An addendum has been included at the end of the Public Summary Document (PSD).

5.17 RESPIRATORY SYNCYTIAL VIRUS VACCINE, Injection (0.5 mL), Abrysvo®, PFIZER AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested National Immunisation Program (NIP) listing for recombinant syncytial pre-fusion F protein vaccine (RSVpreF) for the prevention of lower respiratory tract illness (LRTI) caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunisation of pregnant women.

1.2 Listing was requested on the basis of a cost-utility analysis versus standard medical management of LRTI in infants from birth through 6 months of age. The key components of the clinical issue addressed by the submission are shown in Table 1.

1.3 The pre-subcommittee response (PSCR) acknowledged the updated ATAGI advice which recommended that the vaccine be given from 28 to 36 weeks gestation (see paragraph 3.2). Subgroup data corresponding to this advice were presented in the PSCR and pre-PBAC response.

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

Component	Description
Population	Vaccination of pregnant women between 24 and 36 weeks of gestation to prevent RSV-associated lower respiratory tract illness (LRTI) in infants aged 0 to 6 months.
Intervention	Single dose of RSVpreF to be administered at 24-36 weeks gestation. RSVpreF is a bivalent, unadjuvanted vaccine composed of stable RSV prefusion F antigens representing the two RSV subgroups (RSV-A and RSV-B).
Comparator	Standard of care (no vaccine)
Outcomes	• Efficacy: MA-LRTI and severe MA-LRTI due to RSV, laboratory confirmed cases of RSV, hospitalisation due to RSV, MA-LRTI due to any cause • Immunogenicity • Safety: adverse events (all, serious, severe, life-threatening, medically-attended and vaccine-related), local reactions, systemic events, AESIs
Clinical claim	In pregnant women between 24 and 36 weeks of gestation: • RSVpreF is more effective than placebo (no vaccine) at preventing MA-LRTI and severe MA-LRTI due to RSV among infants during the first 6 months of life. • RSVpreF has inferior safety to placebo (no vaccine)

Source: Table 1.1.1, p4 of the submission.
Abbreviations: AESI = adverse events of special interest; LRTI = lower respiratory tract infections; MA-LRTI = medically attended lower respiratory tract infections; RSV = respiratory syncytial virus; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine.

2 Background

Registration status

2.1 TGA status at time of PBAC consideration: Not yet registered.

2.2 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the Round 1 and Round 2 TGA clinical evaluation reports, TGA Delegate's overview and the Advisory Committee on Vaccines (ACV) minutes, were available. The TGA Delegate was inclined to support registration and requested advice from the ACV regarding the optimal timing of antenatal vaccination in relation to gestational age for prevention of RSV disease in infants. The ACV considered this vaccine to have an overall positive benefit-risk profile for the following indication as proposed in the pre-ACV response:

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

ABRYSVO should be used in accordance with official recommendations.

2.3 The ACV advised that the optimal timing for administration was from 28 to 36 weeks gestational age. It was noted that vaccine effectiveness appeared lower when administered between 24 to 28 weeks, and that administration after 36 weeks could still offer benefit if there was adequate time before delivery to allow maternal immune response and transplacental antibody transfer.

2.4 The ACV noted that pertussis vaccination (as diphtheria-tetanus-acellular pertussis, dTpa) is recommended in Australia in pregnancy from 20 to 32 weeks gestational age, and advised that ideally at least 2 weeks should elapse between administration of dTpa and RSVpreF due to the lower immune response to the pertussis antigen when dTpa and RSVpreF are co-administered.

2.5 The indication regarding the prevention of RSV in individuals 60 years and older is not part of the current PBAC submission.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Nationally Negotiated Price (*requested*)	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ABRYSVO					
RECOMBINANT RESPIRATORY SYNCYTIAL VIRUS PRE-FUSION F PROTEIN VACCINE Pack containing 1 vial of powder for injection, 1 pre-filled syringe of diluent, and 1 vial adapter.	Submission: $[redacted] Pre-PBAC response: $[redacted]	1	1	0	Abrysvo

Details of the proposed NIP schedule listing (as stated in the submission)

Schedule / Program: Respiratory syncytial virus (RSV) vaccination schedule for immunisation during pregnancy (24–36 weeks gestation)*		
Age(s) of administration(s) other restrictions or details:		
Disease	**Vaccine**	**Comments**
RSV in infants aged 0-6 months	RSVpreF (Abrysvo) 0.5 mL containing 120 micrograms (mcg) of stabilised prefusion F proteins (60 mcg RSV-A and 60 mcg RSV-B antigens)	

Source: Table 1.4.2, p31 of the submission
Abbreviations: RSV = respiratory syncytial virus; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine.
*but may be given to unvaccinated women up until 38 weeks gestation.

3.1 The proposed NIP schedule was one dose of RSVpreF given during pregnancy. The draft product information (PI) provided with the submission stated that RSVpreF is to be given between weeks 24 and 36 of the pregnancy.

3.2 The updated ATAGI advice stated RSV vaccine during pregnancy should be given from 28 to 36 weeks gestation, but administration after 36 weeks is acceptable, noting that two weeks are needed for adequate transfer of antibodies (the updated ATAGI advice to the PBAC). The updated ATAGI advice which recommended vaccination from 28 weeks gestation, rather than 24 weeks as proposed by the submission, noted uncertainty about whether there is an association between preterm birth and receipt of the vaccine. As a precaution, the ATAGI recommended maternal vaccination from 28 weeks gestation while awaiting further data regarding the risk of preterm birth.

3.3 Regarding concomitant use of another vaccine, ATAGI noted the following:

- The primary clinical trial data demonstrating efficacy of RSVpreF (Study 1008 [MATISSE]; Study 1003 [SAVVY]) did not allow co-administration.
- There are concerns about the potential impacts on immunogenicity and efficacy of pertussis containing vaccines when co-administered with RSVpreF.

3.4 The sponsor proposed that RSVpreF is administered in isolation (i.e., not co-administered with other pregnancy vaccinations such as adult diphtheria-tetanus-acellular pertussis vaccine (dTpa), quadrivalent inactivated influenza vaccine (QIIV), or SARS-CoV2 mRNA vaccines. However, given the lack of demonstrated safety concerns, ATAGI advised if co-administration was considered necessary and/or there was

insufficient time or a lack of opportunity to separate vaccines, co-administration should be recommended in this setting (the updated ATAGI Advice to the PBAC). The ESC noted ATAGI's advice and considered that co-administration of RSVpreF with dTpa would help address issues of vaccine fatigue, and equity of access. The pre-PBAC response supported this proposal.

3.5 ATAGI also noted that whether administered in isolation or co-administered, RSVpreF will require administration at a time when most pregnant women in Australia would be engaged with health services, either through formal antenatal care programs, or under the care of general practitioners. As recommended in national guidelines, two to four scheduled antenatal visits fall within the 24-36 gestational week period of pregnancy, potentially impacting on the window of opportunity to vaccinate women with other maternal vaccines. The vaccine proposal is not expected to require amendment or removal of any existing vaccine listing (the ATAGI Advice to the PBAC).

3.6 The ESC noted that maternal vaccine uptake is lower in First Nations women, those from culturally and linguistically diverse backgrounds, and those who experience socioeconomic disadvantage. It may improve access for these groups if RSVpreF is co-administered with other maternal vaccines.

3.7 The ESC noted the ATAGI advice that repeat dosing with each pregnancy is anticipated, but a final decision had not yet been made. ATAGI advised it shall await availability of data on the use of RSV vaccine in subsequent pregnancies, including immunogenicity, efficacy and safety, prior to confirming this recommendation. ATAGI continues to advise that revaccination in each pregnancy should be considered in the cost-effectiveness model (updated ATAGI advice to the PBAC, p2). The PBAC noted that the submitted economic model and financial estimates were consistent with this advice as they both assumed one vaccination per pregnancy (see paragraph 7.11).

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

4 Population and disease

4.1 RSV is the most common viral cause of bronchiolitis and pneumonia in children under five (50% to 80% of cases), posing a significant risk to infants in their first six months of life. In Australia it has been estimated that the hospitalisation rates due to RSV range from 2.2 to 4.9 per 1,000 among children under five years old and between 8.7 and 17.4 per 1,000 among children under one year old[1].

4.2 Two publications that reported RSV-confirmed hospitalisation incidence rates in First Nations people were described in the ATAGI advice. The RSV-confirmed hospitalisation rate among First Nations infants was reported to be 2.3 times higher in infants 0-3 months of age and 3.2 times higher in First Nations infants 4-6 months

[1] Ranmuthugala G, Brown L, Lidbury BA, (2011),Respiratory syncytial virus – the unrecognised cause of health and economic burden among young children in Australia. *Communicable Diseases Intelligence*;35(2)

of age based on a large retrospective cohort study of children aged < 2 years (n=866,262) born in New South Wales between 2001–2010 (Homaira et al. 2016)[2]. Le et al (2023)[3] reported RSV-confirmed hospitalisation rates in First Nations children to be 2.4 times higher in infants aged 0-5 months compared to non-Indigenous infants, and 2.9 times higher in infants aged 6-11 months compared to non-Indigenous infants, based on a population-based data linkage study in Western Australia of births during 2000–2012 (n= 360,994 children).

4.3 Symptoms typically include a low-grade fever, cough, and respiratory distress, potentially escalating to severe conditions requiring hospital care[4]. Risk factors for severe RSV include very young age, particularly less than three months' old, preterm birth, certain congenital heart conditions, chronic lung diseases, and environmental factors like exposure to tobacco smoke[5]. High-risk infants often experience longer hospital stays and may require intensive care.

4.4 RSV is primarily transmitted through direct contact with an infected person or by touching surfaces contaminated with the virus[2]. Individuals infected with RSV, including infants and those with weakened immune systems, can remain contagious for a period ranging from 3 to 8 days, and in some cases, up to 4 weeks[6]. In familial settings, infants often contract RSV from older siblings or parents. Research in Australia has shown that infants less than a year old with one, two, or ≥ 3 older siblings face a significantly increased risk of RSV infection (Relative risk [RR] 1.8, 95% confidence interval [CI]:1.6, 2.0, RR 2.3, 95% CI:2.0, 2.7, and RR 2.8, 95% CI:2.5, 3.3), respectively, compared to those infants without siblings[7].

4.5 Although specific risk factors like prematurity increase the likelihood of hospitalisation due to RSV, most hospitalisations occur in full-term infants without underlying health conditions[8].

4.6 RSV also presents risks for women during pregnancy, with evidence suggesting an association with preterm labour[9]. In temperate regions, RSV infections predominantly occur in the winter, mirroring influenza patterns, though this seasonality is less

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[2] Homaira N, Oei JL, Mallitt KA, Abdel-Latif ME, Hilder L, Bajuk B, et al. (2016) High burden of RSV hospitalization in very young children: a data linkage study. *Epidemiol Infect*. 2016 Jun;144(8):1612-21.

[3] Le H, Gidding H, Blyth CC, Richmond P, Moore HC. Pneumococcal Conjugate Vaccines Are Protective Against Respiratory Syncytial Virus Hospitalizations in Infants: A Population-Based Observational Study. Open Forum Infect Dis. 2023;10(4):ofad199. Published 2023 Apr 19.

[4] Smith DK, Seales S, Budzik C. (2017), Respiratory Syncytial Virus Bronchiolitis in Children. *Am Fam Physician*.95(2):pp94-9

[5] Havdal LB, Bøås H, Bekkevold T, Bakken Kran A-M, Rojahn AE, Størdal K, et al. (2022), Risk factors associated with severe disease in respiratory syncytial virus infected children under 5 years of age. *Frontiers in Pediatrics*. 30;p10

[6] Jain H SJ, Justice NA. (2023), Respiratory Syncytial Virus Infection in Children. *In: StatPearls [Internet] Treasure Island (FL): StatPearls Publishing; Available from: https://wwwncbinlmnihgov/books/NBK459215/*. 2023

[7] Jacoby P, Glass K, Moore HC. (2017), Characterizing the risk of respiratory syncytial virus in infants with older siblings: a population-based birth cohort study. *Epidemiol Infect*. 145(2):pp266-71

[8] Hall CB, Weinberg GA, Blumkin AK, Edwards KM, Staat MA, Schultz AF, et al. (2013), Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics*.132(2):e341-8

[9] Hause AM, Avadhanula V, Maccato ML, Pinell PM, Bond N, Santarcangelo P, et al. (2019), Clinical characteristics and outcomes of respiratory syncytial virus infection in pregnant women. *Vaccine*. 37(26):pp3464-71

defined in tropical and subtropical climates[10]. In Australia, the timing of RSV outbreaks varies with the climate across different regions, typically peaking in the cooler months[11]. The ESC noted ATAGI's advice supported a year-round program, given the uncertain RSV seasonality post-COVID-19, varying seasonality in different parts of Australia, and challenges of delivering a seasonal vaccination program to pregnant women (ATAGI pre-submission advice p3). The ESC supported this approach, noting it would allow access to the vaccine through routine antenatal care.

4.7 The COVID-19 pandemic has notably disrupted the typical patterns of RSV transmission. Measures taken to curb the spread of COVID-19, such as physical distancing and mask-wearing, have also impacted the transmission of RSV, leading to changes in the usual seasonal patterns of the virus. For instance, Australia saw a significant decline in RSV cases in 2020 due to COVID-19 related restrictions, followed by a surge in cases in late 2020/early 2021[12].

4.8 The proposed place in therapy for RSVpreF is as a vaccination given during the third trimester of pregnancy to prevent LRTI in infants during the first 6 months of life. So, although the recipient is the mother, the target population is the infant.

4.9 RSVpreF is a bivalent vaccine composed of stable RSV prefusion F antigens representing the 2 major virus subgroups (RSV-A and RSV-B) to ensure broad coverage against RSV illness. In pregnant individuals, the action of neutralising antibodies conferring protection is mediated through passive transfer of these antibodies from mother to infant through the placenta[13]. This means that inoculating pregnant women can provide protection to infants.

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

5 Comparator

5.1 The submission nominated "No vaccine" (standard of care) as the comparator, on the basis there was no alternative vaccine licensed against RSV in Australia at the time of submission. ATAGI considered this comparator was reasonable (the ATAGI Advice to the PBAC).

5.2 ATAGI also noted that the monoclonal antibody (mAb) palivizumab is currently licensed for the prevention of RSV in high-risk infants (the ATAGI Advice to the PBAC). However, the high cost of palivizumab and requirement for monthly injections, limited

[10] Staadegaard L, Caini S, Wangchuk S, Thapa B, de Almeida WAF, de Carvalho FC, et al. (2021), Defining the seasonality of respiratory syncytial virus around the world: National and subnational surveillance data from 12 countries. *Influenza Other Respir Viruses*.15(6):pp732-41

[11] Hogan AB, Anderssen RS, Davis S, Moore HC, Lim FJ, Fathima P, et al. (2016), Time series analysis of RSV and bronchiolitis seasonality in temperate and tropical Western Australia. *Epidemics*.16:pp49-55

[12] Chuang YC, Lin KP, Wang LA, Yeh TK, Liu PY. (2023), The Impact of the COVID-19 Pandemic on Respiratory Syncytial Virus Infection: A Narrative Review. *Infect Drug Resist*. 16:pp661-75

[13] Kampmann B, Madhi SA, Munjal I, Simões EAF, Pahud BA, Llapur C, et al. (2023), Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *New England Journal of Medicine*. 388(16):pp1451-64

its use. ATAGI considered that there was insufficient use in Australia for it to be considered a comparator (ATAGI Advice to the PBAC).

5.3 Nirsevimab is a mAb for prevention of RSV-associated LRTI that received TGA approval in November 2023.[14] Nirsevimab is indicated for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. It can be given as a single subcutaneous injection and has been shown to result in a significant reduction in RSV associated medically attended lower respiratory tract illness (MA-LRTI) (74.5% efficacy [1 - RR] 95% CI: 49.6, 87.1)[15]. Based on the TGA indication, nirsevimab is a near market comparator. ATAGI noted that "there is a real possibility that both products may be registered for use in the Australian market. ATAGI suggests that it is false to assume that monoclonals would be restricted to high-risk populations, with a maternal vaccination program favoured if both prevention strategies were available. The Sponsor should consider the possibility that both products may be available for use in Australia and consider approaches to evaluating/comparing the relevant benefits of both products, alone or in combination, if both are available." (ATAGI Advice to the PBAC). The sponsor noted that to adequately address this would require clinical and cost inputs that were not available at the time of submission.

5.4 Nirsevimab was licensed in the UK in November 2022. The Joint Committee on Vaccination and Immunisation (JCVI) noted that both nirsevimab and RSVpreF are suitable for a universal program to protect neonates from RSV. JCVI does not have a preference for either product or whether a maternal vaccination or a passive immunisation program should be the program chosen to protect neonates and infants. The JCVI concluded that, subject to licensure of the maternal vaccine, both options should be considered for a universal program in the UK[16].

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 organisations (3) via the Consumer Comments facility on the PBS website. The three organisations were consumer

[14] https://www.tga.gov.au/resources/auspmd/beyfortus

[15] Hammitt LL, Dagan R, Yuan Y, Baca Cots M, Bosheva M, Madhi SA, et al. (2022) Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *New England Journal of Medicine*. 2022;386(9):837-46.

[16] Respiratory syncytial virus (RSV) immunisation programme for infants and older adults: JCVI full statement, 11 September 2023 - GOV.UK (www.gov.uk)

organisations that supported the proposed NIP listing for RSVpreF.

6.3 The comments from the Immunisation Foundation of Australia described a range of benefits of the proposed vaccine stating that protecting infants from RSV would provide a healthier start to life and reduce paediatric hospital burden. The comments also described the emotional burden for families of infants needing hospitalisation for RSV and the financial burden for families and society as a whole resulting from RSV-associated medical costs and lost productivity of parents. The input highlighted that some infants are at an increased risk of severe RSV complications, including First Nations infants, infants with weakened immune systems, premature babies, and those with chronic lung or heart conditions.

6.4 The Lung Foundation Australia stated that listing RSVpreF on the NIP would provide clinicians and patients with access to an effective vaccine, reduce the risk of disease, disability and death associated with RSV, and reduce costs to health system, particularly among children and immunocompromised individuals. The input stated that based on a survey of over 800 consumers, on average, Australian consumers were "very worried" about RSV.

6.5 The input from CreakyJoints Australia and parent organisation, Global Healthy Living Foundation Australia supported the rollout of RSV vaccines in Australia, starting with vaccinating pregnant women to provide their babies with some protection during their early months. The input stated that with the number of detected RSV cases increasing, the burden of RSV impacted not only immunocompromised people, but also society as a whole.

Clinical studies

6.6 The submission was based on one head-to-head trial known as the MATernal Immunization Study for Safety and Efficacy (MATISSE) comparing RSVpreF to placebo (n=7,392). Two supporting studies were also included, SAVVY, and Study 1004.

6.7 Details of the studies presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
MATISSE NCT04424316	Protocol and Primary Analysis Report (C3671008): A Phase 3, randomized, double- or observer-blinded, placebo-controlled trial to evaluate the efficacy and safety of a respiratory syncytial virus (RSV) prefusion F subunit vaccine in infants born to women vaccinated during pregnancy.	June 2020
	Kampmann, B., Madhi, S.A., Munjal, I., et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants.	N Engl J Med 2023; 388(16): 1451-64
SAVVY NCT04032093	Protocol and Primary Analysis Report (C3671003): A Phase 2b placebo-controlled, randomized study of an RSV vaccine in pregnant women	July 2019
	Simoes, E.A.F., Center, K.J., Tita, A.T.N. et al. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy.	N Engl J Med 2022; 386: 1615-26
	Simoes, E.A.F., Madhi, S.A., Center, K.J. et al. Establishing Proof of Concept for a Bivalent RSVpreF Subunit Vaccine for Maternal Immunization.	OFID Conference Abstract 2022; 9(Suppl 2): S13
Study 1004 NCT04071158	Protocol and Primary Analysis Report (C3671004): A study of an RSV vaccine when given together with Tdap in healthy nonpregnant women aged between 18 to 49 years	September 2019
	Peterson, J.T., Zareba, A.M., Fitz-Patrick, D. et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F Vaccine When Coadministered With a Tetanus, Diphtheria, and Acellular Pertussis Vaccine.	JID 2022; 225: 2077-86

Source: Table 2.2.1, p40 of the submission.

6.8 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
MATISSE	7,392 women 7,128 infants	R, DB, MC, PC 24 mths	Low	Pregnant women between 24 – 36 weeks gestational age.	MA-LRTI Severe MA-LRTI	Used
SAVVY	581 women 572 infants	R, DB, PC 12 mths	Low	Pregnant women between 24 – 36 weeks gestational age.	MA-LRTI Severe MA-LRTI neutralising antibody titers	Not used
Study 1004	713	R, DB, PC, MC 1 mth	Low	Non-pregnant women between 18 and 49 years old	neutralising antibody titers	Not used

Source: Table 2.3.1, pp44-45, and Table 2.4.1, p49 of the submission.
Abbreviations: DB = double blind; MA-LRTI = medically attended lower respiratory tract illness; MC = multi-centre; PC = placebo controlled; R = randomised; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine.

6.9 MATISSE and SAVVY were both head-to-head randomised controlled trials of RSVpreF versus placebo. However, Study 1004 was designed to look at co-administration of

RSVpreF with dTpa (in non-pregnant women) and so the groups were RSVpreF + dTpa versus placebo + dTpa.

6.10 The submission presented results from the primary analysis of the MATISSE trial, corresponding to a data cut-off date of 30 September 2022. The pre-PBAC response presented a small subset of results from the final analysis of the MATISSE trial, corresponding to a data cut-off date of October 2023 (Munjal et al., 2024[17]). The pre-PBAC response stated that the final data from the MATISSE trial is planned for submission to the TGA later in 2024.

Comparative effectiveness

6.11 The primary endpoint for the MATISSE trial of RSV-positive MA-LRTI in infants through 180 days after birth is summarised in Table 4 and the corresponding Kaplan-Meier (KM) curves are presented in Figure 1.

6.12 RSV-positive MA-LRTI is defined as an infant participant having been seen by a healthcare provider with one or more symptom of a respiratory tract infection and:

- Fast breathing (respiratory rate ≥60 bpm for <2 months of age [<60 days of age] or ≥50 bpm for ≥2 to <12 months of age, or ≥40 bpm for ≥12 months to 24 months of age), OR
- Oxygen saturation (SpO_2) <95%, OR
- Chest wall indrawing, AND
- An RSV-positive test result.

6.13 In the primary analysis, at 90 days after birth there were 24 (0.7%) cases of RSV-positive MA-LRTI in infants in the RSVpreF group and 56 (1.6%) cases in the placebo group, corresponding to a vaccine efficacy (VE) of 57.1% (99.5% CI:14.7%, 79.8%) for RSVpreF. This did not meet the pre-defined statistical criterion for success (CI lower bound >20%). At 180 days after birth, there were 57 (1.6%) cases of RSV-positive MA-LRTI in the RSVpreF group and 117 (3.4%) cases in the placebo group, corresponding to a VE of 51.3% (97.58% CI:29.4%, 66.8%) for RSVpreF. This did meet the predefined statistical criterion for success of a CI lower bound > 20%.

6.14 The pre-PBAC response stated that the final analysis was consistent with the primary analysis for the RSV-positive MA-LRTI endpoint, and that RSVpreF was 57.6% (95% CI: 31.3%, 74.6%) and 49.2% (95% CI: 31.4%, 62.8%) efficacious in reducing the incidence of MA-LRTI within 3 months and 6 months after birth, respectively (Table 4).

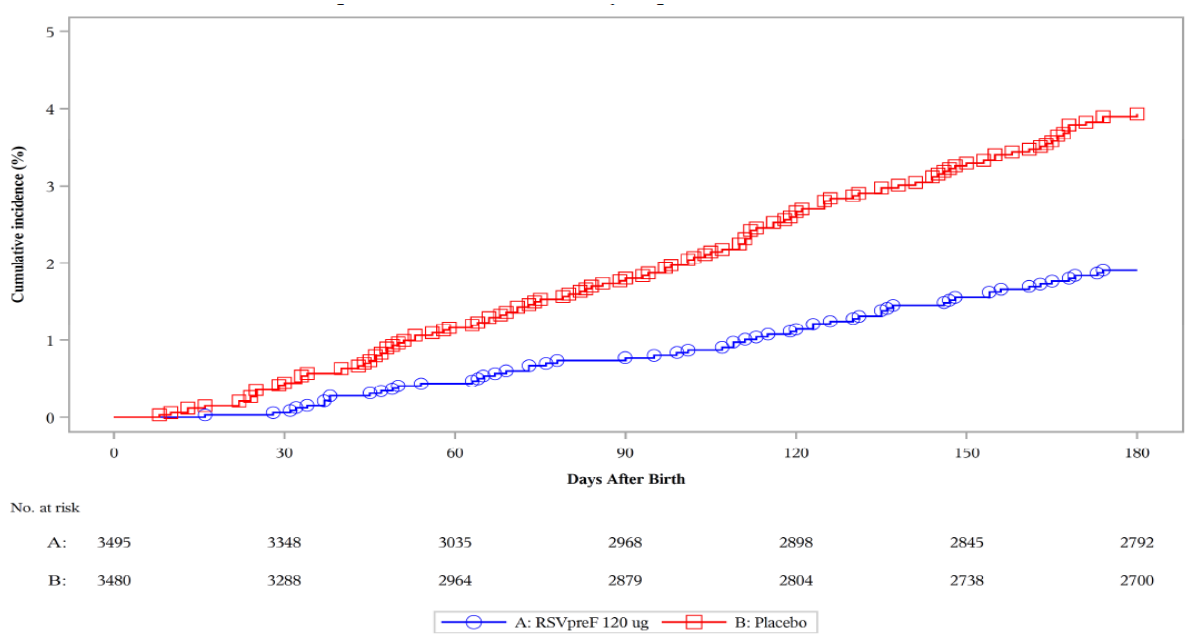
[17] Munjal, I. et al. Prevention of infant RSV illness with a bivalent RSV prefusion F vaccine administered during pregnancy: efficacy results from a phase 3 global clinical trial. 8th ReSViNET Conference, February 13-16, 2024 (Abstract Book, p98).

Table 4: RSV-positive MA-LRTI occurring in infants

Time interval	RSVpreF 120 ug N[a] = 3,495 No. of cases (%)	Placebo N[a] = 3,480 No. of cases (%)	VE[b], % (CI[c])	Nominal P-value[d]
Primary Analysis (reported in submission)				
90 days post birth	24 (0.7)	56 (1.6)	**57.1 (14.7, 79.8)**	**0.0058**
120 days post birth	35 (1.0)	81 (2.3)	**56.8 (31.2, 73.5)**	**0.0012**
150 days post birth	47 (1.3)	99 (2.8)	**52.5 (28.7, 68.9)**	**0.0017**
180 days post birth	57 (1.6)	117 (3.4)	**51.3 (29.4, 66.8)**	**0.0011**
Final Analysis (reported in pre-PBAC response)				
Time interval	**RSVpreF 120 ug N[a] = 3,585 No. of cases (%)**	**Placebo N[a] = 3,563 No. of cases (%)**	**VE[b], % (CI[c])**	**Nominal P-value**
3 months post birth	25 (0.7)	59 (1.7)	57.6 (31.3, 74.6)	n.r.
6 months post birth	67 (1.9)	132 (3.7)	49.2 (31.4, 62.8)	n.r.

Source: Table 2.5.1, p61 of the submission, Pre-PBAC response Table 2 (from Munjal et al., 2024).
Abbreviations: CI = confidence interval; MA-LRTI = medically attended lower respiratory tract illness; N = total participants in group; n.r = not reported; RSV = respiratory syncytial virus; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine; VE = vaccine efficacy.
[a] Number of participants (at risk). Value used as denominator for percentage calculations.
[b] Calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
[c] 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).
[d] Unadjusted 1-sided nominal p-value for the null hypothesis that vaccine efficacy ≤ 20% (P-values were included as a post-hoc analysis)
Bold indicates statistically significant results.

Figure 1: KM curves for RSV-positive MA-LRTI occurring in infants through 180 days after birth.



Source: Figure 2.5.1, p62 of the submission (primary analysis, corresponding to a data cut-off date of 30 September 2022).
Abbreviations: KM = Kaplan-Meier; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine.

6.15 Given the ATAGI advice supporting administration from 28 weeks gestation, the PSCR presented additional analyses for the subgroup vaccinated from 28 weeks to < 37 weeks gestation for RSV-positive MA-LRTI in the MATISSE trial (Table 5). For RSV-positive MA-LRTI, there were 35 cases in infants within 180 days after birth in the

RSVpreF group and 90 cases in the placebo group, corresponding to a VE of 61.0% (95% CI: 41.7, 74.4) for RSVpreF (Table 5) which was higher than that reported for the overall population (VE of 51.3% (97.58% CI:29.4%, 66.8%) for RSVpreF (Table 4). The ESC noted the subgroup of women from 28 weeks to < 37 weeks gestation represented approximately 2/3 of the MATISSE trial population. The ESC noted that the number of cases reported in this subgroup analysis ranged from 18 to 35 in the RSVpreF group and 43 to 90 in the placebo group. The ESC noted that the subgroup results suggested improved efficacy when the vaccine was administered between 28 weeks to < 37 weeks gestation, although the magnitude of effect in the subgroup was less certain due to the relatively small number of cases in comparison with the overall analysis. The pre-PBAC response stated that results based on the final analysis were consistent with the primary analysis for analyses by timing of dosing (Table 5).

Table 5: RSV-positive MA-LRTI occurring in infants through 180 days after birth – Subgroup vaccinated from 28 weeks to <37 weeks gestation

Time interval	RSVpreF 120 ug N[a] = 2,605 No. of cases (%)	Placebo N[a] = 2,614 No. of cases (%)	VE[b], 95% (CI)
Primary Analysis (reported in PSCR)			
90 days post birth	18 (0.7)	43 (1.6)	58.0 (25.6, 77.2)
120 days post birth	25 (1.0)	61 (2.3)	58.9 (33.5, 75.3)
150 days post birth	30 (1.2)	76 (2.9)	60.4 (38.8, 74.9)
180 days post-birth	35 (1.3)	90 (3.4)	61.0 (41.7, 74.4)
Final Analysis (reported in pre-PBAC response)			
Time interval	**RSVpreF 120 ug N[a] = 2,669 No. of cases (%)**	**Placebo N[a] = 2,676 No. of cases (%)**	**VE[b], 95% (CI)**
90 days post birth	19 (0.7)	46 (1.7)	58.6 (27.9, 77.1)
180 days post birth	41 (1.5)	101 (3.8)	59.3 (40.9, 72.4)

Source: PSCR Table 2, Pre-PBAC response Table 3 however the results could not be verified as the source data table was not provided.
Abbreviations: CI = confidence interval; MA-LRTI = medically attended lower respiratory tract illness; N = total participants in group; RSV = respiratory syncytial virus; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine; VE = vaccine efficacy.
[a] Number of participants (at risk). Value used as denominator for percentage calculations.
[b] Calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.

6.16 The results for the second primary end point in MATISSE of RSV-positive severe MA-LRTI occurring in infants out to 180 days after birth are presented in Table 6 and the corresponding KM curves are presented in Figure 2.

6.17 RSV-positive severe MA-LRTI was defined as:

- Infant with an MA-RTI visit, AND
- Fast breathing (respiratory rate ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for ≥2 months to <12 months of age, or ≥50 bpm for ≥12 months to 24 months of age), OR
- SpO_2 <93%, OR
- High-flow nasal cannula or mechanical ventilation (i.e., invasive, or non-invasive), OR

- Intensive care unit (ICU) admission for >4 hours, OR
- Failure to respond/unconscious, AND
- RSV-positive test result

6.18 In the primary analysis, at 90 days after birth there were 6 (0.2%) cases of RSV-positive severe MA-LRTI in infants in the RSVpreF group and 33 (0.9%) cases in the placebo group, corresponding to a VE of 81.8% (99.5% CI:40.6%, 96.3%) for RSVpreF. At 180 days after birth, there were 19 (0.5%) cases of RSV-positive severe MA-LRTI in the RSVpreF group and 62 (1.8%) cases in the placebo group, corresponding to a VE of 69.4% (97.58% CI:44.3%, 84.1%) for RSVpreF. Results for severe MA-LRTI met the statistical criterion for success at all timepoints through to 180 days after birth. The results suggest some waning in vaccine efficacy may occur over time.

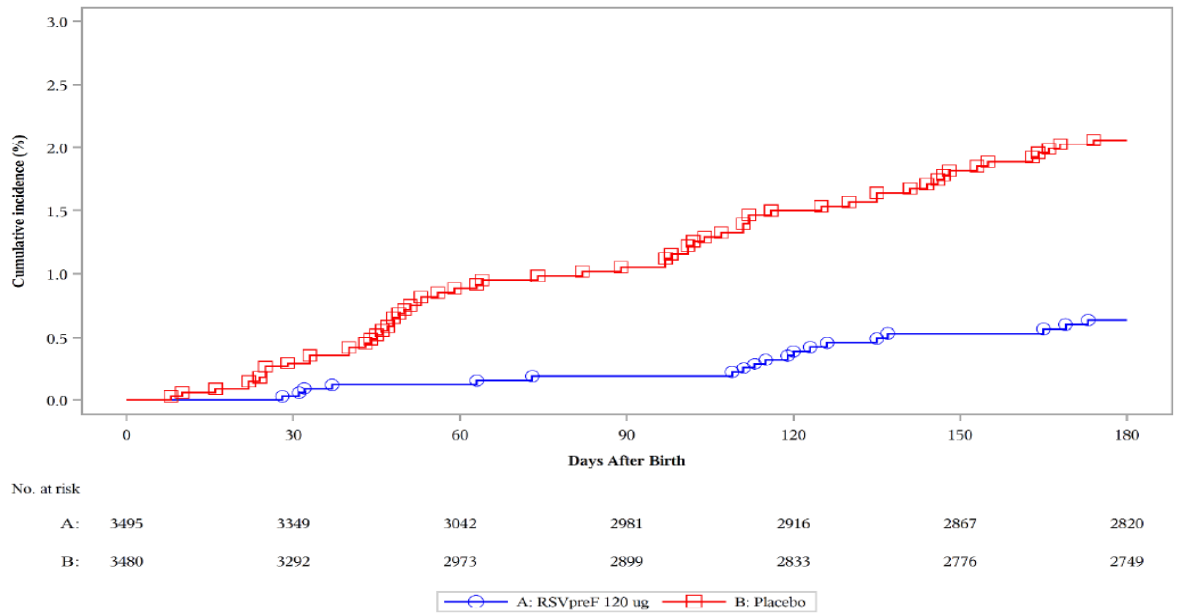
6.19 The pre-PBAC response reported that the final analysis was consistent with the primary analysis for the RSV-positive severe MA-LRTI endpoint, with VE of 82.4% (95% CI: 57.5%, 93.9%) in infants within 90 days after birth and 70.0% (95% CI: 50.6%, 82.5%) within 180 days (Table 6). Results for 12 months and 24 months post birth were also provided, which indicated lower VE at these time points (Table 6).

Table 6: RSV-positive severe MA-LRTI occurring in infants

Time interval	RSVpreF 120 ug N[a] = 3,495 No. of cases (%)	Placebo N[a] = 3,480 No. of cases (%)	Vaccine efficacy[b], % (CI[c])
Primary Analysis (reported in submission)			
90 days post birth	6 (0.2)	33 (0.9)	81.8 (40.6, 96.3)
120 days post birth	12 (0.3)	46 (1.3)	73.9 (45.6, 88.8)
150 days post birth	16 (0.5)	55 (1.6)	70.9 (44.5, 85.9)
180 days post birth	19 (0.5)	62 (1.8)	69.4 (44.3, 84.1)
Final Analysis (reported in pre-PBAC response)			
Time interval	**RSVpreF 120 ug N[a] = 3,585 No. of cases (%)**	**Placebo N[a] = 3,563 No. of cases (%)**	**Vaccine efficacy[b], % (CI[c])**
3 months post birth	6 (0.2)	34 (1.0)	82.4 (57.5, 93.9)
6 months post birth	21 (0.6)	70 (2.0)	70.0 (50.6, 82.5)
12 months post birth	61 (1.7)	102 (2.9)	40.2 (17.1, 57.2)
24 months post birth	75 (2.1)	118 (3.3)	36.4 (14.4, 53.1)

Source: Table 2.5.2, p63 of the submission, Pre-PBAC response Table 1 (from Munjal et al., 2024)
Abbreviations: CI = confidence interval; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus; RSVpreF =respiratory syncytial virus pre-fusion F protein vaccine.
[a] Number of participants (at risk). Value used as denominator for percentage calculations.
[b] Calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
c 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).

Figure 2: KM curves of RSV-positive severe MA-LRTI occurring in infants through 180 days after birth



Source: Figure 2.5.2, p64 of the submission (primary analysis, corresponding to a data cut-off date of 30 September 2022).
Abbreviations: KM = Kaplan-Meier; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine.

6.20 Given the ATAGI advice supporting administration from 28 weeks gestation, the PSCR presented additional analyses for the subgroup vaccinated from 28 weeks to < 37 weeks gestation for RSV-positive severe MA-LRTI in the MATISSE trial (Table 7). There were 8 cases of RSV-positive severe MA-LRTI in infants within 180 days after birth in the RSVpreF group and 43 cases in the placebo group, corresponding to a VE of 81.3% (95% CI: 59.8, 92.4) for RSVpreF (Table 7) which was higher than that reported for the overall population VE of 69.4% (97.58% CI:44.3%, 84.1%) for RSVpreF (Table 6). The ESC noted that the number of cases reported in this subgroup analysis ranged from 2 to 8 in the RSVpreF group and 22 to 43 in the placebo group. The ESC noted that the subgroup results suggested improved efficacy when the vaccine was administered between 28 weeks to <37 weeks gestation, although the magnitude of effect in the subgroup was less certain due to the relatively small number of cases in comparison with the overall analysis. The pre-PBAC response stated that results based on the final analysis were consistent with the primary analysis for analyses by timing of dosing (Table 7).

Table 7: RSV-positive severe MA-LRTI occurring in infants through 180 days after birth – Subgroup vaccinated from 28 weeks to <37 weeks gestation

Time interval	RSVpreF 120 ug N[a] = 2,605 No. of cases (%)	Placebo N[a] = 2,614 No. of cases (%)	VE[b], 95% (CI)
Primary Analysis (reported in PSCR)			
90 days post birth	2 (<0.1)	22 (0.8)	**90.9 (62.9, 99.0**)
120 days post birth	5 (0.2)	31 (1.2)	**83.8 (58.0, 95.1)**
150 days post birth	6 (0.2)	38 (1.5)	**84.2 (62.2, 94.5)**
180 days post-birth	8 (0.3)	43 (1.6)	**81.3 (59.8, 94.2)**
Final Analysis (reported in pre-PBAC response)			
Time interval	**RSVpreF 120 ug N[a] = 2,669 No. of cases (%)**	**Placebo N[a] = 2,676 No. of cases (%)**	**VE[b], 95% (CI)**
90 days post birth	2 (<0.1)	23 (0.9)	91.3 (64.7, 99.0)
180 days post birth	9 (0.3)	49 (1.8)	81.6 (62.1, 92.0)

Source: PSCR Table 1, Pre-PBAC response Table 3 however the results could not be verified as the source data table was not provided.
Abbreviations: CI = confidence interval; MA-LRTI = medically attended lower respiratory tract illness; N = total participants in group; RSV = respiratory syncytial virus; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine; VE = vaccine efficacy.
[a] Number of participants (at risk). Value used as denominator for percentage calculations.
[b] Calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.

6.21 The PBAC noted that the subgroup results (Table 5, Table 7) suggested improved efficacy when the vaccine was administered between 28 weeks to <37 weeks gestation compared with the overall MATISSE trial population (24 weeks to <37 weeks gestation), although the magnitude of effect in the subgroup was less certain due to the relatively small number of cases in comparison with the overall analysis.

6.22 The results for hospitalisations due to RSV in infants through 360 days are presented in Table 8. This was a key secondary outcome in MATISSE.

6.23 At 90 days after birth there were 10 (0.3%) hospitalisations due to end-point adjudication committee (EAC)-confirmed RSV in infants in the RSVpreF group, and 31 (0.9%) hospitalisations in the placebo group, corresponding to a VE of 67.7% (99.17% CI:15.9%, 89.5%) for RSVpreF. At 180 days after birth, there were 19 (0.5%) hospitalisations due to RSV in infants in the RSVpreF group, and 44 (1.3%) hospitalisations in the placebo group, corresponding to a VE of 56.8% (99.17% CI:10.1%, 80.7%). Results up to 180 days after birth all met the statistical criterion for success. However, at 360 days after birth there were 38 (1.1%) hospitalisations due to RSV in the RSVpreF group and 57 (1.6%) in the placebo group, corresponding to a VE of 33.3% (99.17% CI:-17.6%, 62.9%) which did not meet the criterion for statistical success. The pre-PBAC response provided results for 90 and 180 days post birth as shown in Table 8.

Table 8: Hospitalisations due to RSV (confirmed by EAC) occurring in infants through 360 days after birth

Time interval	RSVpreF 120 ug N[a] = 3,495 No. of cases (%)	Placebo N[a] = 3,480 No. of cases (%)	VE[b], % (99.17% CI)
Primary Analysis (reported in submission) – Overall MATISSE trial population			
90 days post birth	10 (0.3)	31 (0.9)	67.7 (15.9, 89.5)
120 days post birth	15 (0.4)	37 (1.1)	59.5 (8.3, 93.7)
150 days post birth	17 (0.5)	39 (1.1)	56.4 (5.2, 81.5)
180 days post birth	19 (0.5)	44 (1.3)	56.8 (10.1, 80.7)
360 days post birth	38 (1.1)	57 (1.6)	33.3 (-17.6, 62.9)
Final Analysis (reported in pre-PBAC response) –- Subgroup vaccinated from 28 weeks to <37 weeks gestation			
Time interval	RSVpreF 120 ug N = n.r. No. of cases	Placebo N = n.r. No. of cases	VE[b], % (95% CI)
90 days post birth	6	23	73.8 (33.9, 91.3)
180 days post birth	12	33	63.5 (27.6, 82.9)

Source: Table 2.5.4, p66 of the submission, pre-PBAC response p2 however the results could not be verified as the source data table was not provided.

Abbreviations: CI = confidence interval; EAC = endpoint adjudication committee; n.r = not reported; RSV = respiratory syncytial virus; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine; VE = vaccine efficacy.

[a] Number of participants (at risk). Value used as denominator for percentage calculations.

[b] Calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The CI was adjusted using Bonferroni procedure and accounting for the primary endpoint results.

6.24 Two studies, SAVVY and Study 1004, provided data to support the key (MATISSE) trial. The Phase 2b SAVVY trial assessed rates of RSV-associated LRTI among infants as an exploratory endpoint. Cases of RSV-associated LRTI ranged from 0 to 2 infants in the RSVpreF groups to 3 infants in the placebo group. When all vaccine groups were combined and compared to placebo, the efficacy of RSVpreF was 75%, 75% and 83% at preventing RSV-associated medically significant LRTI, MA-LRTI and severe MA-LRTI, respectively. None of these results were statistically significant. However, it should be noted that the SAVVY trial was not powered to detect this difference.

6.25 The SAVVY trial additionally provided data on the immunogenicity of RSVpreF to support the clinical claim.

6.26 Key maternal immunogenicity data demonstrated the generation of robust neutralising titres to RSV-A and RSV-B post-RSVpreF 120ug:

- Peak neutralising titres amongst maternal participants was observed two weeks post-vaccination (geometric mean ratio [GMR]: 22.0, 95% CI:17.7, 27.4) following RSVpreF 120ug.
- Sustained neutralising titres amongst maternal participants were observed at the time of delivery (GMR: 12.4, 95% CI:9.7, 15.8) following RSVpreF 120ug and out to 6 months after vaccination.

6.27 Key infant immunogenicity data were:

- Peak neutralising titres amongst infants at birth (GMR: 12.6, 95% CI:9.6, 16.5) following maternal RSVpreF 120ug.

- Maternal-to-infant placental transfer greater than 1.0 (1.83, 95% CI:1.44, 2.31) following maternal RSVpreF 120ug.
- Sustained neutralising titres amongst infants from birth (GMR: 12.6, 95% CI:9.6, 16.5) until 6 months (GMR: 6.8, 95% CI:4.6, 9.9) post-delivery following maternal RSVpreF 120ug.

6.28 A primary objective of Study 1004 (in non-pregnant women) was to examine the immune responses elicited by dTpa when co-administered with RSVpreF (RSVpreF/dTpa) compared to those elicited by dTpa alone.

6.29 A key outcome from this study was that at 1 month after vaccination, the ratios of anti-pertussis toxin, anti-filamentous hemagglutinin, and anti-pertactin antibody GMCs for the combined RSVpreF/dTpa groups relative to the placebo/dTpa group were 0.80 (95% CI:0.64, 1.00), 0.59 (95% CI:0.50, 0.70) and 0.60 (95% CI:0.48, 0.76), respectively. Thus, compared with a 95% lower bound criterion of 0.67, noninferiority was not established for these components.

Comparative harms

6.30 A summary of key adverse events in the MATISSE trial is presented in Table 9. Data are presented for both maternal and infant participants.

Table 9: Summary of key adverse events in the MATISSE trial

MATISSE	RSVpreF n with event/N (%)	Placebo n with event/N (%)
Maternal participants		
Any AE	507/3682 (13.8%)	483/3675 (13.1%)
Serious AE	154/3682 (4.2%)	137/3675 (3.7%)
Pain at injection site	1488/3663 (40.6%)	369/3639 (10.1%)
Muscle pain	972/3663 (27.5%)	623/3639 (17.1%)
Infant participants		
Any AE	1324/3568 (37.1%)	1229/3558 (34.5%)
Serious AE	553/3568 (15.5%)	541/3558 (15.2%)
Jaundice neonatal	257/3568 (7.2%)	241/3558 (6.8%)
Premature baby	202/3568 (5.7%)	169/3558 (4.7%)

Source: Table 18, pp69-70, Table 19 pp71-72, Table 14.72, pp400-405 and Table 14.90, pp809-839 of the MATISSE CSR.
Abbreviations: PBO = placebo; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine; n = number of participants reporting data; N = total participants in group

6.31 In maternal participants, local reactions were more frequently reported in RSVpreF recipients (42.5%) compared with placebo recipients (10.4%). The most common local reaction was pain at the injection site, reported in 1488 (40.6%) participants in the RSVpreF group and 369 (10.1%) in the placebo group. Severe local reactions were rarely reported (10 [0.3%] in RSVpreF recipients [severe redness (>10cm), n=5; severe swelling (>10cm), n=3; severe pain (prevents daily activity), n=4]; none in placebo recipients).

6.32 Systemic reactions within 7 days were reported at a similar rate for any systemic adverse event (AE) in RSVpreF (62.2%) and placebo recipients (59.2%); similarly, for severe systemic AEs (2.3% vs 2.3%). Fatigue, headache, nausea, and muscle pain were

most frequently reported for those injected with RSVpreF, with the difference in muscle pain compared to placebo (26.5% vs 17.1%) being most notable. There were no significant differences in the proportion of recipients reporting moderate to severe adverse events.

6.33 The proportions of infant participants with any AE reported from birth to 24 months of age were 41.3% in the RSVpreF group and 39.4% in the placebo group. The most frequently reported AEs were in the system organ classes of Pregnancy, puerperium and perinatal conditions (16.8% versus 15.6%), Congenital, familial and genetic disorders (8.0% versus 8.3%), and Respiratory, thoracic and mediastinal disorders (7.7% versus 7.3%). By preferred term, the most frequently reported AE in the RSVpreF group from birth to 24 months of age was neonatal jaundice (7.2%) which was also reported in 6.8% of the placebo group.

6.34 Overall, the proportions of infants with any serious adverse events (SAEs) reported from birth to 24 months of age were the same in the RSVpreF (17.5%) and placebo (17.5%) groups. For both groups, most SAEs occurred from birth to 1 month of age (≤ 15.5%). There were no SAEs in infant participants that were considered related to maternal vaccination by the investigators.

6.35 Congenital anomalies reported as SAEs occurred at a similar frequency in the RSVpreF and placebo groups (5.0% and 6.2%).

6.36 There were 17 infant deaths reported from birth to 24 months of age in the study: 5 (0.1%) in the RSVpreF group and 12 (0.3%) in the placebo group. In the RSVpreF group, each death event term was reported for one infant. No infant deaths were assessed by the investigator as related to maternal vaccination. One death in the placebo group, which occurred from 1 month to 6 months of age, was adjudicated by the EAC as being caused by "acute respiratory illness due to RSV".

6.37 AEs of special interest included premature baby (RSVpreF = 5.7% vs. placebo = 4.7%), low birthweight (RSVpreF = 5.1% vs. placebo = 4.3%), and speech disorder development (RSVpreF = 0.1% vs. placebo = <0.1%). The RSVpreF arm reported a higher rate of premature births and low birth weight. The trial was not statistically powered to detect any differences between the intervention arms.

6.38 The potential safety signal of premature birth has been noted by the TGA and ATAGI. ATAGI stated "when focusing on adverse events of special interest, no statistically significant safety signal has been identified. The numerically higher rate of premature deliveries and low birth weight babies observed in the MATISSE trial is not associated with an increased number of foetal or infant deaths with a trend towards lower serious adverse events of infant deaths or congenital anomalies in the vaccine group." (ATAGI Advice to the PBAC). The TGA noted the imbalance and stated that it may be due to the timing of the vaccination with respect to the gestational age (Abrysvo TGA Delegate's Overview). Additionally, the sponsor argued to the TGA that results stratified by high- and low-income countries indicate that the imbalance was not

observed in high income countries implying that it may be related to antenatal care (Abrysvo TGA Delegate's Overview).

6.39 The pre-PBAC response reported that RSVpreF was safe and well tolerated by maternal participants, and no safety signals were detected in infant participants through 24 months after birth, based on the final analysis of the MATISSE trial. It was reported that AE incidences were similar in the vaccine and placebo groups for mothers and infants. It was stated that an additional 9 preterm births (<37 weeks, including 6 RSVpreF and 3 placebo) were included in the final analysis and the relative risk of preterm birth was 1.2 (95% CI: 0.98, 1.46). Munjal et al., 2024 (provided with pre-PBAC response) reported that maternal AEs of hypertensive conditions (including gestational hypertension, preeclampsia, eclampsia and HELLP syndrome) were reported more commonly in those with preterm birth and were more commonly seen in the RSVpreF group.

Benefits/harms

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

Table 10: Summary of comparative benefits and harms for RSVpreF and placebo (primary analysis)

RSV-positive MA-LRTI				
Event	**RSVpreF**	**Placebo**	**Absolute Difference**	**VE[a], %, (CI[b])**
Cases 90 days post birth	24/3495 (0.7%)	56/3480 (1.6%)	0.9%	57.1 (14.7, 79.8)
Cases 120 days post birth	35/3495 (1.0%)	81/3480 (2.3%)	1.3%	**56.8 (31.2, 73.5)**
Cases 150 days post birth	47/3495 (1.3%)	99/3480 (2.8%)	1.5%	**52.5 (28.7, 68.9)**
Cases 180 days post-birth	57/3495 (1.6%)	117/3480 (3.4%)	1.8%	**51.3 (29.4, 66.8)**
RSV-positive severe MA-LRTI				
Cases 90 days post birth	6/3495 (0.2%)	33/3480 (0.9%)	0.7%	**81.8 (40.6, 96.3)**
Cases 120 days post birth	12/3495 (0.3%)	46/3480 (1.3%)	1.0%	**73.9 (45.6, 88.8)**
Cases 150 days post birth	16/3495 (0.5%)	55/3480 (1.6%)	1.1%	**70.9 (44.5, 85.9)**
Cases 180 days post-birth	19/3495 (0.5%)	62/3480 (1.8%)	1.3%	**69.4 (44.3, 84.1)**

Harms						
MATISSE	**RSVpreF n/N**	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				RSVpreF	**Comparator/ PBO**	
Maternal participants						
Any AE	507/3682	483/3675	1.05 (0.93, 1.18)	13.8	13.1	0.01 (-0.01, 0.02)
Pain at injection site	1488/3663	369/3639	**4.00 (3.61, 4.45)**	40.6	10.1	**0.30 (0.27, 0.32)**
Muscle pain	972/3663	623/3639	**1.55 (1.42, 1.70)**	27.5	17.1	**0.09 (0.08, 0.11)**
Infant participants						
Any AE	1324/3568	1229/3558	**1.07 (1.01, 1.14)**	37.1	34.5	**0.03 (0.00, 0.05)**
Jaundice neonatal	257/3568	241/3558	1.06 (0.90, 1.26)	7.2	6.8	0.00 (-0.01, 0.02)
Premature baby	202/3568	169/3558	1.19 (0.98, 1.45)	5.7	4.7	0.01 (-0.00, 0.02)

Source: Table 2.5.1, p61, and Table 2.5.2, p63 of the submission. Table 18, pp69-70, Table 19 pp71-72, Table 14.72, pp400-405 and Table 14.90, pp809-839 of the MATISSE CSR.

Abbreviations: AE = adverse event; CI = confidence interval; MA-LRTI = medically attended lower respiratory tract illness; RD = risk difference; RR = risk ratio; RSV = respiratory syncytial virus; RSVpreF = respiratory syncytial virus pre-fusion F protein vaccine; VE = vaccine efficacy

* Maximum duration of follow-up = 24 months

[a] Calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.

[b] 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure

Bold indicates statistically significant results.

6.41 Based on the direct evidence presented in the submission, for every 100 pregnant women administered RSVpreF in comparison with placebo (no vaccine):

- Approximately 2 fewer infants would have RSV-positive MA-LRTI out to 180 days post birth.
- Approximately 1 less infant would have RSV-positive severe MA-LRTI out to 180 days post birth.
- Approximately 31 additional women would experience pain at the injection site within 7 days after vaccination.
- Approximately 10 additional women would experience muscle pain within 7 days after vaccination.

Clinical claim

6.42 The submission described RSVpreF as superior in terms of effectiveness compared to placebo. The ESC agreed with the commentary that this claim was adequately supported. In the key MATISSE trial, administration of RSVpreF to pregnant women resulted in a reduction in RSV-positive MA-LRTI in infants up to 180 days after birth, corresponding to a VE of 51.3% (97.58% CI:29.4%, 66.8%), which met the statistical criterion for success for the primary endpoint (a CI lower bound > 20%). Additionally, RSVpreF administration resulted in a reduction in RSV-positive severe MA-LRTI in infants up to 180 days after birth resulting in a VE of 69.4% (97.58% CI:44.3%, 84.1%). Hospitalisations due to RSV were also reduced in the RSVpreF group up to 180 days after birth, giving a VE of 56.8% (99.17% CI:10.1%, 80.7%). The key areas of uncertainty include a lack of evidence for the efficacy of the vaccine in infants born prematurely, and those resulting from multiple pregnancies and non-healthy pregnancies.

6.43 The submission described RSVpreF as inferior in terms of safety compared to placebo. The ESC agreed with the commentary that this claim was adequately supported as maternal RSVpreF recipients experienced local reactions more frequently (42.5%) compared with placebo recipients (10.4%). The most common local reaction was pain at the injection site, reported in 1,488 (40.6%) participants in the RSVpreF group and 369 (10.1%) in the placebo group. Maternal participants who received RSVpreF were also more likely to experience muscle pain when compared with participants who received a placebo injection (26.5% vs 17.1%). In the RSVpreF arm of MATISSE, there were numerically higher rates of premature births (RSVpreF = 5.7% vs. placebo = 4.7%) and low birthweight births (RSVpreF = 5.1% vs. placebo=4.3%). The trial was not statistically powered to detect any differences between the intervention arms for these measures.

6.44 The safety and efficacy claims in the submission are consistent with the ATAGI advice and the TGA Delegate's conclusions. ATAGI concluded that the observed efficacy is clinically meaningful, and the data presented in MATISSE provide reassuring evidence about the safety of RSVpreF to both mothers and their babies (the ATAGI Advice to the PBAC). The TGA Delegate concluded that RSVpreF demonstrated a modest but clinically useful vaccine efficacy and that the adverse event profile was acceptable compared to placebo (the TGA Delegates Overview).

6.45 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.46 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.47 The submission presented a cost-utility analysis based on the MATISSE clinical trial, measuring outcomes in quality-adjusted life years (QALYs). This was consistent with the clinical claim of superior effectiveness. Key components of the economic evaluation are presented in Table 11.

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

Component	Summary
Treatments	RSVpreF vaccine vs SOC (no vaccine)
Time horizon	One year (from birth of the infant) vs 360 days follow up post birth in the MATISSE trial. As the model estimates the QALY difference over a lifetime, the time horizon is technically a lifetime.
Methods used to generate results	Decision tree model where costs and QALYs lost are assigned to each event.
Events	Hospitalised due to RSV; ED attendance due to RSV; Outpatient attendance due to RSV and death once hospitalised due to RSV.
Event probabilities	Event probabilities were derived from Australian studies as the MATISSE trial was conducted during the COVID-19 pandemic which may have impacted RSV transmission. ATAGI considered these sources reasonable and mostly accurate given the lack of available data (ATAGI pre-submission advice).
VE of RSVpreF	The VE of RSVpreF for preventing MA-LRTI due to RSV at 360 days (41%) was applied to all event probabilities except for death, in the intervention arm. The use of VE at a single time point may be conservative as it appeared to be higher at earlier time points. However, the VE for preventing hospitalisation at 360 days appeared to be lower in the trial (33%) than what was applied in the economic model. The ESC noted the high sensitivity of the ICER to the VE for preventing hospitalisation and considered the submission's approach was optimistic.
Utility values	Disutility scores were sourced from Mao et al.[18] and were applied to the infant and carer. QALYs lost over a lifetime were also calculated for deaths, assuming life-expectancy in line with the ABS life tables. The Mao study estimated QoL in infants through their carer filling out the EQ-5D-3L-Y questionnaire on their behalf. This introduces uncertainty as the instrument is not recommended for children aged <4 years and the questionnaire was altered to only capture certain domains. Disutilities associated with distress from the carer were included in the base case which is not consistent with the recommendations in the PBAC guidelines.
Costs	Costs for vaccine administration[a], hospitalisation, ED and outpatient attendance were derived from Australian sources. A gap-payment was included for outpatient (GP consultation) costs. Including a gap-payment for GP consultations for infants was not reasonable and in contrast to the PBAC guidelines.

Source: Constructed during the evaluation from the "ABRYSVO_Maternal_CEA_Base_Case" Excel Workbook provided with the submission.

Abbreviations: ABS = Australian Bureau of Statistics; ATAGI = Australian Technical Advisory Group on Immunisation; ED = emergency department; EQ-5D-3L-Y = EuroQol-5 dimensions-3 levels–youth version; ESC = Economic Sub-committee; MA-LRTI = medically attended – lower respiratory tract illness; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life year; RSV = Respiratory Syncytial Virus; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine; SOC = standard of care; VE = vaccine efficacy.

[a] $7.00 vaccine administration cost was applied in the model, sourced from ESC's advice for the maternal dTpa Vaccine Public Summary Document (PSD) (July 2016 PBAC Meeting).

6.48 The submission nominated a time horizon of one year, starting from the birth of the infant. As the model estimated the QALY difference over a lifetime, technically the economic evaluation has adopted a lifetime time horizon. The modelled one-year decision tree reflects the treatment effect duration. However, it is not appropriate to delay the starting point of the model (and hence discounting) to a time after the intervention has been administered as the vaccine is administered at 24 – 36 weeks gestation. This has affected the cost-effectiveness estimate as discounting starts at approximately 14 months after the intervention is administered (and hence 2 months'

[18] Mao Z, Li X, Dacosta-Urbieta A, Billard M-N, Wildenbeest J, Korsten K, et al. 2023. Economic burden and health-related quality-of-life among infants with respiratory syncytial virus infection: A multi-country prospective cohort study in Europe. Vaccine. 41(16):2707-15

worth of costs and outcomes that occurred in the second year of the model are not subject to discounting). To address this, the evaluation explored the effect of "reverse discounting" the vaccine acquisition and administration costs by two months' worth of discounting (resulting in a vaccine acquisition and administration cost of $ vs $ undiscounted).[19] This increased the incremental cost-effectiveness ratio (ICER) by % (from $25,000 to < $35,000 per QALY to $25,000 to < $35,000 per QALY). The sponsor accepted this correction in the PSCR.

6.49 The submission adopted a decision tree model structure where all infants were exposed to the events of hospitalisation due to RSV, attending the emergency department (ED) due to RSV and attending outpatient services due to RSV. Infants who were hospitalised were also at risk dying due to RSV. Each event was associated with costs and QALYs lost.

6.50 All baseline event probabilities, which were applied to the SOC arm, were sourced from Australian studies. While the MATISSE trial did capture hospitalisation rates, the submission considered these to be impacted by the COVID-19 pandemic and hence unreliable. ATAGI agreed that event probabilities based on published literature in the Australian setting were preferable over rates observed in the MATISSE trial and considered the sources used in the economic model to be most appropriate (ATAGI pre-submission advice). A summary of the baseline event probabilities applied in the economic model are presented in Table 12.

[19] $[redacted]/(1+0.05)$^{-2/12}$ + $7/(1+0.05)$^{-2/12}$ = $[redacted]

Table 12: Baseline event probabilities

Event	Probability	Source	Comment
Hospital admission due to RSV	2.33%	Mean predicted hospital incidence rate from 2000-2012 for <1 year RSV cases reported in Gebremedhin et al.[20]	The incidence of hospitalisation appears to be decreasing over time and hence the evaluation considered it may be preferable to select hospitalisation rates from a specific year, towards the end of the observation period, in Gebremedhin et al.[20] The 2012 hospitalisation rate was 2.03%, and the ESC noted the sensitivity of the ICER to this. The PSCR noted that the hospitalisation rate of RSV applied in the base case, which was derived from the average of data for 2000-2012 reported by Gebremedhin, et al., 2022 (2.33%) was consistent with ATAGI advice, and likely to be a conservative estimate. The ESC considered that the submission's base case value was reasonable (2.33%).
ED attendance due to RSV	1.8%	Proportion of ALRI RSV cases (<1 year) who only attended the ED in Takashima et al.[21] multiplied by the symptomatic RSV incidence for infants aged <1 year.	This was reasonable.
Outpatient attendance due to RSV	8.1%	Proportion of symptomatic ALRI RSV cases (<1 year) who had healthcare contact but did not attend the emergency department or were not admitted into hospital in Takashima et al. multiplied by the symptomatic RSV incidence for infants <1 year.	This was reasonable.
Death once hospitalised due to RSV	0.2% of infant cases hospitalised	hCFR for RSV in patients <16 years reported in Saravanos et al.[22]	ATAGI considered this source was reasonable given the lack of available data, however noted that the use of hospital admissions data may underestimate the true hCFR for RSV deaths. The ESC noted an alternative estimate of the in-hospital CFR of 0.1% was reported in the ATAGI pre submission advice to PBAC, derived from the study by Li et al 2022[23] and noted the ICER was sensitive to this. The ESC concluded that both figures were reasonable and noted the sensitivity of the ICER to the value used.

Source: Constructed during the evaluation from the submission (pp 102 – 121) and the "ABRYSVO_Maternal_CEA_Base_Case" Excel Workbook provided with the submission.

Abbreviations: ALRI = acute lower respiratory tract infection; ARI = acute respiratory infection; ATAGI = Australian Technical Advisory Group on Immunisations; ED = emergency department; hCFR = hospital Case Fatality Ratio; MA-LRTI = medically attended – lower respiratory tract illness; NA = not applicable; RSV = Respiratory Syncytial Virus.

6.51 In the intervention arm, the baseline event probabilities (except for the risk of death) were adjusted for a risk reduction associated with the VE of RSVpreF, which was calculated as the complement of the VE of RSVpreF for preventing MA-LRTI due to RSV at 360 days after birth (1 - 0.41 = 0.59), as observed in the MATISSE trial. The

submission has claimed that this was a conservative approach as the VE at earlier time points was higher. This statement was reasonable for the ED and outpatient attendance events. However, the VE for preventing hospitalisations was lower (33%) in the MATISSE trial and hence was more reasonable to apply in the base case analysis. If applying the hospitalisation due to RSV VE, it would then be appropriate to adjust the VE for preventing MA-LRTI (applied to ED and outpatient attendances) to exclude hospitalisation, calculated as 45% during the evaluation (Table 13). This approach increased the ICER by % (from $25,000 to < $35,000 per QALY gained to $75,000 to < $95,000 per QALY gained). The PSCR stated that the MATISSE trial is ongoing and incomplete data are available for 360 day outcomes resulting in relatively uncertain outcomes, as reflected in wide confidence intervals for example in the primary analysis of 360 day VE against hospitalised MA-LRTI, VE was 33.3% (99.17% CI:-17.6%, 62.9%).

Table 13: VE observed in the MATISSE trial versus modelled in the economic evaluation

MATISSE trial observed VEs at 360 days		Submission base case VEs			Hospitalisation specific VE approach		
Hospital admission due to RSV	MA-LRTI RSV	Hospital admission due to RSV	ED attendance due to RSV	Outpatient attendance due to RSV	Hospital admission due to RSV	ED attendance due to RSV	Outpatient attendance due to RSV
33%[a]	41%	41%			33%	45%[b]	

Source: Constructed during the evaluation.
Abbreviations: ED = emergency department; MA-LRTI = medically attended – lower respiratory tract illness; RSV = Respiratory Syncytial Virus; VE = vaccine efficacy.
[a] Not statistically significant.
[b] VE for preventing MA-LRTI RSV, excluding hospitalisation, calculated during the evaluation.

6.52 The economic model included QALYs lost for the infant and the carer for each event. As the MATISSE trial did not capture quality-of-life data, QALYs lost for non-fatal events were sourced from Mao et al.[18] who aimed to measure the QALYs lost that were attributable to RSV infections for infants (<1 year) and carers in several European countries. The QALYs lost were applied as a once-off to the proportion of infants and carers experiencing each event (Table 14).

[20] Gebremedhin AT, Hogan AB, Blyth CC, Glass K, Moore HC. 2022. Developing a prediction model to estimate the true burden of respiratory syncytial virus (RSV) in hospitalised children in Western Australia. *Scientific Reports*. 12(1):332.
[21] Takashima MD, Grimwood K, Sly PD, Lambert SB, Chappell KJ, Watterson D, et al. 2021. Epidemiology of respiratory syncytial virus in a community birth cohort of infants in the first 2 years of life. European journal of paediatrics. 180(7):2125-35.
[22] Saravanos GL, Hsu P, Isaacs D, Macartney K, Wood NJ, Britton PN. 2022. Respiratory Syncytial Virus-attributable Deaths in a Major Pediatric Hospital in New South Wales, Australia, 1998-2018. The Pediatric infectious disease journal. 41(3):186-91.
[23] Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022;399(10340):2047-64 (Extracted from Table 3, Case fatality ratio for industrialised countries).

Table 14: QALYs lost applied in the economic evaluation

Event	QALYs lost per event		Source of estimate	Proportion of patients	
	Infant	Carer		RSVpreF	SOC
Attending the ED	0.00630[a]	0.00055[a]	Mao et al. [18]	1.06%	1.80%
Attending outpatient services				4.78%	8.10%
Non-fatal hospitalisations	0.01013[a]	0.00329[a]		1.37%	2.33%
Dead	19.7990	0	McCaffrey et al.[24] and ABS life tables[25]	0.0027%	0.0047%

Source: Constructed during the evaluation from the "ABRYSVO_Maternal_CEA_Base_Case" Excel Workbook provided with the submission.

Abbreviations: ABS = Australian Bureau of Statistics; ED = emergency department; QALYs = quality-adjusted life year; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine.

[a] Based on quality-adjusted days lost over 14 days in Mao et al.[18] transformed to QALYs.

6.53 For patients who died due to RSV, the submission calculated the number of QALYs lost based on an average life-span (derived through ABS life tables) and a study which estimated the background utility of the metropolitan South Australian population (McCaffrey 2016). After adjusting for a 5% per annum discounting rate, this was derived to be 19.799 QALYs. Several issues were identified during the evaluation and ESC consideration:

- The inclusion of carer quality-adjusted life days (QALDs) lost (1.2 QALDs/0.00329 QALYs lost for infant hospitalisations and 0.2 QALDs/0.00055 QALYs lost for infant ED and outpatient attendances) may not be reasonable as the PBAC guidelines state to only include outcomes "associated with the patient".
- Infant QALDs lost (3.7 QALDs/0.01013 QALYs lost for hospitalisation and 2.3 QALDs/ 0.00630 QALYs lost for ED and outpatient attendances) are uncertain as the EQ-5D questionnaire was filled out by a carer (on behalf of the infant) and EQ-5D questionnaires (including the Youth version) are not recommended for children aged <4 years.[26] The ESC noted the model was sensitive to assumptions regarding infant QALDs lost.
- The ESC noted that the value set used to estimate utilities was from methodological work conducted in Spain, which is unlikely to represent Australian values for EQ-5D-Y health states, but that it is not possible to determine the direction of any bias.

6.54 Excluding carer QALYs from the economic analysis increased the ICER by [redacted]% (from $25,000 to < $35,000 per QALY gained to $25,000 to < $35,000 per QALY gained). To account for the uncertainty regarding infant QALYs, both cost-consequence (CCA) and cost-effectiveness (CEA) analyses were performed during the evaluation (Table 16).

[24] McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. 2016. Health-related quality of life measured using the EQ-5D–5L: South Australian population norms. *Health and Quality of Life Outcomes*. 2016/09/20;14(1):133.

[25] Australian Bureau of Statistics. 2023. Life expectancy. [cited 2023 13 Nov]; Available from: https://www.abs.gov.au/statistics/people/population/life-expectancy/2020-2022#cite-window1.

[26] EuroQol. EuroQol research foundation. 2023 [cited 2023 13 Nov]; Available from: https://euroqol.org/publications/user-guides/.

6.55 As mentioned above, the submission applied a once-off 20 QALYs lost for infants who died due to RSV. This was calculated based on the Australian Bureau of Statistics lifetables and a study which estimated the general age-dependent utility of the South Australia population, adjusted for a 5% per annum discounting rate.[27] This was reasonable, noting that the utility estimates were derived using the UK value set.

6.56 The submission included ED costs ($1,283) sourced from the National Health Cost Data Collection for emergency care and hospitalisation costs ($18,617) derived from Brusco et al. who aimed to estimate the annual cost burden for Australian children <5 years hospitalised with RSV in 2018.[28] While the ED costs were reasonable, the hospitalisation cost sourced from the literature included costs associated with re-admission to hospital for any cause within 6 months after an index RSV admission. The inclusion of re-admission costs for all-causes was not justified as trial data was not designed to capture and did not support a difference in all-cause re-admission after an index RSV infection between the two treatment arms. Instead, it may be reasonable to assume that a certain proportion of patients will require re-admission for RSV related causes after an RSV infection. A study which reported respiratory related re-admission in children showed that approximately 13% of children with an index RSV hospital admission would have an RSV-related re-admission within one year.[29] Assuming that this proportion of patients will re-admit and the remaining patients would incur only the index RSV hospitalisation cost reported in the Brusco et al. ($14,455), the weighted hospitalisation cost was calculated to be $14,991. Using a cost per hospitalisation of $14,991 (compared to $18,617 in the base case) increased the ICER by % (from $25,000 to < $35,000 per QALY gained to $55,000 to < $75,000 per QALY gained). The PSCR proposed a value of 25% would be more appropriate on the basis that causal readmission to hospital following an acute episode of RSV is not limited to respiratory related symptoms, which corresponded to a hospital cost of $15,488. The ESC acknowledged that readmission could be for non-respiratory reasons but considered the appropriate rate of readmission proposed in the PSCR was not well supported.

6.57 The submission costed outpatient attendances as a GP consultation (MBS Item 23). However, citing recent declines in bulk-billing GP clinics and the increase in gap fees, the economic model included out-of-pocket costs.[30] This resulted in the average GP consult costing $64.26. Not directly applying the MBS scheduled fee is not consistent with the PBAC guidelines which recommend that the schedule fee presented in the MBS costs should be used to estimate costs in the outpatient setting. Additionally, the

[27] McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. 2016. Health-related quality of life measured using the EQ-5D–5L: South Australian population norms. *Health and Quality of Life Outcomes*. 2016/09/20;14(1):133.
[28] All costs inflated to 2023 dollars from Brusco NK, Alafaci A, Tuckerman J, Frawley H, Pratt J, Daley AJ, et al. 2022. The 2018 annual cost burden for children under five years of age hospitalised with respiratory syncytial virus in Australia. *Commun Dis Intell*. 46:1-21.
[29] Choi Y, Heller EG, Gesteland PH, Amoafo L, Zhang Y, Finelli L, et al. 2021. 1346. The Risk of Readmission after RSV Hospitalization Among Children Younger than 5 Years. *Open Forum Infectious Diseases*. 2021;8(Supplement_1):S760-S.
[30] Cleanbill Blue Report (January 2023).

Cleanbill Blue Report[30] appeared to only consider bulk billing for adults and hence the above cost is likely to be an overestimate for infants. Multiple Australian studies have reported high bulk billing rates for children (up to 80%).[31, 32] However, it may be more reasonable to assume more than one GP visit per medically attended RSV episode. The model was not sensitive to this at the MBS scheduled fee cost (see Table 18).

6.58 Key model drivers are presented in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
VE of RSVpreF	41% to all event probabilities, except for death.	High, favours RSVpreF. Use of the hospitalisation (33%), ED (45%) and outpatient attendance (45%) specific VEs[a] increased the ICER to $[redacted][2]/QALY gained.
Hospitalisation costs	$18,617. RSV hospitalisation costs for infants aged <1 year, including costs associated with all-cause re-admission six-months after an index RSV admission. The inclusion of re-admissions costs for all-causes was not reasonable.	High, favours RSVpreF. Assuming that 13% of patients would be re-admitted (weighted hospitalisation cost of $14,991) increased the ICER to $[redacted][3]/QALY gained.
Hospitalisation rate	Mean predicted hospital incidence rate from 2000-2012 for RSV cases aged <1 year, reported in Gebremedhin et al (2.33%). The hospitalisation rate appeared to be decreasing over time and hence it may be more reasonable to select a single time point towards the end of the observation period.	High, favours RSVpreF. Use of the 2012 hospitalisation rate (2.03%) increased the ICER to $[redacted][3]/QALY gained.
QALYs lost	Applying the same infant QALYs lost for attending the emergency department and outpatient services does not seem plausible. This is particularly uncertain as EQ-5D instruments are not recommended for infants aged <4 year.	Moderate, favours RSVpreF. Assuming no QALYs lost due to outpatient attendance increased the ICER to $[redacted][4]/QALY gained.

Source: Constructed during the evaluation.

Abbreviations: ED = emergency department; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; RSV = Respiratory Syncytial Virus; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine; VE = vaccine efficacy.

[a] VE for preventing ED and outpatient attendance due to RSV calculated as 45% during the evaluation.

The redacted values correspond to the following ranges:

[1] *$25,000 to < $35,000*

[2] *$75,000 to < $95,000*

[3] *$55,000 to < $75,000*

[4] *$35,000 to < $45,000*

6.59 The submission did not present a stepped economic analysis. This was not reasonable as the economic evaluation was substantially sensitive to model parameters not observed in the trial. Given this uncertainty, the additional economic analyses were explored during the evaluation, including CCAs (based on trial and modelled inputs) and a CEA. This is presented in Table 16.

[31] O'Sullivan BG, Kippen R, Hickson H, Wallace G. 2022. Mandatory bulk billing policies may have differential rural effects: An exploration of Australian data. *Rural and Remote Health*. [Journal Article]. 22(1):[1]-8.

[32] Freed GL, Allen AR. 2018. General paediatrics outpatient consultation fees, bulk billing rates and service use patterns in Australia. *Australian and New Zealand Journal of Public Health*. 2018/12/01/;42(6):582-7.

Table 16: Results of the stepped economic evaluation, assuming a cohort of 1,000 vaccinated women

Step and component	RSVpreF	SOC (no vaccine)	Increment/interpretation
Step 1a: CCA, based on data from the MATISSE trial			
RSV that requires hospitalisation	11	16	5 hospitalisations avoided
RSV that involves medical attendance[a]	26	45	19 medical attendance events avoided
Total costs	$	$	$ additional cost
Step 1b: CCA, based on data in the Australian setting			
RSV that requires hospitalisation	10	23	14 hospitalisations avoided
RSV that involves medical attendance[a]	72	122	50 medical attendance events avoided
Total costs	$	$	$ additional cost
Step 2: CEA, measuring outcomes in terms of LYs gained			
LY lost	0.5608	0.9505	0.3897 LYs gained
Total cost	$	$	$
ICER (cost/LY gained)			$ [1]
Step 3: CUA (submission's base case, including carer QALYs)			
QALYs lost	1.1271	1.9104	0.7833 QALYs gained
Total cost	$	$	$
ICER (cost/QALY gained)			**$** [2]

Source: Constructed during the evaluation Table 15, Table 16 and Table 21 of the "c3671008-report-body" attachment provided with submission and the "ABRYSVO_Maternal_CEA_Base_Case" Excel Workbook provided with the submission.

Abbreviations: CCA= cost-consequence analysis; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; ED = emergency department; LY = life year; QALY = quality-adjusted life year; RSV = Respiratory Syncytial Virus; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine; SOC = standard of care.

[a] Includes hospitalisation, ED and outpatient attendance.

The redacted values correspond to the following ranges

[1] *$55,000 to < $75,000*

[2] *$25,000 to < $35,000*

6.60 The disaggregated summary for costs and health outcomes are presented in Table 17. As expected, the majority of QALYs gained are associated with the prevention of deaths in the vaccine arm. The vaccine acquisition costs comprise the majority of the incremental costs between the intervention and comparator arm. The main cost savings are attributable to reduced hospitalisation costs in the intervention arm, however as mentioned previously, these cost savings may be an overestimate due to the higher VE efficacy applied to hospitalisations over what was observed in the trial.

Table 17: Summary of outcomes and cost impacts included in the economic evaluation, per 1,000 vaccinated women

Patients experiencing each outcome					
Event		**RSVpreF Arm**	**SOC Arm**	**Increment**	
Outpatient attendance		48	81	33	
ED attendance		11	18	7	
Hospitalised		14	23	10	
- Non-fatal		14	23	10	
- Fatal		0.03	0.05	0.02	
No event		928	878	-50	
Total		**100%**	**100%**	**NA**	
QALYs lost					
Event		**RSVpreF Arm**	**SOC Arm**	**Increment**	**% Increment**
Outpatient attendance		0.3009	0.5101	-0.2091	26.70%
ED attendance		0.0669	0.1133	-0.0465	5.93%
Hospitalised		0.6823	1.1564	-0.4741	60.53%
- Non-fatal		0.1390	0.2356	-0.0966	12.33%
- Fatal		0.5433	0.9208	-0.3775	48.20%
Carer distress		0.0771	0.1306	-0.0535	6.84%
Total		**1.1271**	**1.9104**	**-0.7833**	**100%**
Costs					
Outcome	**Resource**	**RSVpreF Arm**	**SOC**	**Increment**	**% Increment**
All patients	Vaccine acquisition	$	**$**	$	%
	Vaccine administration	$7,000	**$**	$	%
Outpatient attendance	GP consultation cost	$3,071	**$**	-$	%
ED attendance	ED attendance cost	$13,631	**$**	-$	%
Hospitalised	Hospitalisation cost	$255,423	**$**	-$	%
- Non-fatal		$254,912	**$**	-$	%
- Fatal		$511	**$**	-$	%
Total		**$**	**$**	**$**	**100.00%**

Source: Constructed during the evaluation from the "ABRYSVO_Maternal_CEA_Base_Case" Excel Workbook provided with the submission.

Abbreviations: ED = emergency department; GP = general practitioner; LY = life year; QALY = quality-adjusted life year; RSV = Respiratory Syncytial Virus; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine; SOC = standard of care.

6.61 Key sensitivity analyses conducted by the submission and during the evaluation are presented in Table 18. Due to the small incremental costs and QALYs in the base case evaluation, most parameters had a substantial effect on the ICER when testing alternative inputs. As hospitalisations were a key driver of costs and QALYs, the model was extremely sensitive to any parameter which affected this outcome.

Table 18: Sensitivity analyses per 1,000 vaccinated women[a]

Analyses	**Incremental cost ($)**	**Incremental QALY**	**ICER**	**% Change**
Base case		**0.783**	[1]	**-**
Discount rate (base case 5% to QALYs lost)				
• 0%		1.865	[2]	%
• 3.5%		0.909	[1]	%
• Reverse discounting to vaccine costs[b] **#5**		0.783	[1]	%
Hospitalisation rate of RSV (base case 2.33%)				
• 2.03%[c] (i.e., 13% lower than base case)		0.719	[3]	%
• 2.63% (i.e., 13% higher than base case)		0.849	Dominant	-
Risk of dying once hospitalised (base case 0.20%)				
• 0.10%		0.594	[4]	%

Analyses	Incremental cost ($)	Incremental QALY	ICER	% Change
VE (base case 41% to hospitalisation, ED and outpatient attendance events)				
• 33% for hospitalisations, 45% for ED and outpatient attendance events[d] **#2**	[redacted]	0.712	[redacted][5]	[redacted]%
• 41% for hospitalisations, 54% for ED and outpatient attendance events (based on VE in subgroup of mothers at 28 to < 37 weeks gestation as provided in the PSCR using evaluation methodology)	[redacted]	0.871	[redacted][6]	-[redacted]%
Infant QALYs lost (base case 0.010 for hospitalisation, 0.00630 for ED and outpatient attendance)				
• No infant QALYs lost for outpatient attendance	[redacted]	-0.574	[redacted][4]	[redacted]%
Carer QALYs lost (base case 0.00339 for hospitalisation, 0.00055 for ED and outpatient attendance)				
• Excluded **#4**	[redacted]	0.730	[redacted][1]	[redacted]%
Vaccine administration cost (base case $7)				
• $5.00	[redacted]	0.783	[redacted][1]	-[redacted]%
• $10.00	[redacted]	0.783	[redacted][1]	[redacted]%
Outpatient attendance cost (base case $64.26)				
• 1.5 × $41.20 (MBS Item 23) **#1**	[redacted]	0.783	[redacted][1]	[redacted]%
Hospitalisation cost (base case $18,617)				
• $14,455[e]	[redacted]	0.783	[redacted][5]	[redacted]%
• $14,991[f] **#3**	[redacted]	0.783	[redacted][3]	[redacted]%
Scenario Analysis				
• 6-month treatment effect period, with adjusted event probabilities, assuming 75% of ED and outpatient attendance events occur by 6-months and CSR VEs, hospitalisations (56.1%), and ED and outpatient attendance (51.3%).[g]	[redacted]	0.748	[redacted][4]	[redacted]%
Pre-PBAC response (Revised version of 6-month model scenario analysis)				
· 6-month treatment effect period, with adjusted event probabilities, assuming 75% of ED and outpatient attendance events occur by 6-months and VEs for subgroup vaccinated between 28 and <37 weeks gestation sourced from final analysis, hospitalisations (63.5%), and ED and outpatient attendance (59.3%)[h], includes carer disutilities and RSVpreF price of $[redacted]	[redacted]	0.847	[redacted][1]	[redacted]%
Multivariate Analyses				
#1, #2	[redacted]	0.712	[redacted][5]	[redacted]%
#1, #2, #3	[redacted]	0.712	[redacted][7]	[redacted]%
#1, #2, #3, #4	[redacted]	0.662	[redacted][7]	[redacted]%
#1, #2, #3, #4, #5	[redacted]	0.662	[redacted][7]	[redacted]%
#1, #2, #3, #4, #5 and RSVpreF price of $[redacted] as proposed in pre-PBAC response	[redacted]	0.662	[redacted][8]	[redacted]%

Source: Constructed during the evaluation from the "ABRYSVO_Maternal_CEA_Base_Case" Excel Workbook provided with the submission.

Abbreviations: ED = emergency department; ICER = incremental cost-effectiveness ratio; MBS = Medicare Benefits Schedule; QALY = quality-adjusted life year; RSV = Respiratory Syncytial Virus; VE = vaccine efficacy.

[a] Cost and QALYs multiplied by 1,000 in order to clearly observe the effect of the sensitivity analyses.

[b] This sensitivity analysis was conducted to estimate the ICER when assuming the base discount year starts from the vaccine administration time point (approximately 2 months before birth). As the discounted incremental QALYs cannot be reliably estimated through this analysis and the choice of discount year does not influence the ICER under equal discounting of costs and outcomes, an alternative method was used by discounting the vaccine acquisition and administration costs by -0.83% (two months' worth of discounting at 5% per annum) as the submission's base case discount year was from birth. While the ICER is an accurate estimate of assuming the model base discount year starts at vaccine administration, the incremental costs and outcomes are indicative.

[c] Predicted hospitalisation rate for children (aged <1 year) in 2012, reported by Gebremedhin et al.
[d] ED and outpatient VE adjusted to exclude hospitalisation.
[e] Hospitalisation cost, excluding re-admission for any cause, sourced from Brusco et al. inflated to 2023 dollars.
[f] Hospitalisation cost, assuming 13% of patients will have a respiratory related re-admission as per Choi et al.[29]
[g] Hospitalisation rate: 1.62% (mean yearly RSV hospitalisation rate for infants aged 3-6 months and <3 months from Gebremedhin et al. divided by 2). 75% of ED and outpatient attendance rate specified in base case (1.35% and 6.08%, respectively) as 75% of MA-LRTI events occurred at the 180-day time point in the MATISSE trial. VE for preventing hospitalisation due to RSV at 180 days (56.1%), the VE for preventing ED and outpatient attendance sourced from the VE for preventing MA-LRTI due to RSV at 180 days (51.3%).
[h] Hospitalisation rate: 1.62% (mean yearly RSV hospitalisation rate for infants aged 3-6 months and <3 months from Gebremedhin et al. divided by 2). 75% of ED and outpatient attendance rate specified in base case (1.35% and 6.08%, respectively) as 75% of MA-LRTI events occurred at the 180-day time point in the MATISSE trial. VE for preventing hospitalisation due to RSV at 180 days (63.5%), the VE for preventing ED and outpatient attendance sourced from the VE for preventing MA-LRTI due to RSV at 180 days (59.3%).
The redacted values correspond to the following ranges
[1] *$25,000 to < $35,000*
[2] *$5,000 to < $15,000*
[3] *$55,000 to < $75,000*
[4] *$35,000 to < $45,000*
[5] *$75,000 to < $95,000*
[6] *$15,000 to < $25,000*
[7] *$115,000 to < $135,000*
[8] *$95,000 to < $115,000*

6.62 The PSCR provided an updated economic model which included VE estimates for the subgroup of infants whose mothers were vaccinated at 28 to <37 weeks gestation. The ESC noted that on average, these infants have higher VEs than the entire population in the MATISSE trial and hence this improves the overall cost-effectiveness of RSVpreF. The ESC noted the ICER using the base case model and VE estimates for the subgroup of infants whose mothers were vaccinated at 28 to <37 weeks gestation (41% for hospitalisations, 54% for ED and outpatient attendance) was $15,000 to < $25,000/ QALY gained. The ESC noted the lower ICER reported when data were used only from those vaccinated from 28 weeks onwards. The ESC considered that a decline in the ICER may be plausible, but that there was considerable uncertainty in this area. Due to the uncertain magnitude of effect, the PBAC did not support the use of data from the 28 to <37 weeks gestation subgroup in the economic model (see paragraph 7.15).

6.63 The ESC recommended that the multi-variate sensitivity analysis based on the entire population which incorporated the following five changes was appropriate and noted the resulting ICER was $115,000 to < $135,000/QALY gained:

#1, Outpatient attendance cost of $61.80 (1.5 × $41.20; MBS Item 23)

#2, VE 33% for hospitalisations, 45% for ED and outpatient attendance events

#3, Hospitalisation cost $14,991

#4, Exclusion of carer QALYs lost

#5, Reverse discounting to vaccine costs

6.64 The PSCR stated that the base case model is conservative in scope and assesses only a limited range of direct healthcare costs and health outcomes associated with MA-LRTI: RSV. It was stated that the model excluded other potential benefits of the proposed immunisation program, including: protection from upper respiratory tract infections in infants, reduction of long term RSV sequelae such as childhood asthma

and wheeze, additional direct protection of mothers, reduction of costly and likely inefficient use of palivizumab, indirect protection of other important populations (unvaccinated mother/infant pairs, grandparents, healthcare and childcare workers, and older siblings) and broader societal benefits, such as relief of seasonal access blocks within the health system and improved workplace productivity.

6.65 The pre-PBAC response provided an updated economic model which was a revised version of the 6-month model (labelled as Scenario Analysis in Table 18 above). The pre-PBAC response model included VE estimates for the subgroup of infants whose mothers were vaccinated at 28 to <37 weeks gestation based on data from the final analysis. The PBAC considered that it would be more robust to apply the observed data for VE from the first year of the trial to the first year of the economic model consistent with the ESC Advice. The PBAC did not consider the pre-PBAC response model reliable for decision making, because the inputs for vaccine efficacy were not adequately supported. Secondly, the PBAC considered that carer QALYs lost should be excluded from the base case, consistent with the PBAC guidelines. The PBAC noted the model provided with the pre-PBAC response incorporated the ESC revisions with respect to reverse discounting (paragraph 6.48), hospital costs (paragraph 6.56) and outpatient attendance costs (paragraph 6.57).

Vaccine cost/patient/course

6.66 The submission proposed cost of RSVpreF was $[redacted] per unit. This is a once-off cost and is not dependent on dose. The pre-PBAC response proposed a lower price of $[redacted].

Estimated PBS usage & financial implications

6.67 This submission was considered by DUSC.

6.68 An epidemiological approach was used to estimate the financial impact of listing RSVpreF for pregnant women on the NIP. The key data sources and values used in the financial estimates are summarised in Table 19.

Table 19: Key inputs for financial estimates

Data	Value	Source	Commentary on the submission
Eligible population			
Number of pregnant women eligible for vaccination	Ranging from 451,428 to 727,029 per year.	Linear extrapolation based on the number of women who gave birth in Australia from 2011 – 2021, reported in the National Perinatal Data Collection dataset[33].	The commentary considered this was reasonable, noting that a small proportion of births occurred prior to 24 weeks (before the vaccination window commences). The DUSC considered this to be reasonable.
Uptake rate	Starting from [redacted]%, increasing to [redacted]% by Year 3.	Assumption based on uptake rates reported in literature for other maternal vaccinations.	While uptake rates are generally uncertain, ATAGI considered this was reasonable. The DUSC considered the uptake rate of RSVpreF might be underestimated based on the uptake rates of influenza and pertussis vaccines in pregnant women. However, it was noted that the uptake of RSVpreF in other countries was less than 50% and the DUSC also considered that the availability of alternatives, such as nirsevimab or other RSV vaccines may influence the uptake of RSVpreF. In addition, DUSC commented that uptake rates will be sensitive to risk communication about adverse events. The pre-PBAC response stated that the uptake rates in the submission were informed by ATAGI's Advice.
Costs			
RSVpreF	$[redacted]	Requested price per unit.	Consistent with the economic model in the submission.
Units of RSVpreF per person	1.00[a]	One vaccine unit per person	Reasonable after correcting for a rounding error[a].
MBS costs	$5.60 per administration.	80% MBS rebate applied to $7 worth of GP consultation time.[b]	While this was consistent with the economic model, the 100% MBS rebate is applicable for GP consultations. This was revised during the evaluation.

Source: Constructed during the evaluation from the "ABRYSVO_Maternal_Section 4 Workbook_Nov 2023" Excel Workbook provided with the submission.

Abbreviations: ATAGI = Australian Technical Advisory Group on Immunisation; GP = general practitioner; MBS = Medicare Benefits Schedule; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine.

[a] The submission attempted to convert the number of women to patient-years, resulting in small rounding error 0.999 (365/365.25) vaccine units per person. This was revised to one vaccine unit per person.

[b] $7.00 vaccine administration cost was applied in the model to account for GP consultation time, sourced from the PSD for maternal dTpa Vaccine (paragraph 6.37 July 2016 PBAC Meeting).

6.69 The submission considered that all women who will give birth will be eligible for vaccination and hence linearly extrapolated the number of women who gave birth from 2011-2022 through to 2029. The commentary considered this was reasonable, as a very small number of births occur before 24 weeks (the start of the vaccination

[33] AIHW. National Perinatal Data Collection. 2021; Available from: https://www.aihw.gov.au/about-our-data/our-data-collections/national-perinatal-data-collection.

window). Uptake rates based on ATAGI advice were applied to the forecasted number of women giving birth, starting from [redacted]% and increasing to [redacted]% by Year 3. ATAGI considered these uptake rates reasonable. Given the different maternal vaccines (influenza, pertussis and COVID-19) recommended during the 24 to 36 weeks gestation period and the lack of scheduled antenatal visits during this period, pregnant women may choose to prioritise some vaccines over others, resulting in modest uptake rates.

6.70 Consistent with the economic model and previous ESC advice from 2016 (para 6.37, dTpa vaccine Public Summary Document , July 2016 PBAC Meeting), the submission included a $7.00 GP administration cost per person. The submission had applied the 80% MBS rebate to the GP administration cost (resulting in a cost per administration of $5.60). This was not appropriate as the 100% rebate applies to GP consultation costs. The MBS implications were re-estimated during the evaluations using the revised number of vaccine units and assuming a 100% MBS benefit.

6.71 The derivation of the vaccinated population and the net financial implications to the NIP and MBS are presented in Table 20.

Table 20: Estimation of number of treated patients and financial implications to the NIP

Description	2024	2025	2026	2027	2028	2029
Predicted number of women who will give birth[a]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Uptake rate[b]	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number of women vaccinated	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Units of vaccine dispensed, revised[c]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Total cost to the NIP, revised[c] ($)	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Total cost to the MBS, revised[c,d] ($)	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Total cost, revised ($)	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]

Source: Constructed during the evaluation from the"ABRYSVO_Maternal_Section 4 Workbook_Nov 2023" Excel Workbook provided with the submission.

Abbreviations: AIHW = Australian Institute of Health and Welfare; ATAGI = Australian Technical Advisory Group on Immunisation; GP = general practitioner; MBS = Medicare Benefits Schedule; NIP = National Immunisation Program; RSVpreF = Respiratory Syncytial Virus.

[a] Based on linear extrapolation of the number of women who gave birth in 2011-2021, reported in the National Perinatal Data Collection dataset provided by the AIHW.

[b] Uptake rates based on ATAGI advice.

[c] Submission assumed 365/365.25 RSVpreF units per woman. Revised to one RSVpreF unit per woman.

[d] Submission only included an 80% MBS rebate associated with GP consultations ($5.60 per administration). Revised to a 100% MBS rebate ($7.00 per administration)

The redacted values correspond to the following ranges

[1] 300,000 to < 400,000

[2] 200,000 to < 300,000

[3] 90,000 to < 100,000

[4] 100,000 to < 200,000

[5] $10 million to < $20 million

[6] $20 million to < $30 million

[7] $30 million to < $40 million

[8] $0 to < $10 million

6.72 The total cost to the NIP for listing RSVpreF was estimated to be $30 million to < $40 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing based on the price proposed in the submission.[34]

6.73 The DUSC considered the utilisation and financial implications associated with the requested NIP listing utilisation of RSVpreF were sensitive to its uptake rate. The following concerns were noted:

- The uptake rate of RSVpreF might be underestimated based on the uptake rates of influenza and pertussis vaccines in pregnant women. A Victorian population-based cohort study found that amongst pregnant women, the uptake rate for influenza and pertussis vaccine was 70.6% and 81.8%, respectively.[35] DUSC also noted a systematic review[36] which suggested uptake rates in Victoria and Western Australia (between 70% to 90%) may be higher than the rest of Australia (less than 58%). The DUSC also noted that pregnant women already scheduled to receive maternal vaccines under current recommendations may have more opportunity to receive RSVpreF in the future, given RSV has become a reportable disease and its awareness has increased.
- Data from other countries indicated that uptake of RSVpreF in Italy[37] and the United States[38] were less than 50%. The DUSC considered that the availability of alternatives, such as nirsevimab or other RSV vaccines may influence the uptake of RSVpreF. DUSC also considered there was potential for 'vaccine fatigue' which may reduce the uptake rate. In addition, DUSC commented that uptake rates will be sensitive to risk communication about adverse events.

6.74 The pre-PBAC response reiterated that the uptake rates in the submission were informed by the ATAGI's advice. It was also noted that the published uptake rates of existing antenatal vaccines had occurred six years (pertussis) to more than 10 years (influenza) since the vaccines were listed on the NIP.

Quality Use of Medicines

6.75 The submission presented the following activities to support the quality use of RSVpreF:

- Providing educational resources for RSVpreF for health care professionals and;

[34] Financial estimates were revised to assume one vaccine unit per vaccinated person.
[35] Giles ML, Krishnaswamy S, Coote W, Davey MA. Factors Associated with Early Versus Late Uptake of the COVID-19 Vaccine during Pregnancy over Time in Australia: A Population-Based Cohort Study. Vaccines (Basel). 2023;11(11):1713. doi:10.3390/vaccines11111713
[36] McRae, J.E., McHugh, L., King, C., Beard, F.H., Blyth, C.C., Danchin, M.H., Giles, M.L., Mohammed, H., Wood, N. and Macartney, K. (2023), Influenza and pertussis vaccine coverage in pregnancy in Australia, 2016–2021. Med J Aust, 218: 528-541. https://doi.org/10.5694/mja2.51989
[37] Miraglia Del Giudice G, Sansone V, Airoma F, Angelillo S, Licata F, Di Giuseppe G. Respiratory Syncytial Virus: Willingness towards a Future Vaccine among Pregnant Women in Italy. *Vaccines (Basel).* 2023;11(11):1691. doi:10.3390/vaccines11111691
[38] Centers for Disease Control and Prevention. Respiratory Syncital Virus (RSV) Vaccination Coverage, Pregnant Persons, United States. Accessed from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10674197/

- Trained field personnel, an information hotline and online portals available to answer queries from health care professionals.

6.76 The DUSC noted RSV hospitalisation rates were higher in First Nations infants compared to non-Indigenous infants and uptake rates of influenza and pertussis vaccines were lower in Indigenous and culturally and linguistically diverse pregnant women and pregnant women from lower socioeconomic backgrounds[39] [40]. The DUSC considered QUM activities would be important to support increased uptake of RSVpreF in pregnant women within these groups. The pre-PBAC response stated that the sponsor is committed to addressing health inequities experienced by First Nations people and those of culturally diverse backgrounds. Culturally appropriate patient information will be developed by the sponsor to address community needs and facilitate informed decision making.

6.77 The submission considered that additional post-marketing surveillance of RSVpreF was not necessary as existing safety monitoring systems (AUSVAXSafety) and the sponsor's global pharmacovigilance system are in place. The DUSC commented that adverse events (such as whooping cough) associated with the coadministration of dTPa may not be reported to the sponsor.

6.78 With regard to post-market surveillance, the pre-PBAC response stated that the sponsor will provide Periodic Safety Update Reports (PSURs) in accordance with the TGA requirements. It was stated that Abrysvo will be included on the TGA's Black Triangle Scheme which actively encourages patients and healthcare professionals to report any suspected adverse events. It was noted that several post-market studies are planned or ongoing to investigate potential or identified risks or missing information.

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

7 PBAC Outcome

7.1 The PBAC did not recommend recombinant syncytial pre-fusion F protein vaccine (RSVpreF) for the prevention of lower respiratory tract illness (LRTI) caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunisation of pregnant women. The PBAC noted the clinical trial evidence presented in the submission showed there was a reduced risk of medically attended lower respiratory tract illness (MA-LRTI) and severe MA-LRTI due to RSV among infants during the first 6 months of life in RSV-vaccinated versus placebo-vaccinated individuals. The PBAC considered that the adverse event profile of RSVpreF was

[39] McRae, J.E., McHugh, L., King, C., Beard, F.H., Blyth, C.C., Danchin, M.H., Giles, M.L., Mohammed, H., Wood, N. and Macartney, K. (2023), Influenza and pertussis vaccine coverage in pregnancy in Australia, 2016–2021. Med J Aust, 218: 528-541. https://doi.org/10.5694/mja2.51989

[40] Javid N, Phipps H, Homer C, et al. Factors influencing uptake of the COVID-19 vaccination among pregnant women in Australia: A cross-sectional survey. *Birth*. 2023; 50: 877-889. doi:10.1111/birt.12741

acceptable compared to placebo. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was high and uncertain. The PBAC considered that a price reduction would be required to ensure the vaccine was cost-effective in the proposed circumstances of use.

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

7.3 The PBAC considered there is a high clinical need for vaccines, or other interventions, to reduce the risk of RSV, noting that RSV is a common respiratory infection and although symptoms are usually mild, some children develop severe disease which poses a significant risk, especially in infants aged up to six months. The PBAC noted the proposed NIP listing for maternal vaccination with RSVpreF for the protection of infants was supported by the consumer comments received for this submission.

7.4 The PBAC noted that RSV infections became a notifiable disease on the National Notifiable Disease List (NNDL) in 2021, however RSV notifications are considered incomplete at this time, as diagnostic testing for RSV is not routinely done.

7.5 The PBAC noted that RSVpreF is a bivalent, unadjuvanted vaccine composed of stabilised prefusion F antigens representing the two major RSV subgroups (RSV-A and RSV-B). When administered to pregnant individuals, protection is mediated through transfer of antibodies from mother to infant through the placenta.

7.6 The PBAC considered the nomination of "no vaccine" as the main comparator was appropriate. It was also noted that nirsevimab is a mAb for prevention of RSV-associated LRTI that received TGA approval in November 2023, and the PBAC considered that nirsevimab should be considered a near market comparator. The PBAC considered that the recommendations for use of either RSVpreF or nirsevimab, or both, for prevention of RSV in infants require further consideration.

7.7 The PBAC noted the proposed place in therapy for RSVpreF is as a vaccination given during the third trimester of pregnancy to prevent LRTI in infants during the first 6 months of life. The PBAC considered this was appropriate, with some minor adjustments to reflect ATAGI's advice regarding the timing of administration in relation to gestational age (see paragraph 7.9).

7.8 The PBAC noted that some infants are at an increased risk of severe RSV complications, including First Nations infants, infants with weakened immune systems, premature babies, and those with chronic lung or heart conditions. In addition, the outcomes for infants with RSV infections could be worse for those living in remote or regional areas, especially those requiring extended travel times to access medical care. While some high-risk pregnancies and high-risk infants can be identified before birth, the majority of risk factors for RSV-related disease cannot be identified until after birth.

7.9 The PBAC noted that ATAGI recommended vaccine administration from 28 weeks gestation, rather than 24 weeks as proposed by the submission, while awaiting further data regarding the risk of preterm birth. The PBAC noted that RSVpreF should ideally

be given from 28 to 36 weeks gestation, but administration after 36 weeks was acceptable.

7.10 The PBAC noted evidence that co-administration of RSVpreF with diphtheria-tetanus-acellular pertussis vaccine (dTpa) resulted in a reduction in anti-pertussis antibodies in non-pregnant women. The clinical significance of this interaction is uncertain but had informed the sponsor's position that RSVpreF should be administered in isolation. The PBAC noted that co-administration was acceptable when considered necessary, e.g. due to insufficient time or a lack of opportunity to separate vaccines.

7.11 The PBAC noted the ATAGI advice that repeat dosing with each pregnancy is anticipated, but it had not yet made a final decision (paragraph 3.7). The PBAC noted that the submitted economic model and financial estimates were consistent with ATAGI's advice to assume that revaccination would occur in each pregnancy. The PBAC noted ATAGI's intention to review additional data when available and include the relevant recommendation in the Australian Immunisation Handbook when appropriate.

7.12 The primary clinical evidence was drawn from one head-to-head trial (MATISSE) comparing RSVpreF to placebo (n=7,392). MATISSE was a phase 3, double-blind trial that evaluated the efficacy and safety of maternal RSVpreF immunisation against RSV-associated MA-LRTI in infants. Eligible participants were healthy women aged 49 years of age or younger, at 24 through 36 weeks gestation on the day of injection, with an uncomplicated, singleton pregnancy and no known increased risk of pregnancy complications. Two supporting studies were also included, SAVVY and Study 1004. The SAVVY trial was a randomised, placebo-controlled phase 2b study (n=581), which assessed rates of RSV-associated LRTI among infants as an exploratory endpoint. The SAVVY trial also provided data on the immunogenicity of RSVpreF to support the clinical claim. Study 1004 was designed to assess co-administration of RSVpreF with dTpa in non-pregnant women.

7.13 The PBAC noted that immunogenicity data from the SAVVY trial demonstrated the generation of robust neutralising titres to RSV-A and RSV-B following RSVpreF injection, in participants and their infants (see paragraphs 6.26 and 6.27).

7.14 The PBAC considered that RSVpreF was superior in terms of effectiveness compared to placebo on the basis of the RSV-positive MA-LRTI and RSV-positive severe MA-LRTI endpoints in the MATISSE trial (Table 4, Table 6). Based on the results of the primary analysis (provided in the submission), administration of RSVpreF to pregnant women resulted in significant reductions in RSV-positive MA-LRTI and RSV-positive severe MA-LRTI, in infants up to 180 days after birth, with a vaccine efficacy (VE) of 51.3%, and 69.4%, respectively. The results of the final analysis, reported in the pre-PBAC response, were similar, with a VE of 49.2%, and 70.0%, respectively at six months post birth.

7.15 The PBAC noted that the PSCR and pre-PBAC response provided data for the subgroup vaccinated from 28 weeks to <37 weeks gestation, however the magnitude of effect

in the subgroup was less certain due to the relatively small number of cases of RSV-positive MA-LRTI and RSV-positive severe MA-LRTI in the subgroup, in comparison with the overall analysis (see Table 5 and Table 7). Additionally, the PBAC noted this data had not been evaluated and no information was provided to support the use of outcomes from a subgroup of the whole trial population to determine the magnitude of benefit (as outlined in Section 2.6.1 of the PBAC Guidelines).

7.16 The PBAC considered that RSVpreF was inferior in terms of safety compared to placebo. The PBAC noted that maternal RSVpreF recipients experienced local reactions more frequently (42.5%) compared with placebo recipients (10.4%). Maternal participants who received RSVpreF were more likely to experience pain at the injection site, and muscle pain when compared with participants who received a placebo injection (40.6% vs 10.1%, and 26.5% vs 17.1%, respectively). The PBAC also noted in the RSVpreF arm of MATISSE, there were numerically higher rates of premature births (RSVpreF = 5.7% vs. placebo = 4.7%) and low birthweight infants (RSVpreF = 5.1% vs. placebo=4.3%). The PBAC noted that the ATAGI was awaiting further data regarding the risk of preterm birth (see paragraph 7.9).

7.17 The PBAC noted that the pre-PBAC response presented some results from the final analysis of the MATISSE trial, corresponding to a data cut-off date of October 2023 (see paragraph 6.10). The results included RSV-positive MA-LRTI, RSV-positive severe MA-LRTI, and hospitalisations due to RSV. This data was not evaluated and some of the results in the pre-PBAC response could not be verified as the source data were not provided (Table 5, Table 7, Table 8).

7.18 The PBAC noted there was a lack of evidence on the safety of RSVpreF and its efficacy in preventing RSV in babies born prematurely, in multiple birth pregnancies, and in non-healthy pregnancies. These groups include patients who are at high risk of RSV-related complications and who would potentially benefit from RSVpreF.

7.19 The submission presented a cost-utility analysis based on the MATISSE clinical trial. The PBAC noted that the base case ICER in the submission was $25,000 to < $35,000/QALY; however, considered the results of the economic evaluation uncertain because the model was highly sensitive to small variations in several inputs as evidenced by sensitivity analyses that resulted in ICERs exceeding $95,000 to < $115,000/QALY (Table 18).

7.20 The PBAC noted the multi-variate sensitivity analysis specified by the ESC (as outlined in paragraph 6.63) that incorporated the following five changes:

- Outpatient attendance cost of $61.80: accepted in the pre-PBAC response (paragraph 6.65);
- VE of 33% for hospitalisations, 45% for emergency department (ED) and outpatient attendance events: the PBAC agreed with the ESC that assuming VE 33% for hospitalisations, and 45% for ED and outpatient attendance events was appropriate (see paragraph 6.51);

- Hospitalisation cost $14,991: accepted in the pre-PBAC response (paragraph 6.65);
- Exclusion of carer QALYs lost: the PBAC advised that exclusion of carer QALYs lost from the base case was appropriate, although it noted that inclusion in a sensitivity analysis was informative;
- Reverse discounting to vaccine costs: accepted in the PSCR (see paragraph 6.48).

7.21 The PBAC noted the ICER using the model specified in the paragraph above and the price proposed in the pre-PBAC response was $95,000 to < $115,000/QALY. The PBAC considered that RSVpreF was not cost effective at the price proposed in the pre-PBAC response and a price reduction would be required to achieve an ICER of no more than $15,000 to < $25,000/QALY. The PBAC considered that an ICER of less than $15,000 to < $25,000/QALY would be required to demonstrate cost-effectiveness for the proposed listing of RSVpreF as a maternal vaccination to reduce the risk of RSV in infants aged up to six months.

7.22 The PBAC noted that First Nations infants are more susceptible to RSV infection and poorer health outcomes and therefore the proposed vaccine may be associated with greater incremental health outcomes in this population. Additionally, the PBAC noted the rates of hospitalisation in First Nations infants are higher than in non-Indigenous infants (see paragraph 4.2) and the model is very sensitive to higher rates of hospitalisation (see Table 18).

7.23 The PBAC considered the utilisation estimates presented in the submission to be reasonable. It was noted that assuming a maximum uptake of % in the eligible population was consistent with ATAGI advice on this matter.

7.24 The PBAC considered the outstanding issues could be resolved in a simple resubmission for RSVpreF. The PBAC also considered RSVpreF addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy/reduction of toxicity, over no vaccine. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- Using the economic model outlined in paragraph 7.20, propose a price that results in an ICER of no more than $15,000 to < $25,000/QALY;
- Recalculation of the financial implications using the revised RSVpreF price.

7.25 The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.

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

Outcome:
Not recommended

8 Context for Decision

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

9 Sponsor's Comment

Pfizer welcomes the PBAC's acknowledgement of the high and urgent unmet clinical need for prevention of RSV in infants from birth through 6 months of age and the clinical benefit of Abrysvo compared to placebo. Pfizer will continue to work collaboratively with the PBAC and Department of Health and Aged Care to deliver access to Abrysvo for pregnant individuals via the proposed National Immunisation Program.

Addendum to the March 2024 PBAC PSD:

7.01 RESPIRATORY SYNCYTIAL VIRUS VACCINE, Injection (0.5 mL), Abrysvo®, PFIZER AUSTRALIA PTY LTD

10 Purpose

10.1 The Early Resolution resubmission requested National Immunisation Program (NIP) listing for recombinant syncytial pre-fusion F protein vaccine (RSVpreF) for the prevention of lower respiratory tract illness (LRTI) caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunisation of pregnant women.

11 Background

11.1 RSVpreF was considered by the PBAC and not recommended for NIP listing at the March 2024 meeting. The PBAC considered there was a high clinical need for vaccines, or other interventions, to reduce the risk of RSV, noting that RSV is a common respiratory infection and although symptoms are usually mild, some children develop severe disease which poses a significant risk, especially in infants aged up to six months. In March 2024, the PBAC considered that the incremental cost-effectiveness ratio (ICER) was high and uncertain. The PBAC considered that a price reduction would be required to ensure the vaccine was cost-effective in the proposed circumstances of use. The PBAC considered that the outstanding issues could be addressed using the early resolution pathway if the matters were addressed as outlined in Table 21. A summary of the resubmission's approach to these matters is also provided in Table 21.

Table 21: Issues to be addressed (March 2024 PBAC PSD)

Matters Raised by PBAC		Resubmission
1	Revision of economic model as outlined in paragraphs 7.20 and 7.24: (i) Outpatient attendance cost of $61.80; (ii) Hospitalisation cost $14,991; (iii) Exclusion of carer QALYs lost from the base case; (iv) Reverse discounting to vaccine costs; (v) VE of 33% for hospitalisations, 45% for ED and outpatient attendance events (based on trial results over 12 months); (vi) ICER of no more than $[redacted][1]/QALY.	The resubmission proposed a revised base case which incorporated the PBAC's advice described in points (i) to (iv). The resubmission proposed a vial price of $[redacted], which resulted in an ICER of $[redacted][1]/QALY using the resubmission's revised base case (see Table 24). The resubmission did not implement the PBAC's advice in relation to the inputs for VE, described in point (v). The resubmission presented an alternative analysis which did incorporate this advice, and it resulted in an ICER of $[redacted][2]/QALY using the resubmission's proposed vial price (see Table 24).
2	Recalculation of the financial estimates using the revised RSVpreF price as outlined in paragraph 7.24.	The resubmission provided revised estimates, consistent with the PBAC's advice (see Table 25).

Source: March 2024 PBAC PSD, and Early Resolution Resubmission.
Abbreviations: ED = emergency department; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine; VE = vaccine efficacy.
The redacted values correspond to the following ranges:
[1] *$15,000 to < $25,000*
[2] *$45,000 to < $55,000*

11.2 Additional advice from ATAGI was provided to the PBAC prior to the PBAC May 2024 Intracycle Meeting (ATAGI post-submission advice to PBAC for Abrysvo).

Registration status

11.3 RSVpreF was entered on the Australian Register of Therapeutic Goods (ARTG) by the TGA on 20 March 2024. The indication was unchanged from the indication described in paragraph **Error! Reference source not found.**. The TGA-approved product information states that:

"ABRYSVO is administered as a single dose (0.5 mL) in late second or third trimester of pregnancy (24-36 weeks of gestation). Revaccination in subsequent pregnancies has not been studied."

For more detail on PBAC's view, see section 12 PBAC outcome.

12 Requested listing

Details of the proposed NIP schedule listing (as stated in the resubmission)

Schedule / Program: Respiratory syncytial virus (RSV) vaccination schedule for immunisation during pregnancy (24–36 weeks gestation)*		
Age(s) of administration(s) other restrictions or details:		
Disease	**Vaccine**	**Comments**
RSV in infants aged 0-6 months	RSVpreF (Abrysvo) 0.5 mL containing 120 micrograms (mcg) of stabilised prefusion F proteins (60 mcg RSV-A and 60 mcg RSV-B antigens)	

Source: Table 3.2, p6 of the resubmission.
Abbreviations: RSV = respiratory syncytial virus; RSVpreF = recombinant respiratory syncytial virus pre-fusion F protein vaccine.
* administration after 36 weeks is acceptable, noting two weeks between vaccination and birth are required for adequate transplacental transfer of maternal antibodies against RSV.

12.1 The resubmission acknowledged the updated ATAGI advice to the PBAC dated 18 December 2023 (herein "updated ATAGI advice"), regarding the recommended gestational age at vaccination with RSVpreF. The updated ATAGI advice stated RSV vaccine during pregnancy should be given from 28 to 36 weeks gestation, but administration after 36 weeks is acceptable, noting that two weeks are needed for adequate transfer of antibodies. This advice was reflected in the proposed NIP schedule listing.

12.2 The resubmission acknowledged the updated ATAGI advice that maternal RSV vaccine can be given either at the same time as, or separate to, other maternal vaccines at the recommended gestational age. The resubmission stated that there should be sufficient time for all potential maternal NIP vaccinations (RSVpreF, dTpa, influenza) to be administered in routine antenatal care, given the ATAGI advice with respect to vaccination window (see paragraph 12.1).

12.3 The resubmission proposed a price of $[redacted] per dose of RSVpreF.

For more detail on PBAC's view, see section 12 PBAC outcome.

13 Consideration of the evidence

Sponsor hearing

13.1 There was no hearing for this item.

Consumer comments

13.2 Previously the PBAC considered comments from three organisations that supported the proposed NIP listing for RSVpreF at the March 2024 meeting (see paragraphs **Error! Reference source not found.** to **Error! Reference source not found.**).

Vaccine efficacy

13.3 At the March 2024 meeting, the PBAC considered that RSVpreF was superior to placebo in terms of effectiveness on the basis of the RSV-positive MA-LRTI and

RSV-positive severe MA-LRTI endpoints for the overall population in the MATISSE trial (paragraph **Error! Reference source not found.**). At that meeting, the PBAC noted that the PSCR and pre-PBAC response had provided data for the subgroup vaccinated from 28 weeks to <37 weeks gestation, however considered the magnitude of effect in the subgroup was less certain due to the relatively small number of cases of RSV-positive MA-LRTI and RSV-positive severe MA-LRTI in the subgroup, in comparison with the overall analysis (paragraph **Error! Reference source not found.**).

13.4 The resubmission maintained that the VE results from the MATISSE study for the subgroup of women vaccinated between 28 and <37 weeks gestation were appropriate to inform the base case economic model. However, no information was provided to address the PBAC's concern discussed in paragraph **Error! Reference source not found.** regarding the use of outcomes from a subgroup of a trial population to determine the magnitude of benefit. The resubmission stated that it applied the overall results from the MATISSE study in the economic model, consistent with PBAC advice, to facilitate the Early Resolution resubmission, and considered that this was conservative.

13.5 At the March 2024 meeting, the PBAC noted that the pre-PBAC response had provided an updated economic model informed by trial data for VE with a follow-up period of only 6 months, compared with 12 months as provided in the submission (paragraph 6.65). At that meeting, the PBAC considered that it would be more robust to apply the observed data for VE from the first year of the trial.

13.6 The resubmission stated that at the time of the primary analysis, the MATISSE trial was ongoing and results for the 360 day VE against hospitalised MA-LRTI remained immature and relatively uncertain. The resubmission referred to the final analysis results reported by Munjal et al., 2024[41], that were provided with the pre-PBAC response (see paragraph 6.10), but did not propose to use these data in the economic model.

13.7 The resubmission stated that the duration of protection of approximately 6 months (rather than 12 months as hypothesised in the initial submission) is reflected in the final TGA-approved indication, and aligns with the highest burden of hospitalisations due to RSV in the first 6 months of an infant's life. The resubmission considered that clinical data for the 6-month time point are more robust, given this was the primary outcome of the pivotal trial and a higher proportion of infant participants had completed the follow-up visit 6 months after birth compared with the follow-up visit at 12 months after birth.

[41] Munjal, I. et al. Prevention of infant RSV illness with a bivalent RSV prefusion F vaccine administered during pregnancy: efficacy results from a phase 3 global clinical trial. 8th ReSViNET Conference, February 13-16, 2024 (Abstract Book, p98).

Economic analysis

13.8 Consistent with the March 2024 submission, the resubmission presented a revised economic analysis assessing the cost-effectiveness of a year-round maternal RSV immunisation program using RSVpreF, in comparison to current practice (no vaccine). The resubmission applied 6-month VE estimates from MATISSE in the revised base case, claiming this would reduce uncertainty in the economic analysis.

13.9 The resubmission's revised base case incorporated the following changes, consistent with PBAC advice as set out in paragraph 7.20: 1) Outpatient attendance cost of $61.80; 2) Hospitalisation cost of $14,991; 3) Exclusion of carer QALYs lost from the base case; and 4) Reverse discounting to vaccine costs. The resubmission did not implement the PBAC's advice in relation to the inputs for VE in its revised base case (ICER $15,000 to <$25,000/QALY). The PBAC had advised that VE of 33% should be applied for hospitalisations, and VE of 45% should be applied for ED and outpatient attendance events, based on trial results over 12 months as presented in Table 13. The resubmission did, however, present an alternative analysis which did incorporate this advice, and this resulted in an ICER of $45,000 to <$55,000/QALY using the resubmission's proposed vial price.

13.10 In March 2024, the PBAC advised that exclusion of carer QALYs lost from the base case was appropriate, although it noted that inclusion in a sensitivity analysis was informative. The resubmission maintained that inclusion of carer QALYs would be appropriate in scenarios impacting infants and their carers (such as for RSV prevention), however it excluded carer quality of life effects in line with the PBAC recommendation.

13.11 Table 22 shows the baseline risk of events and VE estimates recommended by the PBAC in March 2024 for use in the economic model, and the settings used in the resubmission base case.

Table 22: Comparison of settings for economic model

	March 2024 - PBAC recommended settings (used in Resubmission Alternative Analysis	Resubmission Base Case
Follow-up period for estimating VE	12 months	6 months
Baseline risks		
Hospitalised	2.33% [a]	1.62% [e]
Emergency	1.80% [b]	1.35% [f]
Outpatient	8.10% [c]	6.08% [g]
Vaccine efficacy		
Hospitalised	33.0% [d]	56.8% [h]
Emergency	45.0% [d]	51.3% [i]
Outpatient	45.0% [d]	51.3% [i]

[a]. From Gebremedhin 2022, cases aged <1 year.
[b]. From Takashima 2021, cases aged <1 year.
[c]. From Takashima 2021, cases aged <1 year.
[d]. From paragraph 7.20, as presented in Table 13 (VE for preventing MA-LRTI RSV excluding hospitalisation).
[e]. From Gebremedhin 2022, cases aged <6 months
[f]. Calculated as 0.75*1.8%
[g]. Calculated as 0.75*8.1%
[h]. At 180 days after birth, there were 19 (0.5%) hospitalisations due to RSV in infants in the RSVpreF group, and 44 (1.3%) hospitalisations in the placebo group, corresponding to a VE of 56.8% (99.17% CI:10.1%, 80.7%), based on the results of the primary analysis.
[i]. At 180 days after birth, there were 57 (1.6%) cases of RSV-positive MA-LRTI in the RSVpreF group and 117 (3.4%) cases in the placebo group, corresponding to a VE of 51.3% (97.58% CI:29.4%, 66.8%), based on the results of the primary analysis.

13.12 Table 23 shows the results of the economic model in terms of incremental events avoided based on the model settings recommended by the PBAC in March 2024, and the settings used in the resubmission base case.

Table 23: Comparison of incremental events avoided (RSVpreF minus No Vaccination), per 1,000 vaccinated

	March 2024 - PBAC recommended settings (used in Resubmission Alternative Case)	Resubmission Base Case
Analysis	12 months	6 months
Outcome		
Hospitalisation	-7.67	-9.20
Emergency	-8.10	-6.93
Outpatient	-36.45	-31.16
Death	-0.015	-0.018

Source: Results sheet in both models provided with resubmission (ABRYSVO maternal CEA_Base Case 6M_Early Resolution.xlsx and ABRYSVO maternal CEA_12M_Early Resolution.xlsx)

13.13 The estimated ICERs ($ per QALY) from the economic model are shown in Table 24.

Table 24: Results of economic model

Analyses	Incremental cost (per 1,000)	Incremental QALY (per 1,000)	ICER (per QALY)
March 2024 Submission Base Case (vial price $[redacted]) (as per Table 16)	**$[redacted]**	**0.783**	[redacted][1]
PBAC recommended settings and March 2024 pre-PBAC response price (as per Table 18) • 12 month analysis • VE 33% for hospitalisations and 45% for emergency department and outpatient attendance • vial price $[redacted]	$[redacted]	0.662	[redacted][2]
Resubmission Base Case • 6-month analysis • 75% of ED and outpatient attendance events occur by 6-months • VE 56.8% for hospitalisations and 51.3% for emergency department and outpatient attendance • vial price $[redacted]	$[redacted]	0.697	[redacted][3]
Resubmission Alternative Case • 12 month model • VE 33% for hospitalisations and 45% for emergency department and outpatient attendance • vial price $[redacted]	$[redacted]	0.662	[redacted][4]

The redacted values correspond to the following ranges:
[1] $25,000 to < $35,000
[2] $95,000 to < $115,000
[3] $15,000 to < $25,000
[4] $45,000 to < $55,000

Estimated PBS usage & financial implications

13.14 The resubmission provided revised financial estimates, consistent with the PBAC's advice as outlined in paragraph **Error! Reference source not found.**.

Table 25: Net financial implications of RSVpreF for the proposed NIP listing

	2024	2025	2026	2027	2028	2029
Resubmission estimates ($[redacted] per dose)						
Cost of RSVpreF to NIP	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Cost of MBS items[a]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net increase in cost to government health budget	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
March 2024 submission estimates ($[redacted] per dose)						
Cost of RSVpreF to NIP	[redacted][1]	[redacted][2]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Cost of MBS items[a]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net increase in cost to government health budget	[redacted][1]	[redacted][2]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]

Source: ABRYSVO_Maternal_Section 4 Workbook_May 2024.xlsx, March PBAC PSD Table 20.
[a] MBS costs estimated for vaccine administration.
The redacted values correspond to the following ranges:
[1] $10 million to < $20 million
[2] $20 million to < $30 million
[3] $0 to < $10 million
[4] $30 million to < $40 million

For more detail on PBAC's view, see section 12 PBAC outcome.

14 PBAC outcome

14.1 The PBAC recommended that respiratory syncytial virus vaccine (Abrysvo®, 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) in infants from birth through 6 months of age by active immunisation of pregnant women. The PBAC considered that the vaccine was superior to no vaccine in terms of effectiveness, based on the reduced risk of medically attended-lower respiratory tract illness (MA-LRTI) and severe MA-LRTI due to RSV among infants during the first 6 months of life. The PBAC considered that the adverse event profile of RSVpreF was acceptable compared to placebo. The PBAC noted that the resubmission had offered a lower price compared with the price considered by the PBAC in March 2024, and had accepted most of its advice arising from that meeting. However, the resubmission had not accepted the PBAC's advice regarding the estimates of vaccine efficacy (VE) to be applied in the economic evaluation. The PBAC maintained its advice from the March 2024 meeting, that clinical trial data with 12 months of follow-up be used to inform the VE, rather than with 6 months of follow-up as proposed by the resubmission. The PBAC noted using clinical trial data with 12 months of follow-up to inform the VE, resulted in an ICER that was unacceptably high. On this basis, the PBAC considered that a price reduction would be required to ensure the vaccine is cost-effective in the proposed circumstances of use.

14.2 The PBAC recommended the listing of RSVpreF for use as a maternal vaccine, on the basis that it should be available through the National Immunisation Program under the circumstances specified in Section 13 below.

14.3 The PBAC was satisfied that RSVpreF provides, for some patients, a significant improvement in efficacy over standard of care (no vaccine).

14.4 The PBAC considered that the resubmission had addressed the majority of outstanding issues identified at the March 2024 PBAC meeting, via the respecified economic model and recalculated financial estimates. However, for the base case economic evaluation the PBAC's advice in relation to the inputs for VE was not implemented. The PBAC noted its previous advice that a VE of 33% should be applied for hospitalisations, and a VE of 45% should be applied for ED and outpatient attendance events, based on observed events in the trial over 12 months. While the resubmission base case resulted in an ICER of less than $15,000 to < $25,000/QALY, the alternative analysis which incorporated all of the PBAC's previous advice, resulted in an ICER of $45,000 to < $55,000/QALY using the resubmission's proposed vial price.

14.5 The PBAC did not accept the resubmission's claim that use of 6-month data would reduce uncertainty in the economic model (paragraph 13.8). The PBAC noted that the VE results of the 6-month analysis which informed the resubmission's base case had wide confidence intervals: VE of 56.8% (99.17% CI:10.1%, 80.7%) for hospitalisations due to RSV; and VE of 51.3% (97.58% CI:29.4%, 66.8%) for RSV-positive MA-LRTI. The

PBAC also noted that the ICER was highly sensitive to the VE estimates (as seen in Table 24).

14.6 The PBAC maintained that the parameters recommended in March 2024 were appropriate for assessing the cost-effectiveness of the proposed listing and considered that conservative estimates were appropriate for decision-making in this instance. The PBAC noted the proposed use of RSVpreF as a year-round maternal vaccine, administered according to gestational age, differs from the seasonal nature of RSV. The PBAC considered that seasonal factors may impact the future cost-effectiveness of maternal RSV vaccine, with varying seasonality in different parts of Australia, and noting that severity of future RSV seasons was difficult to predict.

14.7 The PBAC noted using clinical trial data with 12 months of follow-up to inform the VE, rather than with 6 months of follow-up as proposed by the resubmission, resulted in an ICER ($45,000 to < $55,000/QALY) that was unacceptably high. On this basis, the PBAC considered that a further price reduction would be required to achieve an acceptable ICER for this listing, using the economic model outlined in paragraph 7.20, and a price that results in an ICER of no more than $15,000 to < $25,000/QALY. The PBAC noted that this analysis supported a price of no more than $ per dose of RSVpreF in order for the vaccine to be considered cost-effective.

14.8 The PBAC noted that data on immunogenicity, efficacy and safety of vaccination with RSVpreF in subsequent pregnancies were not yet available. The updated ATAGI advice stated that ATAGI will review these data when available, and ATAGI will confirm its advice regarding vaccination in subsequent pregnancies in the Australian Immunisation Handbook when appropriate. The PBAC noted that the cost-effectiveness of maternal vaccination may need to be reconsidered if the efficacy in subsequent pregnancies is less than in the first.

14.9 The PBAC noted that the resubmission had recalculated the financial implications using the proposed RSVpreF price as requested, however the estimates would need to be recalculated using the cost-effective price based on the advice in paragraph 14.7.

14.10 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

15 Recommended listing

15.1 Add new item to the Determination:

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Number and timing of doses
Vaccine RSV stabilised prefusion F subunit vaccine (RSVpreF) Circumstances Vaccine may be provided to a person who is pregnant	Abrysvo	0.5 mL containing 120 micrograms (mcg) of stabilised prefusion F proteins (60 mcg RSV-A and 60 mcg RSV-B antigens)	1 dose at 28 to 36 weeks gestation*

Abbreviations: mcg = micrograms; RSV = respiratory syncytial virus; RSVpreF = RSV stabilised prefusion F subunit vaccine
* administration after 36 weeks is acceptable, noting two weeks between vaccination and birth are required for adequate transplacental transfer of maternal antibodies against RSV.

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

16 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.

17 Sponsor's Comment

Pfizer Australia welcomes the PBAC recommendation that Abrysvo® be a designated vaccine on the National Immunisation Program (NIP) for the prevention of lower respiratory tract illness (LRTI) caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunisation of pregnant women; however, we are disappointed with the PBAC's economic evaluation of Abrysvo.

Pfizer Australia supports rapid implementation of a maternal vaccination program and remains committed to ensuring all pregnant women have equitable and affordable access to this vaccine as soon as possible.