among older Australian adults than the approach proposed by ATAGI, using AIHW data with a nominal multiplier. The PSCR noted these data were not available at the time the ATAGI advice request was submitted.
- 6.51 Table 12 presents results for three different methods for estimating RSV hospitalisation including: crude estimates (AIHW NHMD 2016-2019); Multiplier method (NZ Shivers 2012-2015; McLaughlin 2022); and modelling methods (Nazareno 2022; Australian modelling study 2010-2019).

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<sup>9</sup> Bruyndonckx R, Polkowska-Kramek A, Liang C, Nuttens C, Tran TMP, Gessner BD, Begier E. Estimation of Symptomatic Respiratory Syncytial Virus Infection Incidence in Adults in Multiple Countries: A Time-Series Model-Based Analysis Protocol. *Infect Dis Ther.* 2024 Apr;13(4):953-963. doi: 10.1007/s40121-024-00948-9. Epub 2024 Mar 18. PMID: 38499832; PMCID: PMC11058168.

**Table 12: Comparison of estimates of RSV hospitalisation rates per 100,000 population**

Data / Study	Outcome, mean (95% CI)	Adjusted factors (multiplier)	50-64	65-69	70-74	75-79	80+
<b>Crude estimates</b>							
AIHW NHMD 2016-2019 Australia	RSV-coded hospitalisations (principal diagnosis only)	N/A	7 (5 – 10)	19 (44-62) 48 (27-70)	29 (17-40)	41 (27-55)	110 (55-166)
AIHW NHMD 2016-2019 Australia	RSV-coded hospitalisations (any diagnosis fields)	N/A	26 (16 – 32)	53 (44-62) 123 (84 – 189)	80 (53-106)	121 (77-163)	250 (132-363)
<b>Multiplier method</b>							
NZ SHIVERS 2012-2015 New Zealand	Lab-confirmed hospitalisations	Tested patient % (est. 1.5-2.5)	25 (21-29)	74 (65-84)			184 (159-213)
McLaughlin 2022 Systematic Review USA	Lab-confirmed (PCR only) hospitalisations in US	Sensitivity of lab tests (1.5)	67 (40 – 94)	267 (228-306)			
<b>Modelling method</b>							
Nazareno 2022 AIHW NHMD 2009-2017 Australia	Excess ARI (J00-22,44) hospitalisations associated with RSV	Influenza hospitalisations (N/A)	45-64y: 199 (-1,013 – 1,357)	33.5 (-32 – 104)		256 (5 – 487)	
	Excess respiratory (J00-J99) hospitalisations associated with RSV		45-64y: 505 (-1,253 – 2,183)	64 (-17 – 154)		360 <sup>b</sup> (79 – 628)	
Australian modelling study 2010-2019 Australia	RSV-coded hospitalisations (J00-J99)	Viral proxies: RSV hospitalisations children aged <2y; Influenza adults aged >65y (N/A)	Reported for age groups: 18-64y, but not extracted during the evaluation.	107 (0 – 247.8)) Age ≥65y: 236.4		398 <sup>a</sup> (50.4 – 775.5)	

Source: ATAGI Advice December 2023 Table 5.2.-1 p51; Attachment 3 of the submission Table 1 pp18-21, Table 2 pp22-24

AIHW=Australian Institute of Health and Welfare; ARI = acute respiratory illness; CI=confidence interval; N/A = not available; NCIRS= National Centre for Immunisation Research and Surveillance; NHMD=National Hospital Morbidity Database; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; y = years.

a Value used to inform modelling in the base case (value of 398);

b Submission sensitivity analyses used value 384, see “ABRYSVO\_Older Adults\_CEA\_July2024”, worksheet ‘Hosp’. Calculation was based on 121 in the 75-79 age group, 250 in the 80-84 age group, and 250 in the 85+ age group, and using a multiplier of 2. Calculation was weighted by age group.

6.52 The Australian modelling study estimated a higher rate of RSV hospitalisation per 100,000 population compared with the results presented by Nazareno (2022) (398 vs. 360). The incidence of RSV reported on the National Notifiable Diseases Surveillance System (NNDSS) from 2021 to 2023 is significantly higher in children aged from 0 to 4 years compared with all other age groups. The evaluation noted that the Australian modelling study used RSV in children aged <2 years as a viral proxy, which may explain the higher estimates for hospitalisation and deaths derived from the Australian modelling study compared with Nazareno (2022). A sensitivity analysis was also presented in the submission based on ATAGI’s advice to apply a multiplier of 2 to the

2016-2019 AIHW data for incidence, resulting in an estimate of 384 per 100,000 person-years for adults aged ≥75 years.

- 6.53 The RSV incidence and mortality used in the model is summarised in Table 13. Estimates from the Australian modelling study were used for the base case analysis. Alternative estimates were available for sensitivity analyses including hCFR of 4.22% (Adults aged ≥75 years) and 3.83% (Adults aged ≥60 years).

**Table 13: Estimated RSV incidence and mortality by target subgroup**

Population	Rate per 100,000 person-years			
	Hospitalised	Emergency	Outpatient	Mortality
<b>Base case</b>	<b>AUS Model-based study</b>	<b>0.75 fold difference<sup>a</sup></b>	<b>8.6 fold difference<sup>a</sup></b>	<b>AUS Model-based study</b>
Adults aged ≥75 years	398 [A]	299 [= A x 0.75]	3,423 [=A x 8.6]	43 <sup>b</sup>
Aboriginal and Torres Strait Islander adults aged 60 to 74 years	597	448	5,134	43 <sup>b</sup>
Adults at high-risk aged 60-74 years	398	299	3,423	43 <sup>b</sup>
<b>Sensitivity analysis</b>				
Adults aged ≥75 years	384	288	3,302	hCFR: 4.22% (3.92%-4.54%) ATAGI advice: Lower: 1% Upper 8%
Adults aged ≥60 years				hCFR: 3.83%
Adults aged ≥65 years	-	-	-	hCFR: 3.98%
Adults aged ≥80 years	-	-	-	hCFR: 4.55%

Source: Table 3.4.1 p109 of the submission; ATAGI Advice December 2023 Table 5.2-3 p52.

AIHW=Australian Institute of Health and Welfare; ATAGI = Australian Technical Advisory Group on immunisation; AUS = Australia; CEA = cost effectiveness analysis; hCFR = hospital case fatality ratio; PBAC = Pharmaceutical Benefit Advisory Board; RSV = respiratory syncytial virus.

Economic evaluation workbook ABRYSSVO\_Older Adults\_CEA\_July 2024, sheet 'Variables'; Table 5.2-3 p52 ATAGI pre-submission advice to PBAC December 2023.

<sup>a</sup> Fold difference from McLaughlin et al., 2022 applied to hospitalisation rate in Australian model-based study to estimate emergency and outpatient rates, as advised by ATAGI (December 2023).

<sup>b</sup> Value input of 43 per 100,000 person-years is equivalent to a mortality rate of 10.8% of hospitalisations each month in the model.

- 6.54 The submission derived hospitalisation rates for each population as follows:

- Adults aged ≥75 years: The base case used data from the Australian modelling study (2010-2019) to estimate the hospitalisation rate (398 per 100,000 person-years). The evaluation noted that this is not consistent with Advice from ATAGI, which considered that applying a multiplier of 2 to the 2016-2019 AIHW data would be reasonable, which results in a rate of 384 per 100,000 person-years. The PSCR and pre-PBAC response maintained that data from the Australian modelling study should be used to inform the base case. Both methods use AIHW data with an overlapping time period i.e., over 2016 to 2019. The pre-PBAC response noted that results from the Australian modelling study became available only after the sponsor's Request for ATAGI Advice was made and the timing should not preclude their consideration by PBAC.

- Aboriginal and Torres Strait Islander adults aged 60 to 74 years: For this population, a risk ratio of 1.5 relative to the hospitalisation rate in the general Australian population aged  $\geq 75$  years was used. The value used was calculated by multiplying the value for adults aged  $\geq 75$  years by 1.5 (i.e.,  $398 \times 1.5 = 597$  per 100,000 person-years)<sup>10</sup>. ATAGI Advice (December 2023) stated that for Aboriginal and Torres Strait Islanders, an increase in risk could be used from the base case (i.e., apply 1.5 times the hospitalisation rate for the general Australian population aged  $\geq 75$  years), with sensitivity analyses using lower and upper bounds of the 95% CI of the estimated hospitalisation rate. When the rate for adults aged  $\geq 75$  years is adjusted to 384 per 100,000 as described above, the corresponding rate for Aboriginal and Torres Strait Islander adults aged 60 to 74 years is 576 per 100,000 person-years.
- Adults with at least one risk factor aged 60 to 74 years: The value applied was the same as for adults aged  $\geq 75$  years. The submission stated that this value was consistent with ATAGI recommendations. However, the evaluation noted that this was not consistent with ATAGI's advice, which considered that in the absence of robust data on hospitalisation rates for adults at high-risk aged 60-74 years, it may be appropriate to assume the same incidence for all at-risk groups (those aged 75+, individuals 60+ with risk conditions and Aboriginal and Torres Strait Islander peoples) for the purposes of the cost-effectiveness analysis (ATAGI Advice December 2023), which would have resulted in an estimate of hospitalisations based on a minimum age of 60 years (rather than 75 years as used by the submission). If 60 years was used as the lower limit of the analysis, then applying a multiplier of 2 to the 2016-2019 AIHW data as proposed by ATAGI (range 60 years to 85+) results in a rate of 197 per 100,000 person-years. Further to this, estimates from the Australian modelling study were reported for adults aged 60 to 74 years; although the analyses did not include risk-status as a stratifying variable, it is likely that the population modelled would have included people with risk-factors in this age category. The results presented for the lower CI across all years were bound by zero for both hospitalisations and mortality outcomes. The incidence per 100,000 person-years for RSV-attributable hospitalisations across years 2010 to 2019 was lower in the 60-74 years age-group (mean: 107) than for adults aged  $\geq 75$  years (mean: 398).

The evaluation noted that results of sensitivity analyses indicate the model was highly sensitive to assumptions about hospitalisations.

- 6.55 Emergency and outpatient visits were derived by applying a fold-estimate for emergency room visits (fold-estimate value, 0.75) and outpatient visits (fold-estimate value, 8.6) to the rate of assumed rate of hospitalisation for each population based on

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<sup>10</sup> Economic model, ABRYVO\_Older Adults\_CEA\_July 2024, spreadsheet 'variables' cell E14.

McLaughlin (2022). The submission stated the fold-estimates applied were based on ATAGI Advice (December 2023).

- 6.56 The same RSV mortality rate was assumed for all populations modelled i.e., adults aged  $\geq 75$  years, Aboriginal and Torres Strait Islander adults 60-74 years, and adults at high-risk aged 60-74 years. The base case used data from the Australian modelling study to estimate the mortality rate (43 per 100,000 person-years). The evaluation noted that this value was not consistent with the ATAGI advice. The mortality rate used in the model was equivalent to 10.8%<sup>11</sup> of hospitalisations each month, where variables for rates of hospitalisation and mortality were not linked in the economic model. The in-hospital case fatality rate proposed for the base case by ATAGI was 4.22% (95% CI 3.92 to 4.54) for adults aged  $\geq 75$  years (ATAGI Advice December 2024). ATAGI proposed sensitivity analyses be conducted for the in-hospital case fatality rate, with a lower bound of 1% (Leaver et al, 2022) and upper bound of 8% (as requested by the sponsor, based on Savic et al., 2022, Nyuyen-Van-Tam et al., 2022) (ATAGI Advice December 2023).
- 6.57 The submission assumed the duration of VE of RSVpreF was 4 years in the base case. Empirical data from RENOIR were reported for a median follow up period of 16.4 months and were used to inform the extrapolation of the trial data to 4 years. The submission stated that truncation of VE at 48 months was consistent with an RSV vaccine modelling study for older adults projecting linear waning of protection through 4 seasons of follow-up post vaccination of near-market comparator, RSVPreF3 (Molnar 2024)<sup>12</sup>. The evaluation and the ESC considered that data provided by the submission did not support VE/immunogenicity out to 4 years. The PSCR maintained that extrapolation of VE out to 4 years was realistic and reasonable. The pre-PBAC response stated that a sensitivity analysis of extrapolation to 3 years could be considered, and noted this was proposed in a meeting in the United States Center for Disease Control's Advisory Committee on Immunization Practices (ACIP) held on 24 October 2024<sup>13</sup>, however the advice was general in nature and did not apply specifically to RSVpreF.
- 6.58 To estimate QALYs, the submission applied the Australian population utility weights from McCaffrey (2016) and Banham (2019) for the Aboriginal and Torres Strait Islander population. The model used a weighted average of utility values for males and females

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<sup>11</sup> Calculation using Economic model, ABRYSVO\_Older Adults\_CEA\_July 2024, spreadsheet 'ABR':  $10.8\% = 0.000021(\text{cell M5})/0.000191(\text{cell L5}) * 100$ .

<sup>12</sup> Molnar D, La EM, Verelst F, Poston S, Graham J, Van Bellinghen LA, Curran D. Public Health Impact of the Adjuvanted RSVPreF3 Vaccine for Respiratory Syncytial Virus Prevention Among Older Adults in the United States. *Infect Dis Ther.* 2024 Apr;13(4):827-844. doi: 10.1007/s40121-024-00939-w. Epub 2024 Mar 20. PMID: 38507143; PMCID: PMC11058166.

<sup>13</sup> National Center for Immunization and Respiratory Diseases. RSV Vaccination in Adults: Work Group Interpretations. ACIP Meeting, 24 October 2024. <https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/06-RSV-Adult-Melgar-508.pdf>

using the life tables. While the evaluation considered that the published sources and utility values were reasonable, it noted that there are updated utility values using an Australian algorithm for the EUROQoL EQ-5D-5L that have been published and could have been used for alternative estimates. The PSCR included these alternative utility values in an updated version of the model. The PSCR stated that the differences between sources are marginal and results are not sensitive to the estimates used.

6.59 Disutility values were applied for RSV events for hospitalisation, emergency and outpatient visits. QALY decrements were deducted from accruals during each model cycle for these events. Values for such decrements (i.e., annual QALY loss due to RSV) were estimated using an area under the curve (AUC) approach with data from Falsey (2021)<sup>14</sup> and Mao (2022)<sup>15</sup>. The application of the disutility for hospitalisation had a small impact on the ICER (3%), that for outpatients was slightly larger (5%), while that for emergency room visits was negligible (0.5%).

6.60 Direct healthcare costs were derived as follows:

- Hospitalised cases were estimated using an average cost weight for AR-DRG items E62A and E62B from the NHCDC for 2020/21. Cost estimates for Q4 2020 were inflated to Q4 2023 values using the CPI Health Index. The evaluation considered that this was reasonable.
- Emergency department cases were estimated using an average cost weight for Australian Emergency Care Classification (AECC) items E0450A, E0450B, E0450C from the same collection (not specified in the submission). Cost estimates for Q4 2020 were inflated to Q4 2023 values using the CPI Health Index. The evaluation considered that this was reasonable.
- Outpatient management costs assumed an average of 1.5 standard consultations were required using MBS schedule fee for Item 23. Although the application of an outpatient fee 1.5 times the standard amount was not justified in the submission, the evaluation considered that it may be reasonable to assume more than one GP visit per medically attended RSV episode. The model was not sensitive to the assumed costs for outpatient visits.

6.61 Healthcare resource items and costs applied in the model included vaccine costs and costs for the management of acute RSV events are provided in Table 14.

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<sup>14</sup> Falsey AR, Walsh EE, Osborne RH, Vandendijck Y, Ren X, Witek J, Kang D, Chan E, Scott J, Ispas G. Comparative assessment of reported symptoms of influenza, respiratory syncytial virus, and human metapneumovirus infection during hospitalization and post-discharge assessed by Respiratory Intensity and Impact Questionnaire. *Influenza Other Respir Viruses*. 2022 Jan;16(1):79-89. doi: 10.1111/irv.12903.

<sup>15</sup> Mao Z, Li X, Korsten K, Bont L, Butler C, Wildenbeest J, Coenen S, Hens N, Bilcke J, Beutels P; RESCEU Investigators. Economic Burden and Health-Related Quality of Life of Respiratory Syncytial Virus and Influenza Infection in European Community-Dwelling Older Adults. *J Infect Dis*. 2022 Aug 12;226(Suppl 1):S87-S94. doi: 10.1093/infdis/jiac069.

**Table 14: Health care resource items and unit costs included in the economic evaluation**

Resource item	Unit cost	Source of unit cost	Usage in the economic evaluation	
			Proposed medicine	Comparator
<b>Medicines</b>				
RSVpreF	\$█	Proposed NIP price, Pre-filled syringe 0.5 mL	One-off cost for cohort entering the model	No vaccination
<b>Medical services</b>				
Administration cost	\$7	Submission assumption	One-off cost for cohort entering the model. Added to cost of RSVpreF	NA
GP visit	\$62.10	MBS Item 23 (Fee: 100%: \$42.85 <sup>a</sup> )	Applied to outpatient visits each cycle. Assumed cost is 1.5 times MBS fee (=41.4 <sup>a</sup> *1.5=\$62.10)	
Emergency visit	\$1,299.57	AECC items E0450A, E0450B, E0450C	Applied to emergency visits each cycle. Average cost weight for AECC items. Cost inflated \$1,153 to \$1,299.57.	
Hospital admission	\$8,542,43	AR-DRG E62A and E62B, NHCDC 2020/21	Applied to hospital admission each cycle. Average cost weight for AR-DRG items. Cost inflated to \$7,579 to \$8,542.43.	

Source: compiled during the evaluation using Table 3.6.1 p115 of the submission;

AECC = Australian Emergency Care Classification; AR-DRG = Australian Refined Diagnosis Related Groups; GP = general practitioner; MBS = Medicare Benefits Schedule; mL = millilitres; NA=not applicable; NIP = National Immunisation Program; NHCDC = National Hospital Cost Data Collection; RSVpreF = recombinant respiratory syncytial virus prefusion F protein vaccine.

<sup>a</sup> Value has changed to \$42.85 (\$42.85\*1.5=\$64.28<sup>a</sup>); however this was not updated during the evaluation.

6.62 Key drivers of the model are presented in Table 15.

**Table 15: Key drivers of the model based on the population aged ≥75 years**

Description	Method/Value	Impact
		<p><b>Base case (ICER \$ / QALY gained):</b></p> <ul style="list-style-type: none"> <li>• Adults aged ≥75 years: \$ [redacted] <sup>1</sup>.</li> <li>• Aboriginal and Torres Strait Islander adults aged 60 to 74 years: \$ [redacted] <sup>2</sup></li> <li>• Adults with at least one risk factor aged 60 to 74 years: \$ [redacted] <sup>2</sup></li> </ul>
Maximum age	100 years of age	<p>High, favours RSVpreF</p> <p>Reducing the maximum age to 90 years of age increased the ICER to:</p> <ul style="list-style-type: none"> <li>• Adults aged ≥75 years: \$ [redacted] <sup>3</sup>.</li> <li>• Aboriginal and Torres Strait Islander adults aged 60 to 74 years: \$ [redacted] <sup>2</sup></li> <li>• Adults with at least one risk factor aged 60 to 74 years: \$ [redacted] <sup>2</sup></li> </ul> <p>Reducing the maximum age to end at 87 years (i.e., analysis assuming 48 months; 83+4=87) increased the ICER to:</p> <ul style="list-style-type: none"> <li>• Adults aged ≥75 years: \$ [redacted] <sup>4</sup>.</li> <li>• Aboriginal and Torres Strait Islander adults aged 60 to 74 years: \$ [redacted] <sup>5</sup></li> <li>• Adults with at least one risk factor aged 60 to 74 years: \$ [redacted] <sup>6</sup></li> </ul>
Mortality rate for RSV	43 per 100,000 person-years using the Australian modelling study.	<p>High, favours RSVpreF</p> <p>Reducing to lower CI reported in Australian modelling study (12.03 per 100,000 person-years) increased the ICER to:</p> <ul style="list-style-type: none"> <li>• Adults aged ≥75 years: \$ [redacted] <sup>4</sup></li> <li>• Aboriginal and Torres Strait Islander adults aged 60 to 74 years: \$ [redacted] <sup>1</sup></li> <li>• Adults with at least one risk factor aged 60 to 74 years: \$ [redacted] <sup>3</sup></li> </ul> <p>Using ATAGI Advice: hCFR 4.22% increased the ICER to:</p> <ul style="list-style-type: none"> <li>• Adults aged ≥75 years: \$ [redacted] <sup>6</sup></li> <li>• Aboriginal and Torres Strait Islander adults aged 60 to 74 years: \$ [redacted] <sup>2</sup></li> <li>• Adults with at least one risk factor aged 60 to 74 years: \$ [redacted] <sup>5</sup></li> </ul>
VE peak for hospitalisation	84.6%	<p>High, favours RSVpreF</p> <p>Reducing to 50% increased the ICER to:</p> <ul style="list-style-type: none"> <li>• Adults aged ≥75 years: \$ [redacted] <sup>4</sup></li> <li>• Aboriginal and Torres Strait Islander adults aged 60 to 74 years: \$ [redacted] <sup>5</sup></li> <li>• Adults with at least one risk factor aged 60 to 74 years: \$ [redacted] <sup>5</sup></li> </ul>
Truncation of VE	48 months	<p>High, favours RSVpreF</p> <p>Reducing to 24 months increased the ICER to:</p> <ul style="list-style-type: none"> <li>• Adults aged ≥75 years: \$ [redacted] <sup>3</sup></li> <li>• Aboriginal and Torres Strait Islander adults aged 60 to 74 years: \$ [redacted] <sup>1</sup></li> <li>• Adults with at least one risk factor aged 60 to 74 years: \$ [redacted] <sup>1</sup></li> </ul>

Source: Compiled during the evaluation.

ATAGI = Australian Technical Advisory Group on Immunisation; CI = confidence interval; hCFR = hospital case fatality ratio; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; RSVpreF = recombinant respiratory syncytial virus prefusion F protein vaccine; VE = vaccine efficacy.

Table is based on adults aged ≥75 years, and not other populations.

The redacted values correspond to the following ranges:

<sup>1</sup> \$15,000 to < \$25,000

<sup>2</sup> \$5,000 to < \$15,000

<sup>3</sup> \$35,000 to < \$45,000

<sup>4</sup> \$55,000 to < \$75,000

<sup>5</sup> \$25,000 to < \$35,000

<sup>6</sup> \$45,000 to < \$55,000

6.63 Results of the economic evaluation are provided in Table 16.

**Table 16: Results of the economic evaluation**

	RSVpreF	No Vaccination	Increment
<b>Discounted (5%): aged ≥75 years</b>			
Costs	\$█	\$266.76	\$█
QALYs	5.5567	5.5516	0.0051
Incremental cost/ QALY gained			\$█ <sup>1</sup>
<b>Discounted (5%): Aboriginal or Torres Strait Islander, aged 60 to 74 years</b>			
Costs	\$█	\$661.63	\$█
QALYs	9.4299	9.4204	0.0095
Incremental cost/ QALY gained			\$█ <sup>2</sup>
<b>Discounted (5%): aged 60 to 74 HR</b>			
Costs	\$█	\$499.23	\$█
QALYs	10.6546	10.6440	0.0107
Incremental cost/ QALY gained			\$█ <sup>2</sup>

Source: Table 3.8.10, p122 of the submission.

QALYs = quality-adjusted life years. HR = high risk; RSVpreF = recombinant respiratory syncytial virus prefusion F protein vaccine.

The redacted values correspond to the following ranges:

<sup>1</sup> \$15,000 to < \$25,000

<sup>2</sup> \$5,000 to < \$15,000

6.64 Results of the weighted economic evaluation are provided in Table 17. This includes the results presented in the submission, the PSCR (see paragraph 6.70), and the ESC Advice (see paragraph 6.71). Table 17 also includes results of the economic evaluation for the two populations recommended by the PBAC (see section 7 PBAC outcome).

Table 17: Results of the economic evaluation (population weighted)

Scenario and Population	Weighting	Incr. costs	Incr. QALYs	ICER	Weighted ICER
<b>Submission</b>					
Adults aged ≥75 years	%	\$	0.0051	\$ <sup>1</sup>	\$ <sup>1</sup>
Adults with at least one risk factor aged 60-74 years	%	\$	0.0107	\$ <sup>2</sup>	
Aboriginal or Torres Strait Islander, aged 60-74 years	%	\$	0.0095	\$ <sup>2</sup>	
<b>PSCR revised base case</b>					
Adults aged ≥75 years	%	\$	0.0051	\$ <sup>1</sup>	\$ <sup>1</sup>
Aboriginal or Torres Strait Islander, aged 60-74 years	%	\$	0.0093	\$ <sup>2</sup>	
Adults with at least one risk factor aged 60-74 years	%	\$	0.0104	\$ <sup>2</sup>	
<b>PSCR Revised case with 3 year VE truncation</b>					
Adults aged ≥75 years	%	\$	0.0045	\$ <sup>3</sup>	\$ <sup>1</sup>
Aboriginal or Torres Strait Islander, aged 60-74 years	%	\$	0.0081	\$ <sup>2</sup>	
Adults with at least one risk factor aged 60-74 years	%	\$	0.0089	\$ <sup>2</sup>	
<b>ESC re-specified economic evaluation<sup>a</sup></b>					
Adults aged ≥75 years	%	\$	0.0015	\$ <sup>4</sup>	\$ <sup>6</sup>
Aboriginal or Torres Strait Islander, aged 60-74 years	%	\$	0.0036	\$ <sup>3</sup>	
Adults with at least one risk factor aged 60-74 years	%	\$	0.0027	\$ <sup>5</sup>	
<b>PBAC Advice (parameters adjusted according to ESC advice and ICER ≤\$15,000<sup>2</sup>/QALY)<sup>b</sup></b>					
Adults aged ≥75 years	%	\$	0.0015	\$ <sup>2</sup>	n/a
Aboriginal or Torres Strait Islander, aged 60-74 years	%	\$	0.0036	\$ <sup>2</sup>	n/a

Source: Table 3.8.11, p123 of the submission, and model re-specification provided by the sponsor in the PSCR, using the model submitted during the evaluation period. The results from the respecified model have not been evaluated.

a. Analyses performed for the ESC Advice using the evaluation model, see paragraph 6.71.

b. The PBAC considered that an ICER of no more than \$5,000 to < \$15,000/ QALY would be required to demonstrate cost-effectiveness for the proposed listing of RSVpreF as a vaccination to reduce the risk of RSV in 1) adults 75 years of age and above; and (2) Aboriginal and Torres Strait Islander peoples aged 60 to 74 years (see paragraphs 7.17 and 7.19).

QALYs = quality-adjusted life years, ICER = incremental cost-effectiveness ratio; Incr = incremental.

The redacted values correspond to the following ranges:

<sup>1</sup> \$15,000 to < \$25,000

<sup>2</sup> \$5,000 to < \$15,000

<sup>3</sup> \$25,000 to < \$35,000

<sup>4</sup> \$95,000 to < \$115,000

<sup>5</sup> \$55,000 to < \$75,000

<sup>6</sup> \$75,000 to < \$95,000

6.65 The results of key univariate sensitivity analyses for the population of adults aged ≥75 years are summarised in Table 18.

Table 18: Sensitivity analyses for population aged ≥75 years

Sensitivity analyses		Incr costs	Incr QALYs	ICER	% change from base case
<b>Base case (discounted) – aged ≥75 years</b>		\$█	0.0051	\$█ <sup>1</sup>	–
<b>Age horizon (base case: 100 years of age)</b>					
SA.1	Age 90 (low value)	\$█	0.0035	\$█ <sup>2</sup>	+█%
SA.2	4 years	\$█	0.0020	\$█ <sup>3</sup>	+█%
<b>Discount rate (base case: 5% for both costs and health outcomes)</b>					
SA.3	0% for both costs and health outcomes	\$█	0.0067	\$█ <sup>1</sup>	-█%
SA.4	3.5% for both costs and health outcomes	\$█	0.0055	\$█ <sup>1</sup>	-█%
<b>Mortality rate (base case: 43 per 100,000)</b>					
SA.5	12.03 per 100,000 (lower CI reported in Australian modelling study)	\$█	0.0017	\$█ <sup>3</sup>	+1█%
SA.6	In-hospital case fatality rate = 4.22%	\$█	0.0023	\$█ <sup>4</sup>	+█
<b>Case incidence rates (base case hospital: 398 per 100,000 person-years)</b>					
SA.7	AIHW hospital incidence for 75+ (384 per 100,000 person-years)	\$█	0.0051	\$█ <sup>1</sup>	+█%
<b>ATAGI advice (AIHW hospital incidence and In-hospital case fatality rate)</b>					
SA.8	AIHW hospital incidence (384 per 100,000) + hCFR (4.22%)	\$█	0.0022	\$█ <sup>3</sup>	+█%
<b>Vaccine efficacy peak (base case: outpatient (65.1%), emergency (70.4%), hospitalised (84.6%))</b>					
SA.9	Hospital = 50% (low value)	\$█	0.0027	\$█ <sup>3</sup>	+█%
SA.10	Hospital = 100% (high value)	\$█	0.0062	\$█ <sup>1</sup>	-█%
SA.11	Outpatient, emergency & hospital =50%	\$█	0.0026	\$█ <sup>3</sup>	+█%
SA.12	Outpatient, emergency & hospital =100%	\$█	0.0064	\$█ <sup>1</sup>	-█%
<b>Vaccine efficacy timepoints (base case: titration (1.51%), extrapolation (6 months) truncation (48 months))</b>					
SA.13	Truncation = 36 months	\$█	0.0044	\$█ <sup>5</sup>	+█%
SA.14	Truncation = 24 months	\$█	0.0034	\$█ <sup>2</sup>	+█%

Source: Table 3.9.3, p126 of the submission; 'ABRYSVO\_Older Adults\_CEA\_July' spreadsheet, with additional analyses performed during the evaluation.

AIHW = Australian Institute of Health and Welfare; CEA = cost effectiveness analysis; CI = confidence interval; ICER = incremental cost-effectiveness; Incr = incremental; QALY = quality-adjusted life year; SA = sensitivity analysis.

The redacted values correspond to the following ranges:

<sup>1</sup> \$15,000 to < \$25,000

<sup>2</sup> \$35,000 to < \$45,000

<sup>3</sup> \$55,000 to < \$75,000

<sup>4</sup> \$45,000 to < \$55,000

<sup>5</sup> \$25,000 to < \$35,000

6.66 The results of key univariate sensitivity analyses for the population of Aboriginal and Torres Strait Islander people aged 60 to 74 years are summarised in Table 19.

Table 19: Sensitivity analyses for population: Aboriginal and Torres Strait Islander people aged 60 to 74 years

Sensitivity analyses		Incr costs	Incr QALYs	ICER	% change from base case
<b>Base case (discounted) –Aboriginal and Torres Strait Islander adults aged 60 to 74 years</b>		\$█	0.010	\$█ <sup>1</sup>	–
<b>Maximum age/time horizon (base case: 100 years of age)</b>					
SA.1	Age 90 (low value)	\$█	0.0090	\$█ <sup>1</sup>	+█%
SA.2	4 years	\$█	0.0025	\$█ <sup>2</sup>	+█%
<b>Discount rate (base case: 5% for both costs and health outcomes)</b>					
SA.3	0% for both costs and health outcomes	\$█	0.0158	\$█ <sup>3</sup>	–█%
SA.4	3.5% for both costs and health outcomes	\$█	0.0109	\$█ <sup>1</sup>	–█%
<b>Mortality rate (base case: 43 per 100,000 person-years)</b>					
SA.5	12.03 per 100,000 (lower CI reported in Australian modelling study)	\$█	0.0031	\$█ <sup>4</sup>	+█%
SA.6	In-hospital case fatality rate = 4.22%	\$█	0.0059	\$█ <sup>1</sup>	+█%
<b>Case incidence rates (base case hospital: 597 per 100,000 person-years)</b>					
SA.7	AIHW hospital incidence for 75+ multiplied by 1.5 (576 per 100,000 person-years)	\$█	0.0095	\$█ <sup>1</sup>	+█%
<b>ATAGI advice (AIHW hospital incidence and In-hospital case fatality rate)</b>					
SA.8	AIHW hospital incidence (576 per 100,000) + hCFR (4.22%)	\$█	0.0057	\$█ <sup>1</sup>	+█%
<b>Vaccine efficacy peak (base case: outpatient (65.1%), emergency (70.4%), hospitalised (84.6%))</b>					
SA.9	Hospital = 50% (low value)	\$█	0.0048	\$█ <sup>2</sup>	+█%
SA.10	Hospital = 100% (high value)	\$█	0.0116	\$█ <sup>3</sup>	–█%
<b>Vaccine efficacy timepoints (base case: titration (1.51%), extrapolation (6 months) truncation (48 months))</b>					
SA.11	Truncation = 36 months	\$█	0.0081	\$█ <sup>1</sup>	+█%
SA.12	Truncation = 24 months <sup>a</sup>	\$█	0.0061	\$█ <sup>4</sup>	+█%

Source: Table 3.9.5, p128 of the submission; 'ABRYSVO\_Older Adults\_CEA\_July' spreadsheet, with additional analyses performed during the evaluation.

AIHW = Australian Institute of Health and Welfare; CEA = cost effectiveness analysis; ICER = incremental cost-effectiveness; Incr = incremental; QALY = quality-adjusted life year; SA = sensitivity analysis.

The redacted values correspond to the following ranges:

<sup>1</sup> \$5,000 to < \$15,000

<sup>2</sup> \$25,000 to < \$35,000

<sup>3</sup> \$0 to < \$5,000

<sup>4</sup> \$15,000 to < \$25,000

6.67 The results of key univariate sensitivity analyses for the population of adults with at least one risk factor aged 60 to 74 years are summarised in Table 20.

Table 20: Sensitivity analyses for population: adults with at least one risk factor aged 60 to 74 years

Sensitivity analyses		Incr costs	Incr QALYs	ICER	% change from base case
<b>Base case (discounted) – adults with at least one risk factor aged 60 to 74 years</b>		\$█	0.011	\$█ <sup>1</sup>	–
<b>Maximum age/time horizon (base case: 100 years of age)</b>					
SA.1	Age 90 (low value)	\$█	0.0101	\$█ <sup>1</sup>	+█%
SA.2	4 years	\$█	0.0024	\$█ <sup>2</sup>	–█%
<b>Discount rate (base case: 5% for both costs and health outcomes)</b>					
SA.3	0% for both costs and health outcomes	\$█	0.0179	\$█ <sup>1</sup>	–█%
SA.4	3.5% for both costs and health outcomes	\$█	0.0123	\$█ <sup>1</sup>	–█%
<b>Mortality rate (base case: 43 per 100,000)</b>					
SA.5	12.03 per 100,000 (lower CI reported in Australian modelling study)	\$█	0.0033	\$█ <sup>3</sup>	+█%
SA.6	In-hospital case fatality rate = 4.22%	\$█	0.0044	\$█ <sup>4</sup>	+█%
SA.7	In-hospital case fatality rate = 3.83%	\$█	0.0041	\$█ <sup>4</sup>	+█%
<b>Case incidence rates (base case hospital: 398 per 100,000 person-years)</b>					
SA.8	AIHW hospital incidence for 75+(384 per 100,000 person-years)	\$█	0.0106	\$█ <sup>1</sup>	+█%
SA.9	AIHW hospital incidence for 60+(197 per 100,000 person-years)	\$█	0.0104	\$█ <sup>5</sup>	+█%
SA.10	Australian modelling study for 60 to 74 years (107 per 100,000 person-years)	\$█	0.0103	\$█ <sup>5</sup>	+█%
<b>AIHW hospital incidence and In-hospital case fatality rate</b>					
SA.11	AIHW hospital incidence (384 per 100,000) + hCFR (4.22%)	\$█	0.0043	\$█ <sup>4</sup>	+█%
SA.12	Alternative: AIHW hospital incidence (197 per 100,000) + hCFR (3.83%)	\$█	0.0020	\$█ <sup>6</sup>	+█%
<b>Vaccine efficacy peak (base case: outpatient (65.1%), emergency (70.4%), hospitalised (84.6%))</b>					
SA.13	Hospital = 50% (low value)	\$█	0.0053	\$█ <sup>4</sup>	+█%
SA.14	Hospital = 100% (high value)	\$█	0.0130	\$█ <sup>1</sup>	–█%
<b>Vaccine efficacy timepoints (base case: titration (1.51%), extrapolation (6 months) truncation (48 months))</b>					
SA.15	Truncation = 36 months	\$█	0.0090	\$█ <sup>1</sup>	+█%
SA.16	Truncation = 24 months <sup>a</sup>	\$█	0.0067	\$█ <sup>5</sup>	+█%
<b>Exploratory analysis</b>					
SA.17	Alternative: AIHW hospital incidence (197 per 100,000) + hCFR (3.83%) + truncation 2 years	\$█	0.0013	\$█ <sup>7</sup>	+█%

Source: Table 3.9.4, p126 of the submission; 'ABRYSVO\_Older Adults\_CEA\_July' spreadsheet, with additional analyses performed during the evaluation.

AIHW = Australian Institute of Health and Welfare; CEA = cost effectiveness analysis; ICER = incremental cost-effectiveness; Incr = incremental; QALY = quality-adjusted life year; SA = sensitivity analysis.

The redacted values correspond to the following ranges:

<sup>1</sup> \$5,000 to < \$15,000

<sup>2</sup> \$45,000 to < \$55,000

<sup>3</sup> \$35,000 to < \$45,000

<sup>4</sup> \$25,000 to < \$35,000

<sup>5</sup> \$15,000 to < \$25,000

<sup>6</sup> \$95,000 to < \$115,000

<sup>7</sup> \$135,000 to < \$155,000

6.68 The submission presented scenario analyses for alternative populations of adults aged ≥65 years, aged ≥70 years, and aged ≥80 years. Based on the different scenarios, the ESC noted that the key drivers of the model were:

- the age-based eligibility criterion for vaccination;
  - ATAGI's Advice using the AIHW hospital incidence and case fatality rates;
  - the duration of vaccine effectiveness.
- 6.69 For the scenario using the AIHW hospitalisation rate (384 per 100,000 person-years applied to adults aged  $\geq 75$  years and adults with at least one risk factor aged 60 to 74 years; 576 per 100,000 person-years applied to adults aged  $\geq 60$  years) combined with the mortality rate adjusted using the hCFR of 4.22%, the ICER increased to:
- \$55,000 to < \$75,000 in adults aged  $\geq 75$  years (from \$15,000 to < \$25,000, + $\frac{1}{3}$ );
  - \$5,000 to < \$15,000 in Aboriginal and Torres Strait Islander people aged 60 to 74 years (from \$5,000 to < \$15,000, + $\frac{1}{3}$ );
  - \$25,000 to < \$35,000 in adults with at least one risk factor aged 60 to 74 years (from \$5,000 to < \$15,000, + $\frac{1}{3}$ ).
- 6.70 The PSCR stated that the model provided during the evaluation period, containing corrections to the waning estimates, should be used in place of the originally submitted model. Using this model, the PSCR provided a re-specified base case and 3 year vaccine efficacy truncation. The updated parameters for each age/risk-based group were:
- the ATAGI-recommended change to the source for estimated VE against RSV-outpatients (VE against RSV-LRTI  $\geq 2$  symptoms for VE relating to outpatient visits (VE: 65.1%; based on 58 cases in Season 1));
  - the evaluator-recommended change in the source for population normal utility values (an Australian algorithm for the EUROQoL EQ-5D-5L);
  - the duration of vaccine effectiveness of 3 years as an additional scenario (4 years base case), calculated using the updated model.

The ICERs for the PSCR-respecified model are summarised in Table 17 above.

- 6.71 The ESC considered that a reasonable model re-specification (using the first model submitted for evaluation) would be based on use of AIHW hospitalisation rate and hCFR and having VE truncated at 2 years to account for uncertain duration of protection, and therefore involving the following changes to parameters:
- the AIHW hospitalisation rate of 384 per 100,000 person-years (adults 75 years and above) and 576 per 100,000 person-years for Aboriginal and Torres Strait Islander adults aged 60 to 74 years;
  - the mortality rate adjusted using the case fatality rate ratio of 4.22%;
  - the duration of VE of 2 years.

The ICERs for the ESC re-specified model have been added to Table 17 above.

**RSVpreF cost per person**

6.72 The proposed cost per dose of RSVpreF was \$[REDACTED]. The submission requested a single dose per patient for NIP listing. The need for revaccination with RSVpreF for the proposed populations of older adults has not yet been established (paragraph 3.4).

**Estimated PBS usage & financial implications**

6.73 This submission was not considered by DUSC.

6.74 The submission used an epidemiological approach to estimate the extent of use and financial impact of reimbursing a single dose of RSVpreF for:

1) adults aged  $\geq 75$  years;

2) Aboriginal and Torres Strait Islander peoples aged 60 - 74 years;

3) adults with at least one identified risk factor aged 60 - 74 years.

6.75 Key inputs used by the submission are presented in Table 21.

**Table 21: Key inputs for financial estimates**

Parameter	Value applied and source	Evaluation comment
Incidence and prevalent population	<p><u>Incident population</u>: people turning 75 years or 60 years old each year</p> <p><u>Prevalent population</u>: people aged &gt;75y, people with a risk condition aged 61-74y, and Aboriginal and Torres Strait Islander people aged 61-74y.</p>	It may have been more straightforward to include all individuals as part of the Year 1 prevalent pool (given that the same uptake rate is applied to prevalent and incident populations in Year 1, there is no impact anticipated on use).
Size of eligible population		
Adults aged ≥75 years	ABS 3222.0 - Population Projections, Australia, 2012 (base) to 2030 Series B	The submission applied outdated estimates from 2016 for population projection reported by the ABS. The most recent ABS statistics for Series 3222.0 use 2022 as the base year <sup>16</sup> (ABS 2023). Use of the older ABS projections underestimated the incidence population and the financial impact. This was not updated during the evaluation, however updated estimates were provided in the PSCR.
Aboriginal and Torres Strait Islander people aged 60 to 74 years	ABS 3238.0, Series B and Estimates of Aboriginal and Torres Strait Islander Australians, Final Census 2021.	Use of ABS data as the source is reasonable. There is a more recent update of that data; ABS Series 3238.0 used 2011 as the base year <sup>17</sup> but this was not released until 24 July 2024, after the submission cut-off date. These estimates were not updated during the evaluation.
Adults with at least one identified risk factor aged 60 to 74 years	<ul style="list-style-type: none"> <li>Proportion of adults with at least one identified risk factor aged 60 - 74 years; ABS, Customised report, 2024 (Attachment 1 of the submission)</li> <li>ABS 3222.0 - Population Projections, Australia, 2012 (base) to 2030 Series B</li> </ul>	Source is reasonable. The customised report did not include persons with obesity, which has recently been listed as medical risk factor for severe RSV, and the submission did not justify exclusion for this condition. Sensitivity analyses were conducted by the submission using alternative estimates: 25% and 50%.
Uptake rate	<ul style="list-style-type: none"> <li>Adults aged ≥ 75 years: █% in Year 1 increasing to █% in Year 3.</li> <li>Aboriginal and Torres Strait Islander peoples aged 60 years, and Adults at high-risk aged 60 years: █% in Year 1 increasing to █% in Year 3.</li> </ul> <p>Based on</p> <ul style="list-style-type: none"> <li>Uptake based on uptake for influenza vaccine, NCIRS, 2021/2022.</li> <li>ATAGI Pre-Submission Advice to PBAC, December 2023 (p54).</li> </ul>	These uptake rates were applied to persons that would be eligible for RSVpreF turning 75 years or 60 years old each year. The same uptake rate is applied to prevalent and incident populations in Year 1.
Costs		
RSVpreF Dose	Single dose of RSVpreF	This is consistent with the requested listing and the economic evaluation.
MBS item number 3, GP consultation (Level A)	<p>Marginal administration costs: \$7 GP consultation (Level A) MBS item number 3, benefit 100%, fee \$19.60.</p> <p>Submission assumed cost is approx. 0.36 (= \$7/\$19.60) of a level A consultation per person.</p>	This cost was proposed as a marginal administration cost. This assumption is consistent with the economic modelling.

Source: Table 4.1.1 p137, Table 4.2.3 p140, p147 of the submission; Workbook provided by the submission UCM-Release-3-Workbook-RSV OA\_ABRYSVO\_July 2024.xlsx .

ABS=Australian Bureau of Statistics; ATAGI=Australian Technical Advisory Group on Immunisation; GP = general practitioner; MBS=Medical Benefits Schedule; NCIRS = National Centre for Immunisation Research and Surveillance; NIP=National Immunisation Program; PBAC=Pharmaceutical Benefit Advisory Committee; PBS=Pharmaceutical Benefits Scheme; RSV = respiratory syncytial virus; RSVpreF = recombinant RSV prefusion F protein vaccine; y = years.

- 6.76 The derivation of the vaccinated population and the net financial implications to the NIP and MBS are presented in Table 22.

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<sup>16</sup> ABS Population projections, reference period 2022 (base) to 2071, URL: <https://www.abs.gov.au/statistics/people/population/population-projections-australia/latest-release>

<sup>17</sup> ABS Estimates and Projections, Aboriginal and Torres Strait Islander Australians, Reference period 2011 to 2031, URL: <https://www.abs.gov.au/statistics/people/aboriginal-and-torres-strait-islander-peoples/estimates-and-projections-aboriginal-and-torres-strait-islander-australians/latest-release>.

**Table 22: Estimated use and financial implications**

	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
<b>Estimated extent of use</b>						
Total people vaccinated	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Adults ≥75 years	█ <sup>4</sup>	█ <sup>5</sup>	█ <sup>4</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
Adults with a risk condition aged 60-74 years	█ <sup>8</sup>	█ <sup>3</sup>	█ <sup>6</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>
Aboriginal and Torres Strait Islander peoples aged 60-74 years	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>10</sup>	█ <sup>10</sup>	█ <sup>10</sup>
<b>Net financial implications</b>						
Net cost to NIP, total	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>
Adults ≥75 years	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>13</sup>	\$█ <sup>13</sup>	\$█ <sup>13</sup>
Adults with a risk condition aged 60-74 years	\$█ <sup>14</sup>	\$█ <sup>15</sup>	\$█ <sup>16</sup>	\$█ <sup>17</sup>	\$█ <sup>17</sup>	\$█ <sup>17</sup>
Aboriginal and Torres Strait Islander peoples aged 60-74 years	\$█ <sup>18</sup>	\$█ <sup>18</sup>	\$█ <sup>18</sup>	\$█ <sup>18</sup>	\$█ <sup>18</sup>	\$█ <sup>18</sup>
<b>Net cost to MBS</b>	\$█ <sup>18</sup>	\$█ <sup>18</sup>	\$█ <sup>18</sup>	\$█ <sup>18</sup>	\$█ <sup>18</sup>	\$█ <sup>18</sup>
Net cost to Government Health Budget	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>11</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>
<b>Updated net cost Net cost to Government Health Budget as reported in PSCR</b>						
Updated (PSCR) estimate <sup>a</sup>	\$█ <sup>11</sup>	\$█ <sup>19</sup>	\$█ <sup>11</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>	\$█ <sup>12</sup>
% change	2%	3%	4%	4%	5%	5%

Source: Table 4.2.7 p144, Table 4.4.1 p146, Table 4.5.2 p148 of the submission, UCM-Release-3-Workbook\_RSV OA\_ABRYSVO\_July 2024\_updated ABS.xlsx.

a. Updated utilisation estimates for the forecast period (2025-2030) were provided in the PSCR using the population projections from the latest release of the ABS 3222.0 (Series B, Table B9).

MBS = Medical Benefit Scheme; NIP = National Immunisation Program

The redacted values correspond to the following ranges:

- <sup>1</sup> 900,000 to < 1,000,000
- <sup>2</sup> 700,000 to < 800,000
- <sup>3</sup> 200,000 to < 300,000
- <sup>4</sup> 500,000 to < 600,000
- <sup>5</sup> 600,000 to < 700,000
- <sup>6</sup> 100,000 to < 200,000
- <sup>7</sup> 70,000 to < 80,000
- <sup>8</sup> 300,000 to < 400,000
- <sup>9</sup> 10,000 to < 20,000
- <sup>10</sup> 5,000 to < 10,000
- <sup>11</sup> \$100 million to < \$200 million
- <sup>12</sup> \$40 million to < \$50 million
- <sup>13</sup> \$20 million to < \$30 million
- <sup>14</sup> \$70 million to < \$80 million
- <sup>15</sup> \$50 million to < \$60 million
- <sup>16</sup> \$30 million to < \$40 million
- <sup>17</sup> \$10 million to < \$20 million
- <sup>18</sup> \$0 to < \$10 million
- <sup>19</sup> \$200 to < \$300 million

**6.77** The evaluation noted the following points:

- The submission applied outdated estimates from 2012 (base) for population projection reported by the ABS. The most recent ABS statistics for Series 3222.0 use 2022 as the base year (ABS 2023). Use of the older ABS projections

underestimated the incidence population and the financial impact. This was not updated during the evaluation. The PSCR provided estimates based on the latest release of the ABS population projections (Series 3222.0). The PSCR stated that the revised estimates represent a modest (2-5%) increase compared to the submission estimates.

- The main sources of uncertainty relate to the number of eligible patients and uptake rates. The net NIP cost is sensitive to parameters for the prevalence of people with at least one risk condition and assumed uptake.
- The estimate derived in the ABS customised report did not include persons with obesity. Increasing the proportion of people aged 60 to 74 years with at least one risk condition from 35% to 50% increased the total cost over 6 years by 12% to \$700 million to < \$800 million (Table 23). The PSCR stated that obesity was recently added to the list of risk factors in the clinical recommendations for RSV vaccines in the AIH RSV chapter (paragraph 3.2). The PSCR noted that there will be overlap of obesity with other identified risk conditions for severe RSV disease and further analyses of the ABS National Health Survey data for proportion of adults aged 60-74 years with at least one risk condition, including obesity, can be commissioned. The ESC noted the potential overlap, however considered that including obesity as a risk factor would likely increase the financial impact. The ESC also noted that the omission of obesity from the list of risk conditions for the NIP listing would be consistent with influenza, noting that the AIH<sup>18</sup> lists obesity as a risk factor for influenza and severe outcomes, but obesity is not a NIP-funded condition for influenza vaccination. The pre-PBAC response stated that the submission proposed financial estimates in line with the ATAGI advice received prior to the submission, and that the financial estimates can be adjusted, if required, if there is advice to include obesity as a risk factor for the NIP.
- Assuming peak vaccine uptake increased from  $\frac{1}{2}$ % to  $\frac{1}{2}$ % in Years 3 to 6 for the population of adults aged  $\geq 75$  years increased the total costs over 6 years by 9% to \$700 million to < \$800 million .

6.78 Based on the updated estimates in the PSCR, the overall cost of the program was estimated at \$100 million to < \$200 million in Year 1, increasing to \$200 million to < \$300 million in Year 2, followed by \$100 million to < \$200 million in Year 3 before declining in subsequent years. The total cost to NIP of listing RSVpreF over 6 years was estimated to be \$700 million to < \$800 million.

6.79 A summary of the sensitivity analyses for the financial implications to the Government Health Budget is provided in Table 23.

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<sup>18</sup> <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/influenza-flu>

Table 23: Results of sensitivity analyses

	Total cost Years 1 to 6	% change from base case
<b>Base case (total cost to Government – NIP and MBS)</b>	\$ <sup>1</sup>	-
<b>Prevalence of risk conditions (base case: 35%)</b>		
Lower limit: 25%	\$ <sup>1</sup>	-8.0%
Upper limit: 50%	\$ <sup>2</sup>	12.0%
<b>Peak vaccine uptake: ≥ 75 years (base case: Age = 75 years; Year 1, █%; Year 2, █%; Year 3, █%; Age &gt; 75 years; Year 1 = █%; Year 2, █%; Year 3, █%)</b>		
Lower limit: Age=75y, Year 3, █%; Age>75y, Year 3, █%	\$ <sup>3</sup>	-34.1%
Upper limit: Age=75y, Year 3, █%; Age>75y, Year 3, █%	\$ <sup>2</sup>	9.0%
<b>Peak vaccine uptake: 60-74 years with a risk condition (base case: Age = 60 years; Year 1, █%; Year 2, █%; Year 3, █%; Age 61-74 years; Year 1 = █%; Year 2, █%; Year 3, █%)</b>		
Lower limit: Age=60y, Year 3, █%; Age=61-74y, Year 3, █%	\$ <sup>4</sup>	-13.1%
Upper limit: Age=60y, Year 3, █%; Age=61-74y, Year 3, █%	\$ <sup>2</sup>	8.5%
<b>Uptake rates: Aboriginal and Torres Strait Islander peoples aged 60-74 years (base case: Age = 60 years; Year 1, █%; Year 2, █%; Year 3, █%; Age 61-74 years; Year 1 = █%; Year 2, █%; Year 3, █%)</b>		
Lower limit: Age=60y, Year 3, █%; Age=61-74y, Year 3, █%	\$ <sup>1</sup>	-0.7%
Upper limit: Age=60y, Year 3, █%; Age=61-74y, Year 3, █%	\$ <sup>1</sup>	0.4%
<b>MBS administration fee (base case: assumed 0.36 services per patient = \$7.00)</b>		
Upper limit (Assume 0.71; \$14)	\$ <sup>1</sup>	2.7%

Source: Table 4.6.2 p150 of the submission; UCM-Release-3-Workbook-RSV OA\_ABRYSVO\_July 2024.xlsx

MBS = medical benefit scheme; y = years

The redacted values correspond to the following ranges:

<sup>1</sup> \$600 million to < \$700 million

<sup>2</sup> \$700 million to < \$800 million

<sup>3</sup> \$400 million to < \$500 million

<sup>4</sup> \$500 million to < \$600 million

## Quality Use of Medicines

6.80 The submission stated that educational and pharmacovigilance activities will be conducted to support the quality use of medicines.

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

## 7 PBAC Outcome

7.1 The PBAC recommended that respiratory syncytial virus vaccine (Abrysvo<sup>®</sup>, RSVpreF) 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) for adults 75 years of age and above, and for Aboriginal and Torres Strait Islander peoples aged 60 to 74 years. The PBAC considered that the vaccine was superior to no vaccine in terms of effectiveness with an acceptable safety profile, however the duration and magnitude of protection in the requested populations was uncertain. The PBAC advised that inputs for the economic evaluation relating to the duration of protection, and the incidence of hospitalisations due to RSV and associated mortality should be revised, and that RSVpreF would be cost-effective with an incremental cost-effectiveness ratio (ICER) of no more than \$5,000 to < \$15,000 per QALY gained. The PBAC did not recommend NIP listing for adults aged 60 to 74 years with at least one risk factor for severe RSV disease (the third population that was supported by ATAGI)

because it considered that the economic evaluation did not provide a robust estimate of cost-effectiveness for this population, with the baseline risks and benefits unclear, but likely overestimated; with uncertainty around the total financial implications in this group. The PBAC advised that a new submission would be required to assess this population.

- 7.2 The PBAC was satisfied that RSVpreF provides, for some patients, a significant improvement in efficacy over standard of care (no vaccine).
- 7.3 The PBAC recommended the listing of RSVpreF on the basis that it should be available through the National Immunisation Program (NIP) under the circumstances specified in Section 8 below (adults aged 75 years and above, and Aboriginal and Torres Strait Islander peoples aged 60 to 74 years). The PBAC did not recommend listing of RSVpreF for adults aged 60 to 74 years with at least one risk factor for severe RSV disease.
- 7.4 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 the RSVpreF vaccine and the RSVPreF3 OA (Arexvy) vaccine that was considered by the PBAC in July 2024 (paragraph 5.3).
- 7.5 Consistent with its previous advice, the PBAC considered there is a high clinical need for vaccines, such as RSVpreF vaccine, to reduce the risk of RSV in older adults, especially those aged over 75 years, First Nations adults, and those vulnerable due to existing medical conditions (paragraph 7.4, RSVPreF3 OA Public Summary PSD, July 2024). 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 RSVpreF vaccine was supported by the consumer comments received for this submission.
- 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 ATAGI advice supported NIP listing for three populations, that is all adults aged  $\geq 75$  years, Aboriginal and Torres Strait Islander peoples aged 60 to 74 years; and people aged 60 to 74 years with increased risk of severe RSV disease due to pre-defined risk conditions, and consistent with this advice the submission had requested NIP listing for the three populations which described a higher clinical need compared with the TGA-registered population of adults aged 60 years and above. The PBAC considered there was a high clinical need for an effective vaccine for the three populations supported by the ATAGI, however considered that a new submission would be required to demonstrate cost-effectiveness for people aged 60-74 years at increased risk of severe RSV disease (see paragraph 7.23).
- 7.7 The PBAC noted that RSVpreF is an unadjuvanted bivalent vaccine composed of stable RSV prefusion F antigens representing the 2 major virus subgroups (RSV-A and RSV-B).

Prefusion F is the active form of the protein and is capable of mediating fusion of virus and host cell membranes during cell entry. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects against RSV-associated LRTI.

- 7.8 The PBAC accepted the proposed clinical place for RSVpreF as a single dose for the at-risk populations proposed by the submission.
- 7.9 The PBAC noted that listing was requested for a single dose of RSVpreF, and the need for revaccination has not been established. The PBAC noted that the sponsor is intending to seek ATAGI advice on the appropriate revaccination timeframe in older adults when additional data are available (paragraph 3.6). The PBAC noted that if revaccination is requested in the future, this would impact cost-effectiveness and financial implications, and would require further PBAC consideration.
- 7.10 The PBAC accepted the submission's nomination of 'no vaccine' as the main comparator, given that there is neither a vaccine available on the NIP nor a specific RSV treatment currently funded for older adults. The PBAC noted this aligned with ATAGI advice.
- 7.11 The pivotal randomised trial for the clinical analysis (RENOIR) compared the efficacy and safety of RSVpreF to placebo in adults  $\geq 60$  years. A supportive trial (Study 1006) provided evidence for the immunogenicity and safety of RSVpreF coadministered with a seasonal inactivated influenza vaccine in adults  $\geq 65$  years compared to placebo.
- 7.12 Based on evidence from the RENOIR trial, the PBAC considered that RSVpreF vaccine was an effective vaccine for RSV in adults  $\geq 60$  years. The PBAC considered that a superiority claim was adequately supported in that the efficacy outcomes (preventing LRTI for patients with  $\geq 2$  and  $\geq 3$  symptoms) and preventing RSV-ARI in RENOIR were demonstrated for the population of adults aged  $\geq 60$  years for the duration of follow-up in the trial. However, the PBAC noted that a significant reduction in severe RSV-LRTI was not demonstrated in the overall trial population in RENOIR. The PBAC considered there was insufficient evidence to determine the impact of RSVpreF on this outcome (paragraph 6.35).
- 7.13 The PBAC noted there was a decline in VE by the EOS2 for RSVpreF in the RENOIR study, which was evident in the evaluable efficacy population (Table 4) and subgroup analyses (Table 9). The PBAC noted ATAGI's advice that there are no correlates of protection, and no evidence to date, to inform the rate of VE waning after season two. The PBAC noted that vaccine efficacy decreased over time and considered that waning is a key area of uncertainty.
- 7.14 The PBAC noted additional uncertainty in relation to efficacy of RSVpreF in the populations for which listing on the NIP was requested, noting the smaller number of events in the subgroups compared with the overall study sample and that no information was available regarding differential immune response or safety in Aboriginal and Torres Strait Island adults (paragraph 6.38).

- 7.15 Overall, the PBAC considered that a claim of superior comparative effectiveness was reasonable for the comparison between RSVpreF and no vaccination based on the RENOIR trial (patients 60 years and older) noting that the RENOIR trial was not powered to detect statistically significant differences between the arms for subgroup analyses. The PBAC considered that RSVpreF has an inferior but acceptable safety profile compared to placebo.

**Adults aged 75 years and above**

- 7.16 The PBAC noted the key issues raised by the evaluation and the ESC for determining the cost-effectiveness of RSVpreF related to the VE for RSV hospitalisations and duration of effect, RSV incidence and associated mortality. The PBAC noted that the base case economic analysis presented in submission used:

- a VE for preventing RSV hospitalisations of 84.6% based on that observed in the RENOIR trial for the outcome ‘first episode of medically-attended RSV-LRTI with  $\geq 3$  symptoms’. The PBAC considered that the applicability of this outcome to RSV hospitalisations was unclear given, as noted by ATAGI, only two people met the severe RSV-LRTI criteria in RENOIR (requiring hospitalisation, new/increased oxygen supplementation or new/increased mechanical ventilation). ATAGI noted that the remainder of the cases with RSV-LRTI  $\geq 3$  symptoms presumably only sought emergency or outpatient care or did not require increased care and may not be ‘severe’ (paragraph 6.48). The PBAC noted that the estimate of 84.6% was based on 2 cases of RSV in the RSVpreF arm versus 13 cases in the placebo arm, and as a result the 95% CI for this estimate was wide. The PBAC further noted that the point estimate of 86.4% was substantially higher than that for other outcomes based on more cases (70.4% for RSV-LRTI with  $\geq 2$  symptoms based on a total of 35 cases, 65.1% for RSV-ARI based on a total of 58 cases; Table 6). Although the PBAC considered it may be reasonable to use the point estimate of 84.6% in the model (when efficacy is assumed over a 2 year period only, see below), the PBAC noted the ICER was sensitive to this estimate, and to the assumed waning profile.
- a duration of protection of 4 years based on the RENOIR study with an average follow up of 1.4 years (16.4 months). The PBAC noted there was a decline in VE in the second season and that ATAGI noted in its advice that there are no correlates of protection, and no evidence to date, to inform the rate of VE waning after the second season. The PBAC noted that the need and timing for revaccination with RSVpreF has not yet been established, and revaccination would not only impact on the cost-effectiveness of RSVpreF, but it would have a very large impact on the financial estimates. In this context, together with the uncertain VE estimates applied in the model, the PBAC agreed with ESC and considered the vaccine efficacy should be truncated at 2 years.
- the Australian Modelling Study to estimate the incidence of hospitalisation in adults aged 75 years and above (398 per 100,000 person-years). The PBAC noted that the Australian modelling study was not available for ATAGI review when the

sponsor sought pre-submission advice, however the estimate derived from the study (398 per 100,000 person-years) was similar to the estimate derived from ATAGI's advice (384 per 100,000 person-years). The PBAC noted that other available estimates were lower (Table 12), but considered it was reasonable to use the estimate supported by ATAGI (384 per 100,000 person-years).

- the Australian Modelling Study to estimate a RSV mortality rate of 43 per 100,000 person-years; equivalent to 10.8% of hospitalisations per month. The PBAC noted this estimate appeared high and considered the estimate based on ATAGI's advice (an in-hospital case fatality rate (hCFR) of 4.22%) to be more plausible.

7.17 The PBAC noted applying the revisions outlined in paragraph 7.16 to the economic model increased the ICER from \$15,000 to < \$25,000 to \$95,000 to < \$115,000 per QALY gained, and considered these inputs were appropriate (hospitalisation rate of 384 per 100,000 person-years, mortality rate adjusted using the case fatality rate ratio of 4.22%; and duration of VE of 2 years). The PBAC advised that the vaccine would be acceptably cost-effective if the ICER for the revised economic model was no more than \$5,000 to < \$15,000 per QALY for this population.

#### **Aboriginal and Torres Strait Islander peoples aged 60 to 74 years**

7.18 The PBAC noted that to reflect the increased burden of RSV disease in Aboriginal and Torres Strait Islander people, the incidence of RSV hospitalisation applied in the economic model was 1.5 times the rate for people aged  $\geq 75$  years and the magnitude of the increase was consistent with advice provided by ATAGI. The PBAC noted based on an incidence of 384 per 100,000 person years for people aged  $\geq 75$  years, the incidence for Aboriginal and Torres Strait Islander people was 576 per 100,000 person-years (i.e.,  $384 \times 1.5 = 576$ ). Although uncertain, the PBAC considered the assumed incidence of hospitalisations due to RSV to be reasonable in the context of the relatively small population size. As for the population aged 75 years, the PBAC agreed with ESC and considered the vaccine efficacy should be truncated at 2 years, and the hCFR of 4.22% should be applied to estimate mortality in the model.

7.19 The PBAC noted applying the revisions outlined in paragraph 7.18 to the economic model increased the ICER from \$5,000 to < \$15,000 to \$55,000 to < \$75,000 per QALY gained, and considered these inputs were appropriate (hospitalisation rate of 576 per 100,000 person-years, mortality rate adjusted using the case fatality rate ratio of 4.22%; and duration of VE of 2 years). The PBAC advised that the vaccine would be acceptably cost-effective if the ICER for the revised economic model was no more than \$5,000 to < \$15,000 per QALY for this population.

#### **Adults aged 60 to 74 years with at least one risk factor for severe RSV disease**

7.20 The PBAC noted that the population of adults with at least one risk factor aged 60 to 74 years was heterogenous, with a range of different risk factors proposed (see paragraph 3.2). The PBAC also noted that it was uncertain whether obesity should be included as a risk factor for NIP eligibility (see paragraph 6.77). With regard to the

hospitalisation rate for the population, the PBAC noted that the submission's approach was to apply the same rate as for adults aged  $\geq 75$  years, however this appeared to be overestimated, based on available data including the AIHW data and the Australian modelling study (see paragraph 6.54). Similarly, the submission had applied the same mortality rate for this population as for adults aged  $\geq 75$  years, however alternative estimates were available for younger cohorts (Table 13). The PBAC noted that sensitivity analyses testing the impact of alternative inputs resulted in large increases in the ICER (Table 20). The PBAC considered this extent of uncertainty was not acceptable in the context of the large size of this population. The PBAC considered that it would be informative to see a range of ICERs for different subgroups within this population. The PBAC considered that treating this population as a single cohort was a simplification, and that on average, the submission's approach likely overestimated both the baseline risks and the benefits of the vaccine given the submission's approach to estimate life expectancy in this population using the standard Australian Bureau of Statistics (ABS) life tables for 2019-2021 (which reflect the overall population, not the high-risk population proposed for listing).

- 7.21 The PBAC did not recommend NIP listing for adults aged 60 to 74 years with at least one risk factor for severe RSV disease, because it considered that the economic evaluation did not provide a robust estimate of cost-effectiveness for this population, and the financial estimates were uncertain (see paragraph 7.23 below). The PBAC advised that a new submission would be required to support listing for adults aged 60 to 74 years with at least one risk factor for severe RSV disease (see paragraph 7.23 below).
- 7.22 The PBAC noted that the PSCR had presented revised financial implications using more recent population estimates as shown in Table 22, and that the estimates would need to be recalculated for the two recommended populations using the cost-effective prices based on the advice in paragraphs 7.16 to 7.19. The PBAC noted that the cost-effective price differed for the two recommended populations and the submission had estimated  $\frac{1}{2}$ % of use in adults aged  $\geq 75$  years and  $\frac{1}{2}$ % of use in Aboriginal or Torres Strait Islander adults aged 60-74 years (Table 17).
- 7.23 The PBAC noted that the financial impact for the proposed population of adults with at least one risk factor aged 60 to 74 years was large and uncertain. The PBAC noted the cost to the NIP of listing RSVpreF was \$200 million to < \$300 million over 6 years for this population based on the submission's estimates (Table 23). The PBAC noted that the proposed population was heterogeneous with a range of risk factors proposed for NIP eligibility for RSVpreF (see paragraph 3.2), which made estimation of the population size and likely vaccine uptake challenging. The PBAC considered there was a potential risk for usage of RSVpreF in the 60-74 year age group outside of the intended high risk population, due to the number and nature of some of the listed conditions. The PBAC also noted it was uncertain whether obesity should be included as a risk factor for NIP eligibility and this could have a significant impact on the patient estimates (see paragraph 6.77).

- 7.24 The PBAC advised that a submission to request NIP listing of RSVpreF for adults aged 60 to 74 years with at least one risk factor for severe RSV disease should (at a minimum):
- Address the requested population to ensure that the specification of risk factors is consistent with current ATAGI advice or otherwise explain the rationale for any differences (see paragraphs 3.2 and 7.20);
  - Present available clinical evidence for the proposed population and assess to what extent the estimates of vaccine efficacy from the overall trial population are applicable, noting that ATAGI considered that there were gaps in the evidence for some pre-specified high-risk conditions ( see paragraph 6.10) and that people who are considered medically at-risk may have lower immune responses and thus a lower VE following an RSV vaccination (see paragraph 6.45). The PBAC considered that these uncertainties should be addressed in a future submission where possible, with respect to estimates of VE and duration of protection in the requested population. The PBAC advised that the impact of different risk conditions on the baseline risk of severe RSV disease, as well as on efficacy outcomes should be considered.
  - Present an economic evaluation for the proposed population, noting the PBAC’s observation that the population was heterogenous and that it would be informative to see a range of ICERs for different subgroups within this population (paragraph 7.20).
  - Present financial estimates for the proposed population, reflecting the requested population, ensuring that the question about whether obesity should be included as a risk factor for NIP eligibility has been resolved (see paragraph 7.20).
- 7.25 The new submission may be lodged at any future standard due date for PBAC submissions applying to Category 2 submissions.
- 7.26 The PBAC reiterated that the submission requested listing on the NIP for a single dose of vaccine and that if the sponsor wishes to request listing for revaccination in the future, PBAC consideration of a new submission would be required.
- 7.27 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:**

Recommended

## **8 Recommended listing**

- 8.1 Add the following circumstances to the Determination:

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Number and timing of doses
<p><u>Vaccine</u> Respiratory Syncytial Virus (RSV) stabilised prefusion F subunit vaccine (RSVpreF)</p> <p><u>Circumstances</u></p> <ul style="list-style-type: none"> <li>• Adults 75 years of age and above;</li> <li>• Aboriginal and Torres Strait Islander peoples aged 60 to 74 years.</li> </ul>	Abrysvo	Injection (0.5mL)	1 dose

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## 9 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.

## 10 Sponsor's Comment

Pfizer Australia welcomes the Pharmaceutical Benefits Advisory Committee (PBAC) recommendation for Abrysvo® to be funded through the National Immunisation Program for the prevention of lower respiratory tract disease caused by RSV for adults 75 years of age and above and Aboriginal and Torres Strait Islander people 60 to 74 years of age. We will continue to work with the PBAC and the Department of Health and Aged Care to provide funded access, including for adults 60 to 74 years of age with a risk factor for severe RSV disease.