5.11 NIRSEVIMAB,
Solution for injection 50 mg in 0.5 mL pre-filled syringe
Solution for injection 100 mg in 1 mL pre-filled syringe
Beyfortus®,
SANOFI-AVENTIS AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a General Schedule Restricted Benefit listing for nirsevimab for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease (LRTD) 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.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus the main comparator of placebo (no immunisation).

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

Component	Description
Population	(i) Neonates and infants born during or entering their first RSV season; (ii) Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season
Intervention	BEYFORTUS® (nirsevimab) 50 mg/0.5 mL and 100 mg/1 mL solution for injection in prefilled syringe
Comparator	Population (i) • Main comparator – No immunisation (supportive care) in Season 1 • Near market comparator – RSVpreF maternal immunisation (MI) in Season 1 Populations (i) and (ii) • Supplementary comparator – Non-PBS listed palivizumab for children vulnerable to severe RSV disease in Seasons 1 and 2
Outcomes	Efficacy: Incidence of MA-LRTI, incidence of MA-LRTI resulting in hospitalisation. Safety: TEAEs/TESAEs, AESIs, NOCD, immunogenicity.
Clinical claim	<u>Population (i)</u> Nirsevimab vs Placebo (no immunisation) • Superiority in terms of comparative clinical effectiveness versus placebo • Non-inferiority in terms of comparative safety versus placebo Nirsevimab vs Maternal immunisation (near-market comparator) • Superiority in terms of comparative clinical effectiveness versus MI • Non-inferiority in terms of comparative safety versus MI. <u>Populations (i) and (ii)</u> Nirsevimab vs Palivizumab (supplementary comparator) Non-inferiority in terms of comparative clinical effectiveness and safety versus palivizumab.

Source: Table 1.1.1, pp2-3 of the submission.
RSV = respiratory syncytial virus; MA-LRTI = medically attended lower respiratory tract infection; TEAEs/TESAEs = Treatment-emergent adverse/serious adverse events; AESIs = adverse events of special interest; NOCD = new onset chronic disease; MI = Maternal immunisation; PI = product information
Notes: Clinical vulnerability to severe RSV disease is defined as per the palivizumab PI - having a history of prematurity (less than or equal to 35 weeks at birth), or established bronchopulmonary dysplasia, or haemodynamically significant congenital heart disease. Additionally, infants of Aboriginal and Torres Strait Island descent are included in this population, regardless of gestational age at birth or comorbidities.

2 Background

Registration status

2.1 Nirsevimab was TGA registered on 24 November 2023 for the prevention of RSV LRTD in:

- Neonates and infants born during or entering their first RSV season.
- Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

2.2 The TGA-approved indication also states that nirsevimab should be used in accordance with official recommendations.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Nirsevimab, 50mg/0.5 mL, pre-filled syringe	$	1	1	0	Beyfortus
Nirsevimab, 100mg/1 mL, pre-filled syringe	$	1	1	0	
Nirsevimab, 100mg/1 mL, pre-filled syringe	$	2	2	0	

Source: Table 1.4.1 of the submission.

Proposed PBS restriction wording for neonates and infants born during or entering their first RSV season

Category / Program: Section 85 (general schedule)
Prescriber type: ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☒ Midwives
Restriction type: ☒Restricted benefit
Condition: respiratory syncytial virus infection
Indication: Prevention of lower respiratory tract infection caused by respiratory syncytial virus (RSV)
Clinical criteria:
Patient's mother must not have received immunisation against respiratory syncytial virus (RSV) while pregnant, and the patient must not have received a prophylactic antibody treatment against RSV.
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.
Treatment criteria:
Must be treated by a medical practitioner, a nurse practitioner or a midwife.
Population criteria:
Patient must be younger than 12 months of age
AND
Patient is born during or entering their first RSV season.
Administrative Advice: Nirsevimab is intended to prevent and not treat RSV disease. Nirsevimab should be administered prior to the RSV season according to local guidelines and recommendations. If the patient is born during the RSV season, nirsevimab should be administered as soon as possible after birth.

Proposed PBS restriction wording for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season

Category / Program: Section 85 (general schedule)
Prescriber type: ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☒ Midwives
Restriction type: ☒Restricted benefit
Condition: respiratory syncytial virus infection
Indication: Prevention of lower respiratory tract infection caused by respiratory syncytial virus (RSV)
Clinical criteria:
Patient is at risk of severe RSV disease defined as: Having a history of prematurity (less than or equal to 35 weeks at birth),
OR
Patient must have established bronchopulmonary dysplasia
OR
Patient must have haemodynamically significant congenital heart disease
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.

Treatment criteria:
Must be treated by a medical practitioner, a nurse practitioner or a midwife.
Population criteria:
Patient must be 24 months of age or younger
AND
Patient is entering their second RSV season
Administrative Advice: Nirsevimab is intended to prevent and not treat RSV disease. Nirsevimab should be administered in time for the second RSV season according to local guidelines and recommendations.

3.1 The submission requested a PBS listing for nirsevimab in either 50 mg/0.5 mL or 100 mg/1 mL of solution for use in neonates and infants younger than 12 months of age. Infants weighing <5 kg would receive 50 mg and infants weighing ≥5 kg would receive 100 mg[1]. Additionally, for infants requiring nirsevimab in their second year, a 200 mg dose was requested. This would require two 100 mg/1 mL prefilled syringes, as the complete dose must be given in one sitting.

3.2 Only a single administration of nirsevimab is needed (comprising 1 or 2 syringes), therefore there are no repeats needed for any listings. However, the approved Product Information states that if a child is having a heart operation, they may be given an extra dose of nirsevimab after the operation. This was not reflected in the proposed listing.

3.3 Although the submission requested PBS listing for nirsevimab, the sponsor was of the opinion that listing of nirsevimab on the National Immunisation Program (NIP) Schedule would be appropriate. The sponsor argued that the NIP was a better framework for a whole of population program and that it would allow for optimal uptake and coverage to protect against RSV. The sponsor recognised that the current legislative framework underpinning the NIP may not support the inclusion of passive immunisation strategies like nirsevimab. As such, the sponsor requested PBS listing of nirsevimab to provide access until there is further clarification regarding NIP listing.

3.4 The Economic Sub-Committee (ESC) noted that inclusion on the National Immunisation Program would likely increase uptake of nirsevimab and optimise use, in comparison with the proposed PBS listing, as it would reduce prescription and co-payment barriers. The ESC considered that a coordinated population-based program under the NIP would be preferred for nirsevimab, rather than PBS listing.

3.5 The proposed restriction stated that for neonates and infants born during or entering their first RSV season, a patient's mother must not have received immunisation against RSV while pregnant, and the patient must not have received a prophylactic antibody treatment against RSV. The evaluation noted that this may be interpreted to exclude infants who could potentially benefit from nirsevimab, such as infants born before sufficient placental transfer of anti-RSV antibodies could occur (i.e. within

[1] WHO growth charts indicate that 50% of infants should reach 5 kg by 2 months of age. https://www.who.int/tools/child-growth-standards/standards/weight-for-age. Accessed 15 May 2024.

14 days of maternal vaccination with RSVpreF), although this is likely to be a small population. The Pre-Sub-Committee Response (PSCR) clarified that the proposed restriction was based on the consideration that maternal immunisation and nirsevimab would be two alternative forms of immunisation against RSV infection. The ESC noted that any additional benefit of maternal vaccination plus nirsevimab is unable to be predicted due to limited data, and cost-effectiveness would be undermined if infants received passive immunisation from both nirsevimab and maternal RSVpreF.

3.6 The submission proposed that children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season should satisfy at least one of the following risk criteria:

1) history of prematurity (less than or equal to 35 weeks at birth);

2) established bronchopulmonary dysplasia; and

3) haemodynamically significant congenital heart disease.

This is a smaller list in comparison with the risk conditions for severe RSV disease in infants and young children noted in the statement from the Australian Technical Advisory Group on Immunisation (ATAGI) on the clinical use of nirsevimab for prevention of severe disease due to RSV in infants[2] (Table 2). A list of other relevant considerations described by ATAGI is also provided in Table 3.

3.7 The definition of high-risk for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season aligns with the definition used in the MEDLEY trial. The evaluation noted that there are other populations who are at a high-risk of severe RSV disease who may additionally benefit from nirsevimab. Of particular relevance to the Australian setting are children who are Aboriginal or Torres Strait Islander, as there is a higher risk of RSV-associated hospitalisation compared with non-Indigenous Australians[3]. The Product Information for the nominated secondary comparator, palivizumab, includes children of Aboriginal or Torres Strait Islander descent in the definition of high-risk populations.

[2] ATAGI statement on nirsevimab for the prevention of severe disease due to respiratory syncytial virus (RSV) in infants. Publication date 26 March 2024.

[3] Farquharson KA, Anthony D, Menzies R, Homaira N. (2024), Burden of respiratory syncytial virus disease across the lifespan in Australia and New Zealand: a scoping review. *Public Health*. 226:8-16.

Table 2: Risk conditions for severe RSV disease in infants and young children reported by ATAGI statement on nirsevimab 2024

1	Prematurity (particularly infants born <32 weeks gestational age)
2	Haemodynamically significant congenital heart disease
3	Significant immunosuppression, e.g. due to solid organ transplant, haematopoietic stem cell transplant, or primary immune deficiencies such as severe combined immunodeficiency (SCID)
4	Chronic lung disease that requires oxygen or respiratory support beyond 36 weeks gestation or at hospital discharge
5	Neurological conditions that impair respiratory function
6	Cystic fibrosis with severe lung disease or weight for length <10th percentile
7	Trisomy 21 or other genetic conditions that increase the risk of RSV

Source: ATAGI statement on nirsevimab for the prevention of severe disease due to respiratory syncytial virus (RSV) in infants. Publication date 26 March 2024.

Table 3: Other considerations relevant to benefit from nirsevimab reported by ATAGI statement on nirsevimab 2024

1	Infants with multiple risk factors for severe RSV disease are likely to have an even higher risk of severe outcomes – for example, prematurity and a medical risk condition.
2	The risk of hospitalisation from RSV for Aboriginal and Torres Strait Islander infants is approximately 2 times that of other infants of the same age.
3	Infants who cannot readily access advanced care for severe RSV because they live in remote regions may have greater benefit.
4	The availability and eligibility for palivizumab as an alternate RSV mAb.

Source: ATAGI statement on nirsevimab for the prevention of severe disease due to respiratory syncytial virus (RSV) in infants. Publication date 26 March 2024.

3.8 ATAGI's statement on the clinical use of nirsevimab for prevention of severe disease due to RSV in infants states that nirsevimab provides protection for at least 5 months via passive immunisation directly to the infant or young child and works immediately after injection. From 15 March 2024, immunisation providers can report receipt of nirsevimab to the Australian Immunisation Register (AIR).

3.9 The RSV chapter of the Australian Immunisation Handbook (AIH) was recently updated, and includes recommendations for use of vaccines and monoclonal antibodies for prophylaxis of RSV disease[4]. The AIH recommends a single dose of RSVpreF is recommended for use in pregnant women to protect infants. It is noted that infants are not expected to be adequately protected unless they are born at least 2 weeks after their mother received the vaccine. The AIH notes that advice on revaccination in subsequent pregnancies will be provided when data are available.

3.10 The AIH recommends nirsevimab for neonates and infants of mothers who either did not receive RSV vaccine during pregnancy or received the vaccine within 2 weeks of delivery. The AIH also proposes a number of other clinical circumstances in which administration of nirsevimab may be appropriate, such as 1) infants with risk conditions for severe RSV disease regardless of maternal vaccination status; 2) infants born to mothers with severe immunosuppression; and 3) infants whose mothers have received RSV vaccine in pregnancy but have subsequently undergone a treatment that has led to loss of maternal antibodies.

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

3.11 The timing of the RSV season is variable, depending on the region of Australia. The submission stated that in general, nirsevimab should be given either:

- Prior to the typical RSV winter season, in May – In temperate regions, defined as New South Wales, Victoria, South Australia, Tasmania, the Australian Capital Territory, and lower Western Australia (i.e. Perth, Bunbury, Geraldton, etc);
- Throughout the year at birth – In northern subtropical regions, and regions with poorly defined seasons due to climate, defined as Queensland, the Northern Territory, and northern Western Australia (i.e. Broome, the Kimberley Region, etc).

The submission stated that ultimately, treatment should be guided by local recommendations, given seasonal dynamics that vary by region.

3.12 The submission provided further information about the RSV seasons for temperate and tropical regions as follows:

- In temperate regions, the RSV season coincides with the flu season, peaking during winter and trailing off through September and October.
- Typically, the tropical RSV season occurs during the wet season, usually starting in December and peaking in March to May. However, predicting rainfall in northern Australia is difficult as rainfall patterns can vary substantially from year to year, even with regions with similar average rainfall.

3.13 The evaluation noted that the timing of the RSV season can vary year to year. As nirsevimab provides 5 months of protection, monitoring of the RSV season via the National Notifiable Diseases Surveillance System would be important for the optimal use of nirsevimab. A key driver of the economic model is the ability to map the RSV season in different jurisdictions, and provide advice about the optimal timing of nirsevimab administration and for this advice to be accurately followed (see paragraph 6.79).

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. The ESC noted the high rates of hospitalisation associated with RSV; in Australia it has been estimated that hospitalisation rates 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[5]. The RSV-confirmed hospitalisation rate among First Nations

[5] 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)

infants has been reported to be 2.3 times higher in infants 0-3 months of age and 3.2 times higher in Aboriginal infants 4-6 months of age[6].

4.2 Symptoms typically include a low-grade fever, cough, and respiratory distress, potentially escalating to severe conditions requiring hospital care[7]. Risk factors for severe RSV and RSV-associated hospitalisation 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[8]. High-risk infants often experience longer hospital stays and may require intensive care.

4.3 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[9]. 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 compared to those infants without siblings[10].

4.4 The COVID-19 pandemic notably disrupted the typical patterns of RSV transmission. Measures taken to curb the spread of COVID-19, such as social distancing and mask-wearing, 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 the following year[11].

4.5 Nirsevimab is a recombinant neutralising human IgG1κ long-acting monoclonal antibody to the prefusion conformation of the RSV F protein. Nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion. The duration of protection offered by a single dose of nirsevimab is at least 5 months based on clinical and pharmacokinetic data (TGA-approved product information).

4.6 The submission stated that potential emergence of variants of RSV that may theoretically impact the efficacy of nirsevimab is being monitored with surveillance virology and clinical virology analysis programs, to genotypically track the prevalence and emergence of F protein sequence variations among RSV isolates, and to

[6] 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.
[7] Smith DK, Seales S, Budzik C. (2017), Respiratory Syncytial Virus Bronchiolitis in Children. *Am Fam Physician*.95(2):pp94-9
[8] 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
[9] 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
[10] 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
[11] 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

phenotypically evaluate the impact of these amino acid substitutions on the efficacy of nirsevimab using an in vitro neutralisation susceptibility assay. The ESC considered that the potential for resistance to nirsevimab, and the possibility that variants with reduced susceptibility to nirsevimab will emerge and become prevalent in the future, are both areas of uncertainty.

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

5 Comparator

5.1 At the time of the submission, there was no prophylactic therapy or vaccine listed on either the PBS or NIP for the prevention of RSV which nirsevimab would replace. As such, the main comparator nominated was no immunisation (placebo).

5.2 The submission nominated palivizumab as a supplementary comparator. Palivizumab is TGA-registered for the prevention of serious lower respiratory tract disease caused by RSV in children at high-risk of RSV disease as defined by: children with bronchopulmonary dysplasia (BPD), infants with a history of prematurity (gestational age less than or equal to 35 weeks at birth) and children with hemodynamically significant congenital heart disease (CHD). However, palivizumab is not PBS listed and was rejected at the March 2005 PBAC meeting because it was not considered cost-effective.

5.3 The submission noted that a bivalent maternal RSV prefusion F (RSVpreF, Abrysvo®) vaccine was submitted to the PBAC for consideration at the March 2024 meeting, requesting a NIP listing for the prevention of lower respiratory tract illness caused by RSV in infants from birth through to 6 months of age by active immunisation of pregnant individuals. The PBAC did not recommend RSVpreF in March 2024[12]. However, the RSVpreF vaccine was recommended for listing by the PBAC following consideration of a resubmission in May 2024[13].

5.4 In summary, the comparators for nirsevimab nominated in the submission were:

- Main comparator – No immunisation in Season 1;
- Supplementary comparator – non-PBS listed palivizumab for high-risk infants, in both Seasons 1 and 2;
- Near market comparator – RSVpreF maternal immunisation in Season 1.

5.5 While the evaluation and ESC considered that the nominated comparators were appropriate, both agreed that for the high-risk children entering their second season of RSV, both palivizumab and no immunisation should be comparators due to the low use of palivizumab. The PSCR and pre-PBAC response maintained that palivizumab should be considered the only comparator for high-risk infants as, although its use is inconsistent, it receives funding for high-risk infants via some state health programs

[12] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2024-03/pbac-web-outcomes-03-2024.pdf

[13] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2024-05/pbac-web-outcomes-05-2024.pdf

and hospitals. However, the ESC and the PBAC considered that no immunisation should be considered the main comparator for the second season, given that palivizumab is not widely available.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (15), health care professionals (2) and organisations (8) via the Consumer Comments facility on the PBS website.

6.3 The comments from individuals, in particular parents of infants who had experienced RSV infections, described concerns associated with the condition including respiratory distress and need for hospitalisation, noting that nirsevimab would help to prevent severe illness in infants and young children. The comments also described the unaffordability of nirsevimab without subsidy, and health system pressures resulting from RSV-related attendance at hospitals. The comments noted inequity of access due to eligibility criteria and State-based subsidies not being uniform across the nation.

6.4 In addition to the comments from individuals, health care professionals described current treatment options for RSV as only supportive in terms of controlling symptoms and not offering a cure. The clinicians noted that clinical trials have demonstrated the effectiveness of RSV monoclonal antibodies in infants. The clinicians outlined the capacity to educate providers such as midwives, pharmacists, GPs, Primary Healthcare Nurses, and Aboriginal Health Practitioners, about RSV disease and prevention, and the need to implement a nationally-funded monoclonal antibody immunisation program offering equal access to all infants.

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

- Lung Foundation Australia – access to nirsevimab will reduce the risk of disease, disability and death associated with RSV, and strengthen the respiratory health of the Australian community;
- Asthma Australia – RSV infections in infancy have been associated with the development of childhood allergic asthma;
- National Paediatric Medicines Forum – preliminary data has indicated a large uptake by clinicians, parents and carers to protect their infants from RSV this winter season. Expanding access will improve uptake particularly for rural and remote areas that may not be part of a hospital local area network;

- National Aboriginal Community Controlled Health Organisation (NACCHO) – Aboriginal and Torres Strait Islander infants experience a high burden of disease due to RSV, accounting for 86% of RSV hospitalisations in the Northern Territory;
- Immunisation Foundation of Australia – babies with severe RSV have required hospitalisation with some placed in intensive care and intubated, which impacts on breastfeeding and physical/mental health of all involved;
- The Australasian Society for Infectious Diseases (ASID) - noted that hospitals are often overburdened with infants admitted due to RSV infection in winter, and that nirsevimab represents a significant step forward for Australian infants;
- Western Australian Department of Health - if not funded by government the cost may be prohibitive for many families with a newborn child to care for;
- RSV and Other Respiratory Illnesses Community Reference Group – access to nirsevimab will allow children to undergo scheduled hospital-based procedures on the planned dates, even during RSV season.

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

Clinical trials

6.7 The submission was based on two head-to-head trials comparing nirsevimab to placebo (main comparator), MELODY (N = 1490) and Phase IIb (D5290C00003; herein called Phase IIb) (N = 1453) and one study comparing nirsevimab to palivizumab (supplementary comparator), the MEDLEY trial (N = 925). Additionally, the submission used the MATISSE trial (N = 7126), which compared RSVpreF (near market comparator) to placebo, to inform an indirect treatment comparison (ITC). Also used in the indirect comparison were two meta-analyses which combined data from the nirsevimab trials, MELODY and Phase IIb.

6.8 Details of the trials presented in the submission are provided in Table 4.

Table 4: Key trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Nirsevimab vs. standard care/no treatment/placebo		
MELODY	Hammitt, L.L., Dagan, R., Yuan, Y., Baca Cots, M., Bosheva, M., Madhi, S.A., Muller, W.J., Zar, H.J., Brooks, D., Grenham, A. and Wählby Hamrén, U. Nirsevimab for prevention of RSV in healthy late-preterm and term infants	New England Journal of Medicine 2022, 386(9): 837-846.
Phase IIb D5290C00003	Griffin, M.P., Yuan, Y., Takas, T., Domachowske, J.B., Madhi, S.A., Manzoni, P., Simões, E.A., Esser, M.T., Khan, A.A., Dubovsky, F. and Villafana, T. Single-dose nirsevimab for prevention of RSV in preterm infants.	New England Journal of Medicine 2020, 383(5): 415-425.
Nirsevimab vs. palivizumab		
MEDLEY	Domachowske, J., Madhi, S.A., Simões, E.A., Atanasova, V., Cabañas, F., Furuno, K., Garcia-Garcia, M.L., Grantina, I., Nguyen, K.A., Brooks, D. and Chang, Y. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity. Domachowske, J.B., Chang, Y., Atanasova, V., Cabañas, F., Furuno, K., Nguyen, K.A., Banu, I., Kubiak, R.J., Leach, A., Mankad, V.S. and Shroff, M. Safety of re-dosing nirsevimab prior to RSV season 2 in children with heart or lung disease.	New England Journal of Medicine 2022, 386(9): 892-894. Journal of the Pediatric Infectious Diseases Society 2023, 12(8): 477-480.
RSVpreF vaccine vs. placebo		
MATISSE	Kampmann, B., Madhi, S.A., Munjal, I., Simões, E.A., Pahud, B.A., Llapur, C., Baker, J., Pérez Marc, G., Radley, D., Shittu, E. and Glanternik, J. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants.	New England Journal of Medicine 2023, 388(16), pp.1451-1464.

Source: Table 2.2.1, of the submission.

6.9 The key features of the direct randomised studies are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Nirsevimab vs. placebo						
MELODY	1490	R, DB, MC 510 days	low	Healthy infants in their first year of life and born ≥ 35 weeks 0 days GA and entering their first RSV season	• MA RSV LRTI • RSV LRTI-hospitalisations • Safety and tolerability • PK • ADA	used
Phase IIb D5290C00003	1453	R, DB, MC 1 year	low	Healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA.	• MA RSV LRTI • RSV LRTI-hospitalisations • Safety and tolerability • PK • ADA	used
Nirsevimab vs. palivizumab						
MEDLEY	925	R, DB, MC 2 years	low	Preterm infants in their first year of life and born ≤ 35 weeks 0 days GA eligible to receive palivizumab and infants in their first year of life and a diagnosis of CLD or CHD	• MA RSV LRTI • Safety and tolerability • PK • ADA	not used
RSVpreF vaccine vs. placebo						
MATISSE	7126	R, DB, MC 2 years	low	Pregnant women between 24 – 36 weeks GA.	• MA-LRTI • Severe MA-LRTI	used

Source: Table 2.3.1, , Table 2.3.2, , Table 2.4.1, and Table 2.4.2., of the submission.
ADA = anti-drug antibodies; CHD = congenital heart disease; CLD = chronic lung disease; DB = double blind; GA = gestational age; MA RSV LRTI = medically attended respiratory syncytial virus lower respiratory tract infection; MC = multicentre; N = number of participants; PK = pharmacokinetics; R = randomised; RSV = respiratory syncytial virus.

Main comparison: nirsevimab versus placebo

6.10 The MELODY and Phase IIb trials were head-to-head randomised controlled trials of nirsevimab versus placebo. The MELODY trial required infants to be born later than 35 weeks gestational age (GA), whereas Phase IIb only included infants born between 29 weeks 0 days and 34 weeks 6 days GA. Both studies administered the study drug to infants entering their first RSV season (MELODY median age of administration: 2.6 months, range: 0.0–11.1 months). In Phase IIb, all infants in the nirsevimab arm received a single fixed dose of 50 mg regardless of weight. In contrast, infants in the MELODY trial who were under 5 kg received 50 mg/0.5 mL and infants who were over 5 kg received 100 mg/1 mL. Infants in the placebo group received a corresponding volume of normal saline.

6.11 The key efficacy outcome of MA RSV LRTI in both the MELODY and Phase IIb trials was reported through 150 days post administration of study drug, covering the participants' first RSV season.

Supplementary comparison: nirsevimab versus palivizumab

6.12 The MEDLEY trial reported MA RSV LRTI across two RSV seasons with participants receiving a dose of either nirsevimab or palivizumab prior to each RSV season. Two hundred and sixty-two participants were included in the second RSV season analysis with 42 participants receiving palivizumab in both their first and second RSV seasons, 180 participants receiving nirsevimab in both their first and second RSV seasons, and 40 participants who received palivizumab in the first season receiving nirsevimab in their second season (see paragraphs 6.24 and 6.25 for the MEDLEY randomisation methodology).

Near-market comparison: nirsevimab versus RSVpreF maternal immunisation ITC

6.13 The key features of the studies included in the ITC are summarised in Table 6.

Table 6: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Nirsevimab vs. placebo						
Simões 2023 (Meta-analysis)	2350	Included participants from MELODY and participants who weighed <5kg from Phase IIb D5290C00003, as such it included late-preterm and term infants (GA of at least 35 weeks) from MELODY; and preterm infants (GA less than 35 weeks) from Phase IIb.				used
Turalde-Mapili 2023 (Meta-analysis)	2943	Included all participants from MELODY and Phase IIB D5290C00003				not used
RSVpreF vaccine vs. placebo						
MATISSE	7126	R, DB, MC 2 years	low	Pregnant women between 24 – 36 weeks GA.	• MA-LRTI • Severe MA-LRTI	used

Source: Table 2.4.2, , Table 2.6.1Table 2.6.2, and Table 2.6.4, of the submission.
DB = double blind; GA = gestational age; MA-LRTI = medically attended lower respiratory tract infection; MC = multicentre; N = number of participants; R = randomised; RSVpreF = respiratory syncytial virus prefusion F vaccine.

6.14 Simões et al (2023) and Turalde-Mapili et al (2023) were both meta-analyses of the MELODY and Phase IIb trials.

- Simões et al (2023) excluded participants in the Phase IIb trial who were above 5 kg. In the Phase IIb trial, all participants received 50 mg/0.5 mL of study drug. This conflicted with the MELODY trial, the TGA product information (PI), and the requested listing where infants over 5 kg received 100 mg/1 mL and infants under 5 kg received 50 mg/0.5 mL.
- Turalde-Mapili et al (2023) used all participants from both the MELODY and Phase IIb trials in their meta-analysis, including the infants >5 kg who received the dose lower than the dose recommended in the TGA PI.

Comparative effectiveness

Main comparison: nirsevimab versus placebo

MELODY trial

6.15 In the MELODY trial, MA RSV LRTI occurred in 12 infants (1.2%) in the nirsevimab group and in 25 infants (5.0%) in the placebo group, resulting in a relative risk reduction (RRR) of 74.5% (95% CI, 49.6%, 87.1%; P<0.001) for nirsevimab with respect to MA RSV LRTI (Table 7). Kaplan-Meier (KM) curves from a time-to-event analysis of the proportion of participants free from MA RSV LRTI are shown in Figure 1 (HR = 0.23 [95% CI, 0.12, 0.47]).

6.16 Statistically significant relative reductions in the incidence of MA RSV LRTI were observed with nirsevimab vs. placebo across all prespecified subgroups (data not shown), except for infants who weighed <5 kg on Day 1 and infants with a gestational age of ≥35 weeks to <37 weeks. However, the evaluation noted that both subgroups had a low number of reported MA RSV LRTI cases (14 in the <5 kg subgroup and 7 in the gestational age of ≥35 weeks to <37 weeks subgroup).

6.17 Hospitalisation for RSV-associated LRTI occurred in 6 infants (0.6%) in the nirsevimab group and in 8 infants (1.6%) in the placebo group (RRR 62.1%; 95% CI, −8.6%, 86.8%; P = 0.07) (Table 7).

Table 7: MA RSV LRTI and hospitalisations through 150 days post dose in the MELODY trial

End Point and Analysis	Nirsevimab (N = 994) N (%)	Placebo (N = 496) N (%)	Relative Risk Reduction (%) (95% CI)[a]	P Value
MA RSV LRTI				
Observed events	12 (1.2)	25 (5.0)	74.5 (49.6, 87.1)	<0.001
Participants with imputation of data[b]	15 (1.5)	6 (1.2)		
Hospitalisation for RSV LRTI				
Observed events	6 (0.6)	8 (1.6)	62.1 (−8.6, 86.8)	0.07
Participants with imputation of data[b]	15 (1.5)	6 (1.2)		

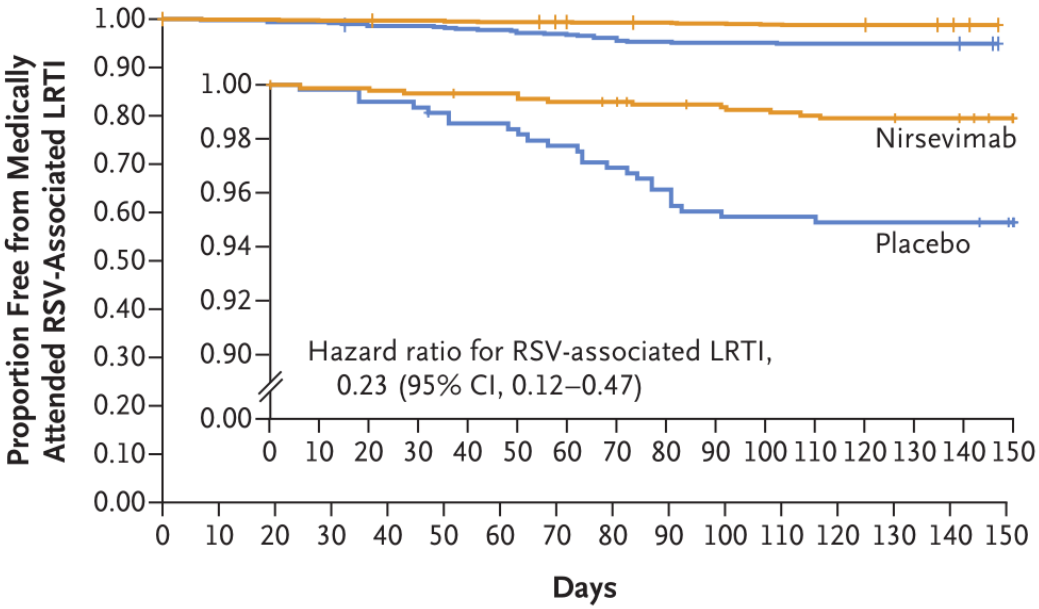
Source: Table 2.5.1, of the submission.

CI = confidence interval; MA RSV LRTI = medically attended RSV associated lower respiratory tract infection; RSV = respiratory syncytial virus.

a Efficacy was defined as the relative risk reduction (calculated as 1 minus the relative risk, where the relative risk was estimated with the use of a Poisson regression model with robust variance) in the nirsevimab group compared with the placebo group (observed data) and is expressed as a percentage.

b For subjects who did not have an event and were lost to follow-up before 150 days, their event status was imputed assuming the observed placebo event rate conditional on stratification factor (age at randomisation).

Figure 1: RSV-associated MA-LRTI – time-to-event analysis.



No. at Risk

Nirsevimab	994	984	980	975	970	966
Placebo	496	488	479	467	465	464

Source: Figure 2-16, of the submission (from Hammitt et al., (2022)).
CI = confidence interval; LRTI = lower respiratory tract infection; MA-LRTI = medically attended lower respiratory tract infection; RSV = respiratory syncytial virus.

6.18 From 151 to 360 days post dose, 20.6% (7/977) of participants in the nirsevimab arm were positive for MA RSV LTRI compared to 26.1% (6/488) of participants in the placebo arm. Although a lower rate of MA RSV LRTI was observed in the nirsevimab arm, of the 34 participants who had MA LRTI, 10 (29.4%) of them were not tested for RSV. This contrasts with the placebo arm where of the 23 participants who had MA LRTI, only 1 (4.3%) was not tested for RSV (Table 35, p113 of the MELODY CSR).

<u>Phase IIb (D5290C00003) trial</u>

6.19 In Phase IIb, a total of 1453 infants born between 29 weeks and 34 weeks, 6 days GA were randomly assigned to receive nirsevimab (n=969) or placebo (n=484) at the start of the RSV season. Nirsevimab demonstrated significantly improved efficacy with respect to MA LRTIs, with a 70.1% RRR compared with placebo through 150 days post dose (p<0.001) (Table 8).

6.20 Similar differences between nirsevimab and placebo were demonstrated in RSV-confirmed LRTI hospitalisation through 150 days post dose, with 0.8% and 4.1% of subjects experiencing the outcome, respectively. This resulted in a RRR of 78.4% (95% CI: 51.9%, 90.3%, p=0.0002) (Table 8).

6.21 KM curves from time to first MA RSV LRTI through to 150 days post dose and RSV LRTI hospitalisation through 150 days post dose are presented in Figure 2.

Table 8: MA RSV LRTI in Phase IIb through 150 days post dose

End Point and Analysis	Nirsevimab (N = 969) N (%)	Placebo (N = 484) N (%)	Relative Risk Reduction (%) (95% CI)[b]	P Value
MA RSV LRTI				
Observed events	25 (2.6%)	46 (9.5%)	70.1% (52.3, 81.2)	<0.0001
Participants with imputation of data[a]	11 (2.3%)	24 (2.5%)		
Hospitalisation for RSV LRTI				
Observed events	8 (0.8%)	20 (4.1%)	78.4% (51.9, 90.3)	0.0002
Participants with imputation of data[a]	24 (2.5%)	11 (2.3%)		

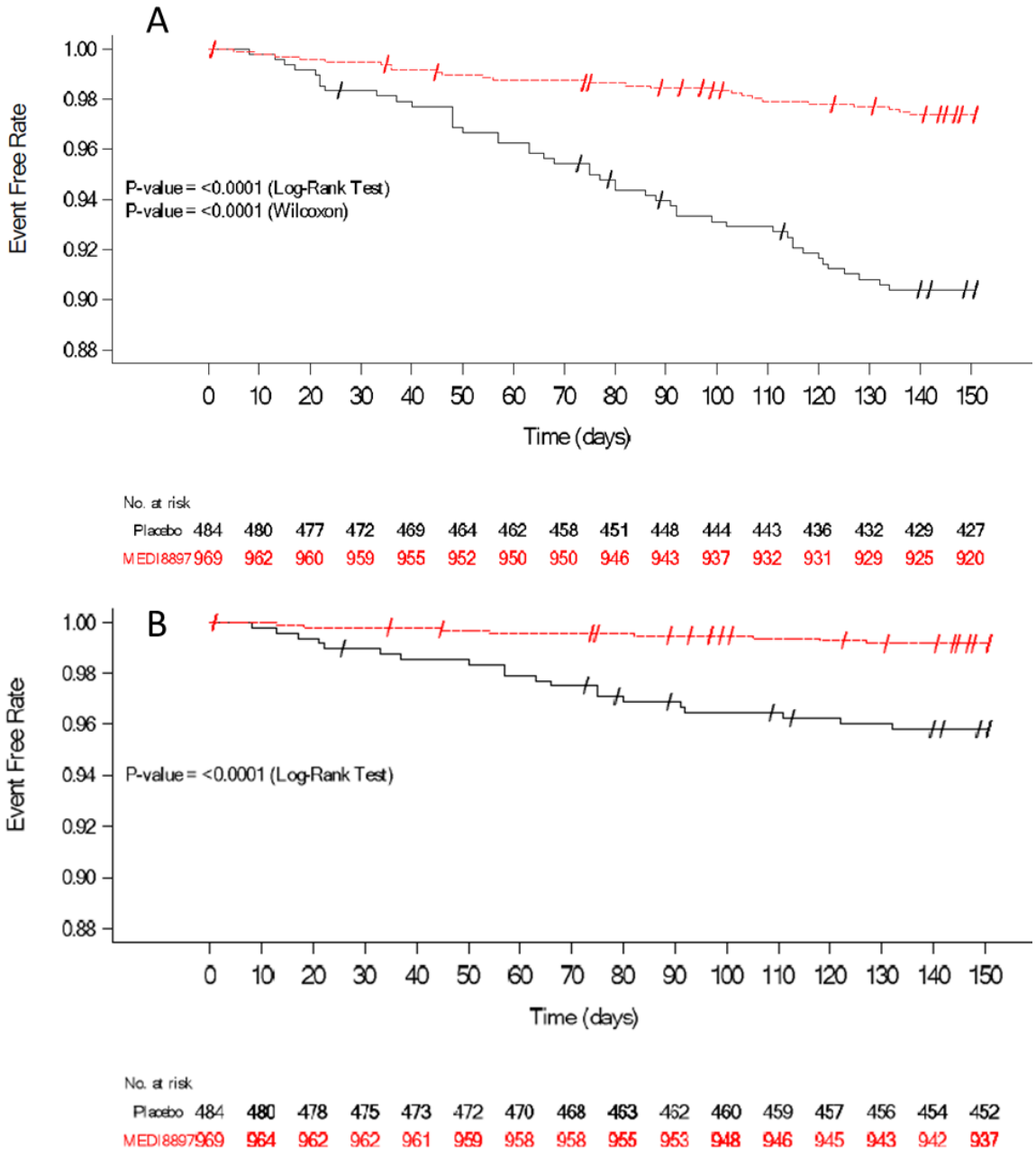
Source: Table 2.5.4 of the submission.

CI = confidence interval; MA RSV LRTI = medically attended RSV associated lower respiratory tract infection; N = number of participants; RSV = respiratory syncytial virus.

a For subjects who did not have an event and were lost to follow-up before 150 days, their event status was imputed assuming the observed placebo event rate conditional on stratification factor (age at randomisation).

b Efficacy defined as the relative risk reduction (calculated as 1 minus the RR, where the RR was estimated with the use of a Poisson regression model with robust variance) in the nirsevimab group compared with the placebo group (observed data) and is expressed as a percentage.

Figure 2: Kaplan-Meier estimate from time to first medically attended RSV confirmed (A) LRTI through to 150 days post dose (ITT population) and (B) LRTI hospitalisation through 150 days post dose (ITT population) in Phase IIb study



Source: Figure 2-19, of the submission
ITT = Intent-to-treat; LRTI = lower respiratory tract infection; No = number; RSV = respiratory syncytial virus.
P values were obtained from stratified log-rank test and Wilcoxon test with 2 stratification factors (age at randomization and hemisphere) as the strata.

Supplementary comparison: nirsevimab versus palivizumab

MEDLEY trial

6.22 The incidence of MA RSV LRTI in Season 1 for the overall population, preterm cohort, and chronic lung disease (CLD)/ chronic heart disease (CHD) cohort is summarised in Table 9. In the overall population, the incidence of MA RSV LRTI through 150 days post first dose in Season 1 was 0.6% (4/616) in the nirsevimab group compared with 1.0% (3/309) in the palivizumab group. Similarly, low rates were reported across the preterm cohort (0.5% each) and CLD/CHD cohort (1.0% vs 2.0%). Although a difference was not observed between the nirsevimab and palivizumab arms, the evaluation noted that this may have been due to the small number of subjects enrolled which resulted in a small number of cases reported across the study, making the results uncertain. The MEDLEY trial was not designed or powered to assess efficacy as a primary outcome.

6.23 Incidence of MA RSV LRTI with hospitalisation through 150 days post first dose was low: 0.3% (2/616) in the nirsevimab group compared with 0.6% (2/309) in the palivizumab group. None of these events occurred in the preterm cohort and all occurred in the CLD/CHD cohort. Hospitalisations continued to be rare up to 361 days with most occurring in the CLD/CHD cohort. The evaluation noted that as with MA RSV LRTI, the small number of cases of hospitalisation may not have provided enough power to detect a difference between the nirsevimab and palivizumab arms.

Table 9: Incidence of MA RSV LRTI and hospitalisations in the MEDLEY trial

	Overall		Preterm		CLD/CHD	
	Nirsevimab (N = 616) n (%)	**Palivizumab (N = 309) n (%)**	**Nirsevimab (N = 407) n (%)**	**Palivizumab (N = 208) n (%)**	**Nirsevimab (N = 209) n (%)**	**Palivizumab (N = 101) n (%)**
MA RSV LRTI						
Through 150 days post first dose [95% CI] [a]	4 (0.6) [0.18, 1.65]	3 (1.0) [0.20, 2.81]	2 (0.5) [0.06, 1.76]	1 (0.5) [0.01, 2.65]	2 (1.0) [0.12, 3.41]	2 (2.0) [0.24, 6.97]
From 151 to 360 days post first dose [b]	8/593 (1.3)	4/293 (1.4)	6/389 (1.5)	3/198 (1.5)	2/204 (1.0)	1/95 (1.1)
Through 360 days post first dose	12 (1.9)	7 (2.3)	8 (2.0)	4 (1.9)	4 (1.9)	3 (3.0)
MA RSV LRTI with hospitalisation						
Through 150 days post first dose	2 (0.3)	2 (0.6)	0	0	2 (1.0)	2 (2.0)
From 151 to 360 days post first dose [c]	3/593 (0.5)	1/293 (0.3)	1/389 (0.3)	0	2/204 (1.0)	1/95 (1.1)
Through 360 days post first dose	5 (0.8)	3 (1.0)	1 (0.2)	0	4 (1.9)	3 (3.0)

Source: Table 2.5.5, of the submission

CHD = congenital heart disease; CI = confidence interval; CLD = chronic lung disease; MA RSV LRTI = medically attended respiratory syncytial virus-associated lower respiratory tract infection; N =number of participants.

a two-sided 95% (or one-sided 97.5% for incidence rates of 0% or 100%) CIs were calculated using the Clopper-Pearson method.

b the incidence rate was calculated using the number of ITT subjects who were followed for at least 151 days post first dose as a denominator.

c the incidence rate was calculated using the number of ITT subjects who were followed for at least 151 days post first dose as a denominator.

6.24 The MEDLEY trial also gave either palivizumab or nirsevimab to participants with CLD/CHD heading into their second RSV season. Participants who were randomised to nirsevimab in the first season received a single dose of 2 x 100 mg/mL nirsevimab followed by 4 once monthly doses of placebo to maintain blinding.

6.25 Participants who had been randomised to palivizumab for season 1 were re-randomised 1:1 to either nirsevimab or palivizumab. Subjects who were re-randomised to the nirsevimab group received one dose of 2 x 100 mg/mL nirsevimab followed by 4 once monthly doses of placebo, while participants re-randomised to the palivizumab arm received 5 once monthly 15 mg/kg doses of palivizumab.

6.26 No cases of MA RSV LRTI were reported through 150 days post the first dose in the second RSV season in any of the groups (Table 10). The evaluation considered that the small number of participants and small number of cases of MA RSV LRTI make these data uninformative for a comparative analysis of efficacy.

6.27 The PSCR stated that MEDLEY was not powered as an efficacy trial, but it was reasonable to think that nirsevimab would be effective in preventing LRTI in the high-risk population of MEDLEY given the results in other efficacy trials (MELODY, Phase IIb). The PSCR also cited a network meta-analysis[14] which reported no significant differences between nirsevimab and palivizumab. The ESC noted that the nirsevimab trials included in the network meta-analysis did not include high-risk participants entering their second RSV season and so was not informative on this matter.

Table 10: Incidence of MA RSV LRTI in Season 2

	NIRS/NIRS (N = 180) n (%)	PALI/PALI (N = 42) n (%)	PALI/NIRS (N = 40) n (%)
Through 150 days post first dose	0	0	0
From 151 to 360 days post first dose [a]	0	1/40 (2.5)	1/40 (2.5)
Through 360 days post first dose	0	1 (2.4)	1 (2.5)

Source: Table 30, of the MEDLEY CSR

CSR = clinical study report; MA RSV LRTI = medically attended respiratory syncytial virus associated lower respiratory tract infection; NIRS = nirsevimab; PALI = palivizumab.

[a] the incidence rate was calculated using the number of ITT subjects who were followed for at least 151 days post first dose as a denominator.

Near-market comparison: nirsevimab versus RSVpreF maternal immunisation ITC

6.28 Pooled efficacy analyses from Simões et al (2023) and Turalde-Mapili et al (2023) were used to inform an ITC against RSVpreF as represented by the MATISSE trial. These meta-analyses used data from the MELODY and Phase IIb trials. A summary of MA LRTI in the nirsevimab meta-analyses and the RSVpreF MATISSE trial is presented in Table 11. The nirsevimab trials reported MA RSV LRTI through 150 days post dosing, while the MATISSE trial reported MA RSV LRTI 150 days post birth.

6.29 The comparison reported in Table 11 is based on MA RSV LRTI. At 150 days post injection, the RRR for nirsevimab vs placebo was between 74% and 79.5% based on

[14] Sun, M., et al., Monoclonal Antibody for the Prevention of Respiratory Syncytial Virus in Infants and Children: A systematic review and network meta-analysis. JAMA Network Open, 2023. 6(2): p. e230023-e230023.

the results of two meta-analyses. At 150 days post birth, the vaccine efficacy (VE) for RSVpreF was 52.5% (97.58% CI: 28.7–68.9). Based on the endpoint of severe MA RSV LRTI in the MATISSE trial[15], the VE of RSVpreF vaccine through 90 days post birth was 81.8% (99.5% CI: 40.6–96.3) and through 150 days post birth was 70.9% (97.58% CI: 44.5–85.9). The evaluation noted that severe MA RSV LRTI was not measured in the nirsevimab trials and therefore nirsevimab could not be compared with RSVpreF for this endpoint.

Table 11: Summary of MA RSV LRTI at the 150-day time point in the nirsevimab meta-analyses and the RSVpreF MATISSE trial

Source of data	Nirsevimab	Placebo	Relative Risk Reduction (95% CI)
Simoes et al (2023)	19/1564 (1%)	51/786 (6%)	79.5% (49.6 to 87.1)
Turalde-Mapili et al. (2023)	37/ 1963 (1.8%)	71/ 980 (7.2%)	74% (62 – 82)
	RSVpreF	**Placebo**	**Vaccine Efficacy (97.58% CI)**
MATISSE	47/3568 (1.3%)	99/3558 (2.8%)	52.5% (28.7–68.9)

Source: Table 2.6.7 of the submission.
CI = confidence interval; MA RSV LRTI = medically attended respiratory syncytial virus associated lower respiratory tract infection; RSVpreF = respiratory syncytial virus prefusion F vaccine.

6.30 The ITCs for nirsevimab versus RSVpreF vaccine are presented in Table 12. Both comparisons suggested that there was a lower risk of MA RSV LRTI in participants treated with nirsevimab compared to those treated with the RSVpreF maternal vaccine. This ranged from a 56.8% improvement (p=0.012) using the reduced population from Simões et al (2023), to a 45.3% improvement (p=0.034) using the full study populations as described by Turalde-Mapili et al (2023).

6.31 However, underlying differences in the trials such as the proportion of premature infants, the timing of administration (with nirsevimab targeting the RSV season), and the timing of the end point assessment (the nirsevimab trials reported MA RSV LRTI from the time of dosing while MATISSE reported from the time of birth) violated the transitivity assumption. The event rates in the placebo arms of both sets of trials differ; consequently, the evaluation and the ESC considered that the results of these ITCs were unreliable.

Table 12: Results of the indirect comparison (Bucher method) of MA RSV LRTI at the 150-day time point

Results	Relative Risk (95% CI)	RRR (95% CI)	p-value
Simões et al (2023) (nirsevimab) vs MATISSE (RSVpreF) MA RSV LRTI	0.432 (0.224, 0.833)	56.8% (16.7, 77.6)	0.012
Turalde-Mapili et al (2023) (nirsevimab) vs MATISSE (RSVpreF) MA RSV LRTI	0.547 (0.313, 0.957)	45.3% (4.30, 68.7)	0.034

Source: Table 2.6.10 and Table 2.6.11, of the submission.
CI = confidence interval; MA RSV LRTI = medically attended respiratory syncytial virus-associated lower respiratory tract infection; RRR = relative risk reduction; RSVpreF = respiratory syncytial virus prefusion F vaccine.
Note: The nirsevimab trials reported MA RSV LRTI through 150 days post dosing while the MATISSE trial reported MA RSV LRTI 150 days post birth.

[15] Kampmann B, Madhi SA, Munjal I, Simões EA, Pahud BA, Llapur C, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. New England Journal of Medicine. 2023;388(16):1451-64. Figure 2.

Comparative harms

Main comparison: nirsevimab versus placebo

6.32 In the MELODY trial, 87.4% of participants in the nirsevimab group and 86.8% of participants in the placebo group had at least 1 adverse event (AE). Most AEs were Grade 1 or 2 in severity, and only 1.0% of adverse events in the nirsevimab group and 1.4% in the placebo group were related to study treatment. Serious AEs (SAEs) were reported in 67 of 987 infants (6.8%) who received nirsevimab and in 36 of 491 infants (7.3%) who received placebo (Table 13).

6.33 Three deaths were reported in the nirsevimab arm while none were reported in the placebo arm. None of these were considered to be related to study drug

Table 13: Summary of key adverse events in the MELODY trial through 360 days post injection

Adverse event	Nirsevimab (n=987) N (%)	Placebo (n=491) N (%)	Total (n=1,478) No (%)
≥1 AE	863 (87.4)	426 (86.8)	1,289 (87.2)
≤1-day post-dose	18 (1.8)	3 (0.6)	21 (1.4)
≤3 days post-dose	56 (5.7)	23 (4.7)	79 (5.3)
≤7 days post-dose	132 (13.4)	63 (12.8)	195 (13.2)
≤14 days post-dose	279 (28.3)	119 (24.2)	398 (26.9)
≥1 AE considered related to IP	10 (1.0)	7 (1.4)	17 (1.2)
≥1 skin reaction related to IP	4 (0.4)	2 (0.4)	6 (0.4)
≥1 AE of ≥Grade 3 severity	36 (3.6)	21 (4.3)	57 (3.9)
≥1 SAE[c]	67 (6.8)	36 (7.3)	103 (7.0)
Considered related to trial drug	0	0	0
Any AE with outcome death[a] (Grade 5 severity)	3 (0.3)	0	3 (0.2)
≥1 AE of special interest[b]	1 (0.1)	0	1 (0.1)
≥1 AE related to COVID-19	7 (0.7)	7 (1.4)	14 (0.9)
Confirmed COVID-19 case	6 (0.6)	6 (1.2)	12 (0.8)
Suspected to be related to COVID-19	1 (0.1)	1 (0.2)	2 (0.1)

Source: Table 2.5.9 of the submission

AE = adverse event; COVID-19 = coronavirus disease 2019; SAE = serious adverse event; IP = investigational product.

a No deaths were considered related to the trial drug by blinded investigators.

b AEs of special interest included hypersensitivity, immune complex disease and thrombocytopenia.

c SAEs were defined as death, events that were life-threatening or required inpatient hospitalisation, events that prolonged hospitalisation, events that were persistent or that were associated with clinically significant disability or incapacity or events that were considered to be of medical significance.

6.34 In the Phase IIb Study, the safety profile for nirsevimab was similar to that of placebo (Table 14). Overall, 86.8% of subjects in the placebo group and 86.2% of subjects in the nirsevimab group had at least 1 AE. AEs of ≥Grade 3 severity were reported in 60 subjects (12.5%) in the placebo group and 77 subjects (8.0%) in the nirsevimab group. Grade 4 or 5 events occurred in ≤ 1% of subjects in each group. The most common Grade 3 AEs (≥ 1% of subjects) reported with nirsevimab compared with placebo were LRTI (1.5% vs 2.3%) and bronchiolitis (1.0% vs 2.5%).

6.35 Five deaths (3 in the placebo group and 2 in the nirsevimab group) were reported during the study through to Day 361. One additional subject in the placebo group died on Day 367. None of these deaths were considered related to treatment.

Table 14: Adverse events in Phase IIb Study

Adverse event[a]	Nirsevimab (n=969) N (%)	Placebo (n=479) N (%)
≥1 AE	834 (86.2%)	416 (86.8%)
≤1-day post-dose	24 (2.5%)	12 (2.5%)
≤7 days post-dose	121 (12.5%)	73 (15.2%)
≥1 AE considered related to IP	22 (2.3%)	10 (2.1%)
≥1 AE of ≥Grade 3 severity[b]	77 (8.0%)	60 (12.5%)
Death[c] (grade 5 severity[b])	2 (0.2%)	3 (0.6%)
≥1 SAE[d]	108 (11.2%)	81 (16.9%)
≥1 SAE[d] or ≥Grade 3 severity[b]	124 (12.8%)	92 (19.2%)
≥1 SAE[d] related to trial drug	0	0
≥1 AE of special interest[b]	5 (0.5%)	3 (0.6%)
≥1 AESI related to IP	5 (0.5%)	3 (0.6%)
≥1 skin reaction	318 (32.9%)	148 (30.9%)
≥1 IP related skin reaction	9 (0.9%)	4 (0.8%)
≥1 skin hypersensitivity reaction	5 (0.5%)	3 (0.6%)
≥1 IP related skin hypersensitivity reaction	5 (0.5%)	3 (0.6%)
≥1 NOCD	4 (0.4%)	4 (0.8%)
≥1 IP related NOCD	0	0

Source: Table 2.5.10, of the submission.

AE = adverse event; AESI = adverse event of special interest; IP = investigational product; NOCD = new onset chronic disease; SAE = serious adverse event.

Note: Events that occurred after 360 days post dose were excluded.

a Subjects were counted once for each category regardless of the number of events.

b Grade 3: severe, Grade 4: life-threatening, Grade 5: fatal.

c One additional death occurred in the placebo group after 360 days post dose.

d Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the patient).

Supplementary comparison: nirsevimab versus palivizumab

6.36 In the MEDLEY trial, the frequency of AEs was similar between the treatment groups (72.3% vs 70.7%). Adverse events were most frequently reported (>20% of subjects in either the nirsevimab or palivizumab group) in the system organ classes of infections and infestations (59.1% vs 57.2%) and gastrointestinal disorders (22.6% vs 23.7%). The most common AEs (>10% of subjects) reported for nirsevimab (vs palivizumab) were upper respiratory tract infections (24.3% vs 26.0%), pyrexia (13.5% vs 14.1%), rhinitis (12.2% vs 13.2%), and nasopharyngitis (9.3% vs 12.8%). No clinically relevant imbalances were observed between the treatment groups. The AE profile of nirsevimab and palivizumab in the preterm (<29 wGA) and CLD/CHD cohorts was generally similar to that observed in the overall population (Table 15).

Table 15: MEDLEY Summary of AEs through 360 days post dose in Season 1

Adverse events	Preterm (N=612)		CHD/CLD (N=306)	
	Nirsevimab (n=406) n (%)	Palivizumab (n=206) n (%)	Nirsevimab (n=208) n (%)	Palivizumab (n=98) n (%)
≥1 AE	268 (66.0)	134 (65.0)	148 (71.2)	72 (73.5)
≥1 TRAE	6 (1.5)	4 (1.9)	4 (1.9)	2 (2.0)
≥1 AE of Grade ≥3 severity[a]	14 (3.4)	7 (3.4)	30 (14.4)	13 (13.3)
≥1 TRAE of Grade ≥3 severity[a]	0	0	0	0
Any AE with outcome of death (Grade 5 severity) [a]	2 (0.5)	0	3 (1.4)	1 (1.0)
≥1 SAE[b]	28 (6.9)	11 (5.3)	40 (19.2)	20 (20.4)
≥1 SAE, Grade ≥3 adverse event, or both[a]	28 (6.9)	11 (5.3)	45 (21.6)	21 (21.4)
≥1 treatment-related SAE	0	0	0	0
≥1 AESI[c]	1 (0.2)	0	1 (0.5)	0
≥1 COVID-19–related adverse event	8 (2.0)	1 (0.5)	2 (1.0)	1 (1.0)

Source: Table 2.5.11, of the submission.

AE = adverse event; AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; COVID-19 = coronavirus disease 2019; SAE = serious adverse event; TRAE = treatment-related adverse event.

a An AE of Grade 3 denotes a severe event, an adverse event of Grade 4 a life-threatening event, and an AE of Grade 5 a fatal event.

b SAEs were defined as death, events that were life-threatening or required inpatient hospitalisation, events that prolonged hospitalisation, events that were persistent or that were associated with clinically significant disability or incapacity, or events considered to be of medical significance.

c AESI included hypersensitivity, immune complex disease, and thrombocytopaenia and was determined based on blinded investigator assessment.

Near-market comparison: nirsevimab versus RSVpreF maternal immunisation ITC

6.37 A formal comparison of safety between nirsevimab and RSVpreF was not presented. Due to the previously mentioned transitivity issues, an indirect comparison of harms would not be informative. Additionally, as the target populations for the two therapies are different (pregnant women for RSVpreF and infants for nirsevimab), it was likely that there would be different safety profiles reported (adult vs infant).

Benefits/harms

Main comparison: nirsevimab versus placebo

6.38 A summary of the comparative benefits and harms for nirsevimab versus placebo is presented in Table 16.

Table 16: Summary of comparative benefits and harms for nirsevimab and placebo derived from the MELODY trial

	nirsevimab n/N	PBO n/N	Efficacy (95% CI)	Event rate/100 participants*		RD (95% CI)
				nirsevimab	PBO	
Benefits (through 150 days)						
MA RSV LRTI	12/994	25/496	74.5% (49.6, 87.1)	1.2	5	**-0.04 (-0.06, -0.02)**
MA RSV LRTI hospitalisations	6/994	8/496	62.1% (-8.6, 86.8)	0.6	1.6	-0.01 (-0.02, 0.00)
Harms (through 360 days)						
URTI	421/981	215/491	0.98 (0.87, 1.11)	42.7	43.8	-0.01 (-0.06. 0.05)
Pyrexia[a]	141/981	63/491	1.12 (0.85, 1.48)	14.3	12.8	0.02 (-0.02, 0.05)
Nasal congestion	120/981	68/491	0.88 (0.67, 1.17)	12.2	13.8	-0.02 (-0.05, 0.02)

Source: Table 2.5.1of the submission and Table 46, pp135-137

CI = confidence interval; MA RSV LRTI = medically attended respiratory syncytial virus-associated lower respiratory tract infection; n = number of participants affected; N = number of participants in group; PBO = placebo; RD = risk difference; RR = risk ratio; URTI = upper respiratory tract infection.

* Median duration of follow-up for the MELODY trial was 472 days, although efficacy was only reported through to 150 days and safety through to 360 days.

[a] pyrexia occurring within 7 days post dose.

6.39 On the basis of direct evidence presented in the submission, for every 100 infants treated with nirsevimab in comparison with placebo over a median duration of follow-up of 472 days:

- Approximately 4 fewer infants would have MA RSV LRTI.
- Approximately 1 less infant would have MA RSV LRTI associated hospitalisation.
- Approximately 1 less infant would experience an upper respiratory tract infection.
- Approximately 2 additional infants would experience pyrexia (fever) within 7 days of administration.

Supplementary (nirsevimab versus palivizumab) and near market (nirsevimab versus RSVpreF maternal immunisation) comparisons

6.40 A benefits and harms table was not presented for nirsevimab versus palivizumab as the submission made a claim of non-inferiority. Additionally, the ITC versus RSVpreF was not informative, and a comparison of safety was not performed, so a benefits and harms table was not presented.

Clinical claim

6.41 With respect to the main comparison, the submission described nirsevimab as superior in terms of effectiveness compared to placebo. The evaluation considered that this claim was adequately supported. In the key MELODY trial, administration of nirsevimab resulted in a reduction in MA RSV LRTI through 150 days post administration in infants born at >35 weeks GA, corresponding to a RRR of 74.5% (95% CI: 49.6, 87.1). Additionally, nirsevimab resulted in a reduction in hospitalisation for RSV-associated LRTI, with a RRR of 62.1 (95% CI: -8.6, 86.6), however this reduction was not statistically significant. In the Phase IIb study, administration of nirsevimab resulted in a RRR in MA RSV LRTI of 70.1% (95% CI: 52.3, 81.2) in healthy pre-term

infants born between 27- and 35-weeks GA. The ESC and the PBAC considered that the efficacy claim was supported by the reduction in MA RSV LRTI for nirsevimab infants compared with placebo in the MELODY and Phase IIb studies.

6.42 With respect to the main comparison, the submission described nirsevimab as non-inferior to placebo in terms of safety in Season 1. The evaluation considered that this claim was adequately supported. In the key MELODY trial, at least 1 AE was experienced by 87.4% of infants receiving nirsevimab, compared to 86.8% of infants receiving placebo. Most AEs were Grade 1 or 2 in severity, and only 1.0% of AEs in the nirsevimab group and 1.4% in the placebo group were considered to be related to study treatment. SAEs were reported in 67 of 987 infants (6.8%) who received nirsevimab and in 36 of 491 infants (7.3%) who received placebo. The ESC and the PBAC considered that the safety claim was supported by the data from MELODY and Phase IIb studies.

6.43 With respect to the supplementary comparison, the submission described nirsevimab as non-inferior to palivizumab in terms of both effectiveness and safety for high-risk infants in both Seasons 1 and 2. The ESC agreed with the evaluation that this claim was not adequately supported. In the MEDLEY trial, the incidence of MA RSV LRTI in the overall population through 150 days post first dose in Season 1 was 0.6% in the nirsevimab group compared with 1.0% in the palivizumab group. Similarly low rates were reported across the preterm cohort (0.5% each) and CLD/CHD cohort (1.0% vs 2.0%). Use of the prophylactic treatments in the second RSV season resulted in no cases of MA RSV LRTI reported in any of the trial arms, noting that only 262 participants were included in the second season analysis. Although the available evidence did not show a difference between the two treatment arms, the evaluation noted that the number of participants and the number of cases of MA RSV LRTI were low and the trial was not sufficiently powered to detect a difference, making any conclusions uncertain. The frequency of AEs was similar between the treatment groups (72.3% vs 70.7%). Consequently, the ESC and the PBAC considered the effectiveness estimates for nirsevimab compared to palivizumab in the second RSV season to be highly uncertain.

6.44 With respect to the near-market comparison in Season 1, the submission described nirsevimab as superior in terms of clinical efficacy compared to maternal vaccination with RSVpreF based on two ITCs, using the reduced nirsevimab population from MELODY and Phase IIB as reported by Simões et al (2023) and the full MELODY and Phase IIB populations as reported by Turalde-Mapili et al (2023).

- The submission stated that both comparisons indicate there was a lower risk of MA RSV LRTI in infants treated with nirsevimab compared to those treated with the RSVpreF maternal vaccine. This ranged from a 56.8% improvement (p=0.012) using Simões et al (2023), to a 45.3% improvement (p=0.034) using Turalde-Mapili et al (2023).
- However, the evaluation considered that the conclusions were unreliable due to the transitivity issues between the nirsevimab trials and the MATISSE trial, such as the difference in the proportion of premature infants and event rates in the placebo arms. The populations in the nirsevimab studies were enriched with those at high risk, with a high proportion of premature infants, and were undertaken when there was a high risk of viral exposure as they were carried out during RSV seasons (in line with its proposed use). This was reflected in the higher rate of medically attended RSV associated lower respiratory tract infection (MA RSV LRTI) in the placebo groups of the nirsevimab trials (6 to 7%) compared to the RSVpreF trial (<3%). This indicates that the nirsevimab and maternal immunisation studies being indirectly compared were not transitive.
- Additionally, the submission stated that nirsevimab was at least clinically non-inferior to RSVpreF in terms of comparative safety. However, the evaluation noted that a formal comparison of safety between nirsevimab and RSVpreF was not presented, and the previously stated transitivity issues would make a comparison uninformative. The evaluation also noted that as RSVpreF and nirsevimab are administered to different populations (pregnant mothers for RSVpreF and infants for nirsevimab), there would likely be differences in the impact of reported AEs. The PSCR stated that a key advantage of nirsevimab compared to a maternal vaccine was that nirsevimab can be used to immunise pre-term infants without the concerns of seasonal dose timing, antibody placental transfer failure, or premature birth, all of which are inherent risks with utilising a maternal vaccine for passive immunisation of infants. Notwithstanding, the ESC and the PBAC considered that the ITC between nirsevimab and maternal vaccination presented by the submission was uninformative, and the submission's claim of superior comparative effectiveness versus maternal vaccination was not supported by the data.

6.45 The PBAC considered there was limited evidence presented in the submission to support the proposed listing of nirsevimab in the second season. The comparative effectiveness for nirsevimab in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season compared with no immunisation was not addressed by the submission.

Economic analysis

Main comparison: nirsevimab versus placebo

6.46 The submission presented a static state-transition cohort model in which the duration of effect and annual incidence of RSV was derived from the key comparative study (MELODY) and the treatment effectiveness of nirsevimab was derived from a pooled analysis of two key studies (MELODY and the Phase IIb study). The model compares nirsevimab with standard of care (no immunisation). The model contained two populations based on their location with respect to climate, tropical or temperate, to permit the simulation of different timing and duration of the RSV season. Each population simulated twelve birth cohorts (January through to December) to incorporate the timing of dosing of nirsevimab on the number of RSV cases avoided throughout the seasons. Nirsevimab was assumed to be given at the beginning of the RSV season (specific to each climate) or at birth for an infant born during the season. The model simulated a single season of RSV (1 year). The economic evaluation steps are: cost per avoided MA RSV (referred to as MA RSV LRTI in the clinical evidence); cost per additional life year gained; and cost per additional quality adjusted life year (QALY) gained.

6.47 The population entering the model was all infants at birth. Infants moved immediately to Never RSV or to an RSV health state if they had MA RSV in the first month of life. Nirsevimab administration occurred at birth for infants born within the RSV season, or was delayed until the start of the season for infants born before the season. Infants in whom administration was delayed until the beginning of the RSV season were assumed to receive nirsevimab in January in tropical climates and April in temperate climates.

6.48 Although the annual incidence of MA RSV (10.8%) was estimated from a key study (MELODY), the distribution of the cases across the season was informed by an Australian study comparing RSV cases in Adelaide, South Australia (temperate population) and Cairns, North Queensland (tropical population)[16].

6.49 The model results were estimated across three different timelines. The impact of nirsevimab on the number of MA RSV cases was estimated over one year. The impact of hospitalised MA RSV on recurrent wheezing was estimated over three years. Infants who remain alive at the end of Year 1 accrue life years and QALYs based on Australian life expectancy (at the age of two years).

6.50 The model structure and key inputs were given in Table 17.

[16] Butler J, Gunnarsson R, Traves A, Marshall H. Severe respiratory syncytial virus infection in hospitalized children less than 3 years of age in a temperate and tropical climate. The Pediatric infectious disease journal. 2019;38(1):6-11.

Table 17: Summary of model structure and key inputs

Component	Summary
Treatments	Nirsevimab vs standard of care (no treatment)
Time horizon	1 year for avoiding MA RSV cases (and related health states). 3 years for accruing costs and outcomes related to recurrent wheezing. Lifetime for accruing life years and QALYs for infants surviving after Year 1.
Outcomes	Cases of MA RSV, cases of hospitalised RSV, deaths, life years gained and QALYs gained.
Methods used to generate results	A static cohort model, with two populations (tropical and temperate), and twelve birth cohorts. Individuals entered the model at birth and were treated at the beginning of the RSV season, or at birth if this was in the RSV season. The timing of nirsevimab administration was important in the model because nirsevimab protection was estimated to be 5 months (i.e., nirsevimab was assumed to prevent 79.5% of all MA RSV cases for five months, then have no effect on MA RSV). Therefore, nirsevimab administration at the beginning of the season will prevent more MA RSV than administration out of season.
Health states	Never RSV, Recovered RSV, Primary Care RSV (GP or emergency presentation), Hospitalised RSV or death. Health states within the hospitalised RSV health state were attendance in ICU, mechanical ventilation, asthma or recurrent wheezing.
Cycle length	1 month
Transition probabilities	<u>Background incidence of MA RSV:</u> RSV incidence was derived from the key MELODY study. The evaluation commented that the applicability of the incidence of RSV from an RCT where participants may be more likely to be tested than in clinical practice was unclear. There were few Australian sources for the incidence of MA RSV, however based on a study of MA RSV incidence between 2000-2012[1] and a surveillance report for Queensland (presented in the submission), the estimated MA RSV incidence was unlikely to be considerably overestimated. <u>RSV hospitalisations:</u> Hospitalisations per 1000 infants were sourced from a Sanofi RSV surveillance report for Central Queensland, provided with the submission. The evaluation noted that the report provided several estimates across 6 years. 4.2% was the highest estimate (in 2022 and 2023) and was used in the submission. It was not clear whether 2022 and 2023 represent 'normal' RSV seasons, or whether hospitalisations were higher or lower following the period of the COVID pandemic. The probability of RSV hospitalisation varies by the age of an infant. <u>Non-hospitalised RSV cases:</u> The rates of RSV attended by a GP, or in the Emergency Department (without subsequent admission to hospital), were estimated to be the difference between the incidence of MA RSV and RSV hospitalisations. Rates varied by the age of an infant. <u>Health states conditional on hospitalisation:</u> For hospitalised infants, the model estimated a proportion will be admitted to the ICU, ventilated, may experience asthma (over 1 year) or may experience recurrent wheezing (over 3 years). As the model permitted individuals to be hospitalised with RSV more than once, the evaluation noted that modelling of asthma and recurrent wheezing included some double counting (individuals who were admitted twice would have a chance of experiencing 2 x 3 years of wheezing). <u>RSV specific mortality:</u> The submission applied an RSV specific mortality only to hospitalised infants. The evaluation considered that the nominated case fatality rate was very low compared with the Australian study that was stated to be the source. <u>All cause mortality:</u> The submission sourced the infant mortality rate (applied in the first year of the model) from the ABS.

Component	Summary
	Life expectancy was applied to survivors after year 1. <u>Treatment effectiveness:</u> Nirsevimab was modelled to avoid 79.5% of all MA RSV within the 5-month period of protection. Following this, it had no effect on MA RSV cases. The estimate of effectiveness was derived from a pooled analysis of the MELODY study and a Phase IIb study (Simões et al (2023)). The evaluation considered that the treatment effectiveness estimate may not be reliable. The meta-analysis excluded approximately 20% of the infant population from one of the studies as an inadequate dose was provided. The resulting treatment effect from the pooled analysis was greater than either of the reported effects from the individual studies.
Extrapolation method	Full life expectancy (from the age of 2) to estimate the differential impact of nirsevimab vs SOC on life years. QALYs were also modelled to full life expectancy.
Health related quality of life	Disutilities were applied to primary care visits, ED visits, hospitalisations, attendance in ICU, and mechanical ventilation. QALY losses were applied to represent a year of asthma, or a year of recurrent wheezing.
Costs	Nirsevimab administration and GP costs were sourced from MBS items. Costs for hospitalisation, ICU admission and visits to the emergency department were sourced from an Australian study of the annual cost burden of RSV in children <5 years of age (Brusco et al 2022). Costs for mechanical ventilation were assumed to be Australian Refined-DRG E41A – respiratory system disorders with non-invasive ventilation, major complexity. The evaluation noted that this source includes hospitalisation costs. As hospitalisation costs were already calculated for all individuals in the model who were ventilated, the hospitalisation costs were double counted for ventilated individuals. Costs for asthma for a year were assumed to be a single admission coded to Australian Refined-DRG E69B – bronchitis and asthma, minor complexity. The evaluation considered that the use of an episode of hospitalisation to represent the cost of managing asthma for 1 year was highly uncertain. Costs for recurrent wheezing were sourced from an economic evaluation of RSV prevention strategies in Norway. The evaluation noted that the costs were stated to represent 5.5 primary visits per year and one infant beta agonist inhaler. Costs of wheezing in Year 2 and Year 3 were discounted by [redacted]%.

Source: Generated during the evaluation from Section 3.4, 3.5 and 3.6 of the submission.
ABS = Australian Bureau of Statistics; DRG = Diagnosis-related groups; ED = Emergency department; GP = General practitioner; ICU = Intensive care unit; MA RSV = Medically attended RSV; MBS = Medicare Benefits Schedule; QALY = quality-adjusted life year; RCT = Randomised controlled trial; RSV = Respiratory syncytial virus; SOC = standard of care.

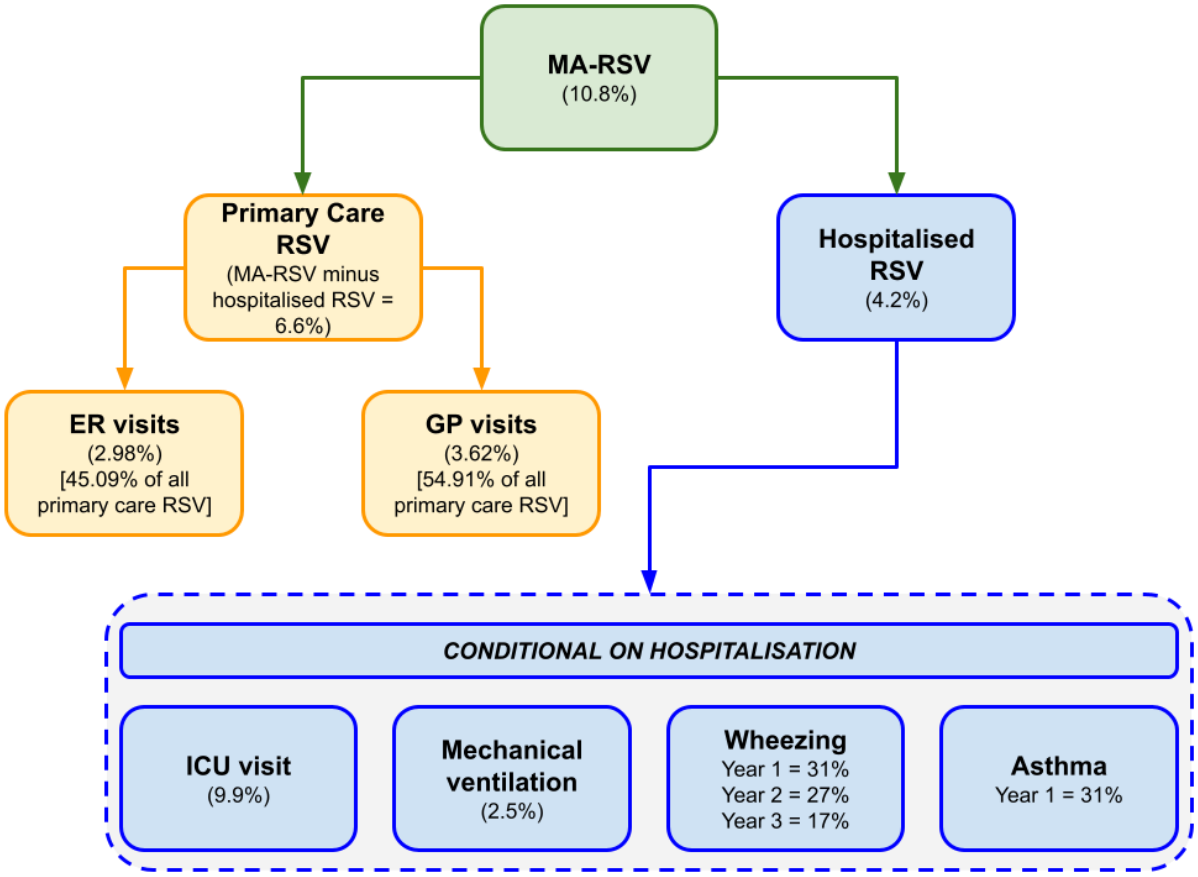
6.51 Nirsevimab was estimated to avoid 79.5% of MA RSV during the period of protection (5 months). The duration of protection was based on the observed incidence of MA RSV in the MELODY study over 5 months. The evaluation considered the five month duration to be appropriate, although acknowledged it may underestimate the actual duration of protection in clinical practice as immunity will wane rather than cease abruptly. The treatment effect has been estimated from a pooled analysis of the MELODY study and the Phase IIb study (Simoes et al. 2023). The pooled analysis excluded approximately 20% of participants from the Phase IIb study who weighed >5 kg as they did not receive the recommended 100 mg dose of nirsevimab. The evaluation noted that the pooled analysis of these two studies reported a treatment effect that was higher than the ITT derived treatment effect in either the individual MELODY (74.5%) or Phase IIb (70.1%) studies. It may be more reasonable to use the ITT results from MELODY as the dosing in this study matches the proposed dosing in Australian clinical practice. The model was very sensitive to the treatment effect. The

PSCR and pre-PBAC response maintained that the efficacy rate of 79.5% reflects a more realistic patient population (pooled infants both ≥35 weeks gestation and 29-35 weeks gestation) than the MELODY trial alone (≥35 weeks gestation), at the correct dose. The PSCR also stated that a key benefit of nirsevimab treatment, especially when compared to the RSV maternal vaccine, was its ability to immunise high-risk significantly pre-term infants who would not be covered otherwise by maternal immunisation. The ESC noted that the MELODY trial was a randomised trial undertaken in the target population, whereas the pooled data utilised by the submission was a post hoc analysis that excluded a proportion of infants from the analysis. The ESC considered that the estimate of 74.5% seemed reasonable unless more robust data were presented. It was also noted that the effectiveness (RRR) of nirsevimab for preventing MA RSV hospitalisations was lower than for preventing all MA RSV (62.1% vs 74.5%), a differential not considered in the economic model. The PBAC considered that the result from the MELODY trial (74.5%) should be used, as this was sourced from a randomised trial undertaken in the target population, rather than a post hoc analysis.

6.52 Transition probabilities in the model were derived from multiple sources that were, with the exception of the probability of asthma and wheezing, Australian based studies. Once an infant in the model moved to an RSV health state (primary care or hospitalised), the probabilities were common across both arms. The treatment effect for nirsevimab was applied as a reduction in the number of MA RSV cases.

6.53 The annual probabilities of MA RSV health states are presented in Figure 3. The proportion of individuals in health states "conditional on hospitalisation" are percentages of the hospitalised cohort (e.g., 9.9% of the 4.2% of hospitalised individuals will be admitted to an intensive care unit). All other proportions are annual percentages of all infants under the age of 1 year.

Figure 3 Probability of entering health states for infants born in a single year.



Source: generated during the evaluation from the transition probabilities reported in Section 3.4 of the submission.
ED = emergency department; GP = general practitioner; ICU = intensive care unit; MA RSV = medically attended RSV; RSV = Respiratory syncytial virus.

6.54 The model derived the incremental differences between the nirsevimab and standard of care arm by reducing the incidence of hospitalised and primary care RSV by 79.5% if the cases of RSV fall within the duration of protection of nirsevimab. For well-defined RSV seasons (temperate climates), the use of nirsevimab at the beginning of the season was modelled to provide protection against almost 90% of the yearly cases of RSV. In tropical climates, where the RSV season is more dispersed, it was assumed that nirsevimab administered at the beginning of the season provided protection against almost 80% of all yearly cases of RSV.

6.55 The probability of hospitalised MA RSV was sourced from an RSV surveillance report for Central Queensland. The annual probability of RSV hospitalisation (4.2% of all infants <1 year of age) was distributed across age groups of infants based on an Australian study of RSV hospitalisations between 2013-2014. The evaluation noted that the model was not sensitive to the distribution of annual rates across age groups. The hospitalisation rate was not linked to the overall annual probability of MA RSV, and sensitivity analyses exploring seasons with higher or lower probabilities of MA RSV did not affect the probability of an infant being hospitalised with RSV. Although

the rate of hospitalisation in the base case may be reasonable, it was implausible that it would not change in seasons with lower or higher burdens of RSV unless the incidence was driven by a change in testing rates, rather than a true change in the likelihood of RSV disease. The model therefore has some structural limitations for sensitivity analyses. The submission stated that annual RSV-confirmed infant hospitalisation rates were taken from three unpublished studies[17], which ranged from 3.4% to 4.2%, and the submission applied the highest estimate in the economic model, i.e. 4.2%. The ESC noted that the estimated rate of RSV hospitalisations (4.2%) was high in comparison with published estimates, such as Saravanos 2019 (1.7%) and Gebremedhin 2022 (2.33% based on cases aged <1 year). Consistent with advice received from the ATAGI, the PBAC considered that the hospitalisation rate in the submission was overestimated, and that a rate of 2.33% would be appropriate, based on a publication by Gebremedhin et al (2022), which reported on the burden of RSV based on a cohort of over 300,000 children born in Western Australia, noting that the submission had used data from this study in another part of the economic model (see paragraph 6.58).

6.56 The ICU, mechanical ventilation, asthma and recurrent wheezing health states were populated by applying a probability to infants who were hospitalised. Infants in these health states accrued costs and disutilities or QALY losses in addition to hospitalisation. As the model permitted individuals to be hospitalised with RSV more than once, the evaluation noted that the modelling of asthma and recurrent wheezing included some double counting (individuals who were admitted twice would have a chance of experiencing 2 x 3 years of wheezing).

6.57 The probability of an ICU admission (9.9% of all RSV hospitalisations) was derived from an Australian study of RSV hospitalisations in children up to the age of 3[18]. The evaluation noted that another study undertaken in Western Australia reported a rate of 5.7% ICU attendance, however included children hospitalised with RSV up to the age of 5[19]. The estimate in the model was therefore uncertain. Applying a rate of ICU admission of 5.7% increases the model ICER by more than 30%.

6.58 The probability of mechanical ventilation (2.5% of all hospitalisations) was based on the Western Australian study of RSV in hospitalised children referenced above (Gebremedhin et al, 2022). The evaluation considered that although this rate may be reasonable, the model structure applies costs and utilities of mechanical ventilation

[17] The three unpublished studies were in NSW (Sydney Children's Hospital Network [SCHN], Attachment A to the submission), Queensland (Central Queensland Hospital and Health Service [CQHHS], Attachment B to the submission), and WA (WA Health registry data, Attachment C to the submission).

[18] Butler J, Gunnarsson R, Traves A, Marshall H. Severe respiratory syncytial virus infection in hospitalized children less than 3 years of age in a temperate and tropical climate. The Pediatric infectious disease journal. 2019;38(1):6-11.

[19] Gebremedhin AT, Hogan AB, Blyth CC, Glass K, Moore HC. Developing a prediction model to estimate the true burden of respiratory syncytial virus (RSV) in hospitalised children in Western Australia. Scientific reports. 2022;12(1):332.

separately from ICU costs and utilities. As the rates of ICU attendance, and the costs and disutilities of ICU attendance, already incorporate the proportion of infants that require ventilation, by modelling these two (sub) health states separately, the model was likely to be double counting. The model was substantially sensitive to the removal of mechanical ventilation.

6.59 The evaluation considered that the probabilities of asthma (for 1 year) and wheezing (for up to 3 years) were highly uncertain. No evidence to support the impact of nirsevimab on rates of asthma or wheezing was presented in the clinical section of the submission. These have been sourced from an economic evaluation of RSV prevention strategies undertaken in Norway[20]. The Norwegian economic evaluation referenced two systematic reviews as the source of the probabilities, however the derivation of the probabilities was unclear. The authors of the economic evaluation acknowledged that a randomised trial showed that RSV had no major effect on physician diagnosed asthma or lung function at 6 years of age in healthy preterm infants[21]. Consequently, the authors of the published economic evaluation only included the costs and disutilities of asthma and wheezing in a supplementary analysis.

6.60 The submission justified the inclusion of wheezing based on an observational study that reported recurrent wheezing in children following RSV[22], a German study of 42 children with RSV (13/42 had recurrent wheezing in year 1, however no background rate of wheezing was discussed)[23], and a study that reported improvements in the rate of wheezing over time[24]. The ESC noted the age of the evidence, and its observational nature, and considered that the applicability of the data was uncertain.

6.61 Removing asthma and recurrent wheezing from the nirsevimab analysis more than doubles the model ICER. The PSCR maintained that the source for asthma/wheezing rates (Li et al 2022) provided the best available data in the absence of Australian data. However, the ESC considered the estimates of asthma and recurrent wheezing were uncertain. The pre-PBAC response reiterated that the removal of these complications was not consistent with the available evidence or clinical practice. Consistent with advice received from the ATAGI, the PBAC noted the discussion in the pre-PBAC response, however agreed with the ESC that the estimates of asthma and recurrent

[20] Li X, Bilcke J, Vázquez Fernández L, Bont L, Willem L, Wisløff T, et al. Cost-effectiveness of respiratory syncytial virus disease prevention strategies: maternal vaccine versus seasonal or year-round monoclonal antibody program in Norwegian children. The Journal of infectious diseases. 2022;226(Supplement_1):S95-S101.

[21] Scheltema NM, Nibbelke EE, Pouw J, Blanken MO, Rovers MM, Naaktgeboren CA, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. The Lancet Respiratory Medicine. 2018;6(4):257-64.

[22] Bont L, Steijn M, Van Aalderen W, Brus F, Draaisma JT, Van Diemen-Steenvoorde R, et al. Seasonality of long term wheezing following respiratory syncytial virus lower respiratory tract infection. Thorax. 2004;59(6):512-6.

[23] Schauer U, Hoffjan S, Bittscheidt J, Köchling A, Hemmis S, Bongartz S, Stephan V. RSV bronchiolitis and risk of wheeze and allergic sensitisation in the first year of life. *European respiratory journal*. 2002;20(5):1277-83.

[24] Zomer-Kooijker K, van der Ent CK, Ermers MJ, Uiterwaal CS, Rovers MM, Bont LJ, Group RCS. Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PloS one*. 2014;9(1):e87162.

wheezing were uncertain and should be removed from the economic model as the estimates were not robust.

6.62 In the nirsevimab model, individuals who were hospitalised and survive hospitalisation entered a recovered RSV health state. In this health state, they were exposed to the same probability of MA RSV as the never RSV health state. The evaluation noted that a proportion of individuals who re-entered the hospitalisation health state were counted as experiencing a year of asthma, and up to three years of recurrent wheezing. However, this was double-counting given that it had been accounted for already in the initial hospitalisation event.

6.63 RSV-specific mortality was sourced from a retrospective observational study undertaken over 21 years between 1998 and 2018 in New South Wales[25]. The study estimated RSV attributable deaths in hospitalised infants. The evaluation considered that this source may be appropriate, although there may have been advances in supportive care over this time that have resulted in a reduction of RSV specific mortality in hospitalised infants. The published study reported 20 RSV attributable deaths from 9,779 RSV hospitalised cases, resulting in a fatality ratio of 0.002. The submission applied a probability of death in hospitalised infants of 0.000033, which was approximately 60 times lower. The submission estimated that, of 315,705 infants entering the model, the difference in survivors across the arms at the end of year 1 was 0.25 infants. Applying a higher fatality ratio (of 0.002 as suggested by the NSW study) reduces the ICER by approximately 24%. The PSCR agreed with the evaluation that the case fatality rate used in the submission was an under-estimation. The PBAC agreed with the ESC that a case fatality rate of 0.002 was appropriate for the model, as noted by the evaluation, based on the study by Saravanos et al (2022).

6.64 Health outcomes in the model were derived by applying disutilities to RSV related health states for primary care visits (-0.16), ED visits (-0.20), hospitalisation (-0.41), ICU admissions (-0.41 – 0.2 = -0.61) and mechanical ventilation (-0.41 – 0.2 = -0.61). The evaluation noted that as individuals can be in both an ICU and mechanical ventilation sub-health state, a proportion of individuals will have a disutility of -0.81 applied (-0.41 – 0.2 – 0.2 = -0.81). The model applies these disutilities for the duration of a single cycle, which the evaluation considered to be inappropriate. The source of the disutilities (an economic analysis undertaken for RSV prevention in Canada[26]) intended for the disutilities to be applied for the duration of each episode. The durations of RSV related health events were considerably shorter than 1 month. Applying the disutilities for a full month rather than the duration of the episode of RSV results in a substantially higher QALY loss. To correct this overestimate, the evaluation

[25] Saravanos GL, Hsu P, Isaacs D, Macartney K, Wood NJ, Britton PN. Respiratory Syncytial Virus-attributable deaths in a Major Pediatric Hospital in New South Wales, Australia, 1998–2018. The Pediatric infectious disease journal. 2022;41(3):186-91.

[26] Nourbakhsh S, Shoukat A, Zhang K, Poliquin G, Halperin D, Sheffield H, et al. Effectiveness and cost-effectiveness of RSV infant and maternal immunization programs: A case study of Nunavik, Canada. EClinicalMedicine. 2021;41.

derived the QALY loss from the Canadian economic analysis based on the reported durations of each type of RSV health event, and adjusted the disutilities applied in the model (for a full month) so that the QALY loss matches what would be expected if the disutilities had been applied for the appropriate duration. Applying these updated disutilities in the model had a marked impact on the model results, increasing the ICER by almost 50%. The PSCR stated that even if disutilities were 20% of their current value, nirsevimab was still cost-effective and that the model results were not sensitive to changes in disutilities associated with RSV health states. The PBAC agreed with the ESC that the submission's approach had overestimated the disutilities for RSV health events, and that the disutilities should be adjusted as proposed by the evaluation.

6.65 The disutility values and their derivation are provided in Table 18. Some assumptions were made to ensure that the duration of the event of hospitalisation, and ICU attendance, were considerably longer than the duration of an RSV event addressed in primary care.

Table 18 Update of disutility values applied for RSV related health states in the nirsevimab model to match the QALY loss had the disutilities been applied for the duration of the episode (provided during the evaluation)

Health state	Nourbakhsh et al 2021			Disutility required in model to match QALD loss in publication[c]
	Disutility	Duration of event[a]	Total QALD loss[b]	
Primary care RSV	-0.16	6.16 days	-0.99	-0.0324
Emergency department RSV[d]	-0.2	6.16 days	-1.23	-0.0405
Hospitalised RSV	-0.41	4 days + 6.16 days of primary care (-0.16)	-2.63	-0.0863
ICU RSV	-0.61	12.5 days +4 days hospitalised (-0.41) + 6.16 days of primary care (-0.16)	-10.25	-0.3368 (-0.2505 applied in the model as hospitalisation was counted separately)[e]
Mechanical ventilation RSV[d]	-0.61	assume same as ICU		

Source: generated during the evaluation based on Nourbakhsh et al 2021, and the Nirsevimab model ("Health Events" tab).
ICU = Intensive care unit; QALD = quality-adjusted life day; RSV = Respiratory syncytial virus.
[a] Where a range of duration of events was provided in Nourbakhsh et al 2021, the longest duration has been used. This will favour the Nirsevimab arm.
[b] To estimate the hospitalised RSV QALD loss, the commentary has assumed that infants spend 4 days in hospital, and an additional 6.16 days symptomatic (based on primary care RSV duration). To estimate the ICU RSV QALD loss, the commentary has assumed that individuals have a symptomatic period (6.16 days), a hospitalised period (4 days) and a period in ICU (12.5 days).
[c] The utility require to match the target QALD loss was derived by dividing the QALD loss by 30.44 days in a month. Therefore, if the disutility was applied for the full 30.44 days (as in the Nirsevimab model), it will result in the same QALD loss as estimated from the Nourbakhsh et al 2021 study.
[d] Disutilities for emergency department RSV and mechanical ventilation cannot be located in the Nourbakhsh et al 2021 publication.
[e] The disutility applied in the model for ICU (and mechanical ventilation) was estimated by subtracting the disutility associated with hospitalisation (as this was counted separately in the Nirsevimab model).

6.66 To estimate the health outcome impact of asthma and recurrent wheezing, a loss of QALYs was applied to each patient entering the health state. As the loss of QALYs for recurrent wheezing may occur in Year 2 or Year 3, QALY losses were discounted by 5% per annum. The evaluation considered that the derivation of the QALY losses was

poorly explained in the submission, and represent a disutility of -0.04 applied for a full year for asthma and Year 1 recurrent wheezing. As noted previously, there were a proportion of individuals who will be hospitalised twice in Year 1, and therefore there were a proportion of individuals who will receive a QALY loss for a year of asthma or 1 or 2 or 3 years of wheezing on two occasions (double counting).

6.67 Lifelong accrual of QALYs was estimated by multiplying the life year gains for survivors at the end of Year 1 by a utility value of 0.996. The evaluation noted that although this utility value was high, particularly for adults, as the difference in survivors across the arms was small (even with a higher case fatality ratio (CFR) applied), and as life years were discounted, incorporating a declining utility value with age would be unlikely to markedly impact the model results.

6.68 Costs in the model have been derived from various sources including MBS items, Australian-Refined Diagnosis Related Groups data and published studies.

6.69 The administration of nirsevimab was costed to occur during a GP visit (MBS item 23) or at birth. However, the submission assumed that no administration cost would be incurred if nirsevimab was given at birth (this would occur for 5 months of the year), and no administration cost would be incurred if infants were attending a GP for their 2, 4 or 6 month NIP immunisations. Consequently, the administration cost was reduced from $41.40 to $13.80 on the basis that a unique GP visit was only required for one third of nirsevimab administrations. The evaluation noted that as nirsevimab was not proposed for listing on the NIP, it was not clear whether it would be routinely available as proposed by the submission. Parents or carers may need to retrieve nirsevimab from a pharmacy prior to attending a GP visit, and this may require a unique GP visit for administration. Assuming a unique GP visit for administration for each nirsevimab dose increases the ICER by more than 50%. The PSCR emphasised the overlap between the existing childhood immunisation program at 0, 2, 4, and 6 months and the administration window of nirsevimab. The ESC noted that administration of nirsevimab during GP visits for NIP immunisations at 2, 4 or 6 months may be feasible in some cases, however some parents may opt for a separate appointment due to concerns about the number of needles at one visit, and the need to fill a prescription at a pharmacy before the appointment. The PBAC agreed with the concern raised by the ESC regarding underestimation of administration costs for nirsevimab. The PBAC considered that a higher proportion of injections would be given in unique consultations in general practice than estimated in the submission, and in other instances higher costs of administration may be incurred for example for hospital clinics and these should be considered.

6.70 The costs of emergency department attendances, hospitalisations and admission to ICU were sourced from an Australian study of the cost burden of RSV in hospitalised children under the age of 5 (Brusco et al 2022)[27]. The submission inflated these costs

[27] Brusco NK, Alafaci A, Tuckerman J, Frawley H, Pratt J, Daley AJ, et al. The 2018 annual cost burden for children under five years of age hospitalised with respiratory syncytial virus in Australia. 2022.

to 2023 prices using the RBA inflation calculator. The costs from the study included both an index admission associated with RSV and all subsequent admissions over the next 6 months, regardless of cause of hospitalisation. The submission applied the aggregated cost of all hospitalisations over 6 months in the economic model which was not justified. Excluding the ED, ICU and hospitalisation costs associated with readmissions increased the ICER by more than 250%. The PSCR stated that the costs of subsequent admissions were not included in the model. However, the ESC agreed with the evaluation that the cost used was an aggregated cost of all hospitalisations over 6 months. The ESC considered that an analysis that assumed a proportion of individuals would be readmitted would be informative, and noted that a rate of 13% would be supported by a study that specifically assessed the risk of readmission after RSV hospitalization among children younger than 5 years (Choi 2021), based on reported respiratory related re-admissions[28].

6.71 The cost of emergency department attendances represents the costs for infants who were subsequently hospitalised. However, the evaluation noted that in the model, ED attendances were non-hospitalised RSV cases. The Round 24 National Hospital Cost Data Collection (NHCDC) reported that the average cost of an emergency department attendance resulting in hospitalisation was roughly twice as costly as ED presentations that did not result in admission. Assuming ED costs for primary care attended RSV were 50% of the model's estimate, increased the ICER by 46%.

6.72 The cost of hospitalisation applied in the model excluded the cost of an emergency department attendance. However, almost 90% of infants who were hospitalised in the costing study were admitted through the emergency department. Therefore, the evaluation considered that the cost of hospitalisation may be underestimated. The PSCR confirmed that the costs for hospital admission were derived from an Australian study (Table 6 of Brusco 2022) and applied appropriately in the model.

6.73 The cost of mechanical ventilation was stated to be sourced from "DRG E41A – respiratory system disorders W non-invasive ventilation, major complexity". The evaluation noted that no source was provided. The cost provided in the submission ($) cannot be derived from Round 22 – Round 25 of the NHCDC, inflated using the RBA calculator. Costs estimated during the evaluation were between $ - $ lower. Costs sourced from AR-DRGs in the NHCDC include the cost of hospitalisation (and other costs). The model already includes the cost of hospitalisation and ICU in a proportion of individuals, which likely represents double-counting. More importantly, the costs of hospitalisation and ICU attendance used in the model, sourced from the Australian costing study (Brusco et al 2022), already include costs associated with mechanical ventilation. The PSCR maintained that mechanical ventilation should be costed separately using AR-DRG E41A because Brusco et al did not report ventilation costs.

[28] 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.

However, Brusco et al stated that respiratory support costs have been incorporated into the general ward and ICU costs for each admission. The pre-PBAC response confirmed that mechanical ventilation costs were included in the study by Brusco et al, however maintained that it was appropriate to add further costs for mechanical ventilation in the model. The PBAC agreed with the ESC that the cost of mechanical ventilation should be removed from the model as the submission's approach double-counted these costs.

6.74 In general, Brusco et al 2022 would have been a simpler source of costs for all hospitalisations, because it already includes all costs for an average admission, including ventilation. The PSCR states that costs were disaggregated so that they could be applied separately to individuals who experience different health states. However, the costs in Brusco et al represent the total cost of hospitalisation for the average patient (which includes ambulance costs, ED costs, ICU costs, ventilation costs and ward costs). Therefore, the only health state required for costs would be hospitalisation. The PBAC noted ESC's advice in paragraph 6.70 that an analysis that assumed a proportion of individuals would be readmitted would be informative, and noted that a rate of 13% could be supported based on the study by Choi et al (2021).

6.75 The costs associated with managing 1 year of asthma were estimated using an AR-DRG (E69B – bronchitis and asthma, minor complexity). The use of this source was not justified in the submission. The evaluation considered it to be unclear how a single hospitalised episode was related to the management of asthma for a year.

6.76 The costs associated with managing recurrent wheezing were sourced from a cost-effectiveness study of RSV prevention strategies in Norway[29]. The evaluation noted that the cost of managing recurrent wheezing in the Norwegian economic evaluation was stated to be based on 5.5 GP visits and one infant salbutamol inhaler.

6.77 The evaluation considered that the submission's model comparing nirsevimab with standard of care has multiple highly uncertain inputs. In many cases, applying alternative estimates results in large impacts on the model results. Key drivers of the modelled ICER are provided in Table 19.

[29] Li X, Bilcke J, Vázquez Fernández L, Bont L, Willem L, Wisløff T, et al. Cost-effectiveness of respiratory syncytial virus disease prevention strategies: maternal vaccine versus seasonal or year-round monoclonal antibody program in Norwegian children. The Journal of infectious diseases. 2022;226(Supplement_1):S95-S101.

Table 19: Key drivers of the model

Description	Method/value	Impact
Incidence of MA RSV	10.8% from MELODY study	Changing this value by 5% (e.g. to 11.34% or to 10.26% annual incidence), and linking the incidence rate to the hospitalisation rate, results in a 50%-60% change in the ICER of the corrected submission base case. If the incidence was varied, but the hospitalisation rate remains at 4.2% of all infants, the effect on the model was substantially less. This indicates that the impact of greater MA RSV notifications may be minor if this solely reflects a change in GP attendances and was not linked to hospitalisations. However, more or less severe RSV seasons that result in a decrease or increase in hospitalisations will have a large impact on the cost-effectiveness of nirsevimab. The ESC noted that the estimated rate of RSV hospitalisations (4.2%) was high in comparison with published estimates, such as Saravanos 2019 (1.7%) and Gebremedhin 2022 (2.33% based on cases aged<1 year) (see paragraph 6.55).
Timing of nirsevimab administration	Modelled to be at the beginning of the season, or at birth if in the season.	High, favours nirsevimab. The model represents (near) optimal timing of nirsevimab administration. This was unlikely to reflect the use of nirsevimab in clinical practice. Delaying the administration by one month in the model, as may occur if the season begins unpredictably, or if parents/carers were unable to attend a GP at the optimal time, increased the ICER by more than 75%. The PSCR noted that the practicality of the timing of nirsevimab administration would be best addressed by Federal and State experts. The ESC noted that timing of administration was a key driver of the model, and the ability to map the RSV season in different jurisdictions, and provide advice about the optimal timing of nirsevimab administration will be critical for achieving cost-effectiveness in clinical practice (see paragraph 6.81).
Nirsevimab season	21% of the Australian population was assumed to have a Tropical RSV season.	The cost-effectiveness of nirsevimab differs by climate. This was due to the tropical regions having less well-defined RSV seasons. The ICER was sensitive to the proportion of individuals in the Tropical region vs Temperate region. In addition, if the RSV season was unknown in a jurisdiction, or if the advice for the timing of administration of nirsevimab was not aligned with the season (i.e., if Southern Queensland has a more Temperate distribution than Cairns, yet follows the same timing of dosing nirsevimab), then this will have a marked impact on the treatment effectiveness of nirsevimab (see paragraphs 6.79 and 6.80).
Nirsevimab effectiveness	79.5% from a meta-analysis of MELODY and a subgroup of Phase IIb study.	High, favours nirsevimab. The meta-analysis excluded infants who were greater than 5 kg and did not receive the 100 mg dose of nirsevimab. However, the MELODY trial employed the correct dosing and the treatment effect from that trial alone was 74.5%. Applying a treatment effect of 74.5% increases the ICER by 80%. The PSCR maintained that the efficacy rate of 79.5% reflects a more realistic patient population (pooled infants both ≥35 weeks gestation and 29-35 weeks gestation) than the MELODY trial alone (≥35 weeks gestation), at the correct dose. The ESC considered that the estimate of 74.5% seems reasonable unless more robust data were presented. It was also noted that effectiveness of nirsevimab for preventing MA RSV hospitalisations was lower than for preventing all MA RSV (62.1% vs 74.5%) (see paragraph 6.51). The effectiveness of nirsevimab for preventing MA RSV hospitalisations was lower than for preventing all MA RSV (62.1% vs 74.5%). The impact of applying a different estimate of effectiveness for hospitalisation cannot be tested in the model, however it was expected to be large as

Description	Method/value	Impact
		hospitalisations have higher costs and disutilities than primary care attended RSV. The ESC considered that the structural limitation adds uncertainty to the economic evaluation.
Proportion of hospitalised MA RSV cases that were admitted to ICU.	9.9% sourced from an Australian study (Adelaide and Cairns) in hospitalised children with RSV.	Moderate, likely favours nirsevimab. An alternative source from Western Australia reported a probability of 5.7% admission to ICU in hospitalised children with RSV. Using this input results in an increase in the ICER of 31.9% (see paragraph 6.57).
Probability and cost of mechanical ventilation	2.5% of infants hospitalised with RSV were modelled to receive mechanical ventilation. The cost of mechanical ventilation was derived from an AR-DRG and was $44,682.02.	Moderate or High, favours nirsevimab. If mechanical ventilation is retained in the model, there is double counting of the costs as the mechanical ventilation cost already includes hospitalisation costs (which were therefore costed twice in the model). Removing mechanical ventilation from the model results in an increase in the ICER of 89%. The ESC considered that the cost of mechanical ventilation should be removed from the model (see paragraph 6.73).
Asthma and wheezing	31% of hospitalised infants experience 1 year of asthma. 31%, 27% and 17% of hospitalised infants experience 1, 2 and 3 years of recurrent wheezing, respectively.	High, favours nirsevimab. The derivation of the rates of asthma and wheezing were highly uncertain. Studies were conflicting regarding whether there were ongoing impacts of RSV on rates of asthma and wheezing, and the economic analysis from which the rates were sourced only applied these in a supplementary analysis. Removing asthma and wheezing from the economic model results in an increase in the ICER of 122.9%. The PSCR maintained that the source for asthma/wheezing rates (Li et al 2022, Norwegian national registry) was the best available data in the absence of Australian data. However, the ESC considered the estimates of asthma and recurrent wheezing to be uncertain (see paragraph 6.61).
Case fatality ratio applied to hospitalised infants	The proportion of infants hospitalised with RSV who die is modelled to be 0.0033%.	Moderate, favours standard of care. The estimate of mortality due to RSV in hospitalised infants used in the submission could not be replicated. The stated source for the model reports 20 RSV attributable deaths in 9,779 RSV hospitalisations. This results in a case fatality ratio of 0.2%. Applying this in the model reduces the ICER by approximately 24%. The PSCR agreed with the evaluation that the case fatality rate used in the submission was an under-estimation (see paragraph 6.63).
Emergency attendance costs	The cost of an ED attendance, $1,907.81, was based on a costing study in children who were hospitalised with RSV.	Moderate, favours nirsevimab. ED costs in individuals who were hospitalised were substantially greater than ED costs in individuals who were discharged without admission. The NHCDC indicates that a non-admitted ED attendance was about 50% of the cost of an admitted ED attendance. Reducing this cost by 50% results in an increase in the ICER of 45.78% (see paragraph 6.71).
Duration over which disutilities for RSV health states were applied.	Disutilities were applied for a full model cycle (1 month).	Moderate to high, favours nirsevimab. The disutilities for primary care RSV attended by a GP, emergency department attended RSV, hospitalised RSV and ICU RSV were sourced from a study that applied these disutilities for the duration of the event. The duration of the events in this study were substantially shorter than 1 month. Adjusting the disutilities in the model so that the same loss in QALYs was observed as would have been had the duration of the event been implemented increases the ICER by 48.5% (see Table 18 for derivation of disutilities). The PSCR stated) that even if disutilities were 20% of their current value, nirsevimab was still cost-effective and that the model results were not sensitive to changes in disutilities associated with RSV health states. However, the ESC considered that the submission's approach was not reasonable (see paragraph 6.64).
Hospitalisation costs	Hospitalisation costs exclude ED costs.	High, favours standard of care. The source of the hospitalisation costs excludes emergency department costs. However, almost 90% of all

Description	Method/value	Impact
		individuals in the study were admitted to hospital via the emergency department. The adjustment based on reported respiratory related re-admissions should also be considered as described in the following row (see paragraph 6.72).
Hospitalisation, ICU and ED costs	Costs include both the index admission associated with RSV, and all subsequent admissions over the next 6 months.	High, favours nirsevimab. It was unlikely that all subsequent admissions can be attributed to RSV, particularly in the high-risk population. Using estimates of costs for hospitalisation, ED and ICU for just the index admission results in an increase in the ICER of 299.5%. The ESC considered that an analysis that assumed a proportion of individuals would be readmitted would be informative, and noted that a rate of 13% would be supported by a study that specifically assessed the risk of readmission after RSV hospitalization among children younger than 5 years (Choi 2021), based on reported respiratory related re-admissions[30] (see paragraph 6.70).
Nirsevimab administration costs	Only one third of all administrations require a unique GP visit, therefore the cost of administration was $41.40 / 3 = $13.80	High, likely favours nirsevimab. It was unclear whether nirsevimab will be administered by a GP at the same time as NIP listed vaccinations. Assuming a unique GP visit was required for each nirsevimab administration results in an increase in the ICER of 78.9% (see paragraph 6.69).

Source: Generated during the evaluation from the nirsevimab economic model workbook.
DRG = Diagnosis-related groups; ED = Emergency department; GP = General practitioner; ICER = incremental cost-effectiveness ratio; ICU = Intensive care unit; MA RSV = Medically attended RSV; NHCDC = National Hospital Cost Data Collection; NIP = National Immunisation Program; QALD = quality-adjusted life day; QALY = quality-adjusted life year; RSV = Respiratory syncytial virus.

6.78 Results of the stepped economic evaluation for the aggregated population were presented in **Error! Reference source not found.**.

Table 20 Results of the stepped economic evaluation

AGGREGATED POPULATION (n = [redacted][1]): includes tropical and temperate regions					
Step	**Model output**	**Standard of care**	**Nirsevimab**	**Difference**	**ICER**
1	Costs	$[redacted]	$[redacted]	$[redacted]	
	Corrected	$[redacted]		$[redacted]	
2	RSV cases	[redacted][5]	[redacted][6]	-[redacted][6]	-$[redacted][2]
	Corrected				-$[redacted][2]
3	Life years	6,007,586	6,007,591	4.896	$[redacted][3]
	Corrected				$[redacted][3]
4	QALYs	5,984,282	5,985,217	936	$[redacted][4]
	Corrected				$[redacted][4]

Source: Table 3.8.2, of the submission.
ED = Emergency department; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RSV = Respiratory syncytial virus.
The redacted values correspond to the following ranges
1 300,000 to < 400,000
2 Dominant
3 > $1,055,000
4 $5,000 to < $15,000
5 30,000 to < 40,000
6 10,000 to < 20,000

6.79 The evaluation noted that the results for the tropical population and the temperate population differed considerably. The incremental cost per additional QALY in the

[30] 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.

tropical population was estimated to be $35,000 to < $45,000. In the temperate population, this was $5,000 to < $15,000 (Table 21). The key driver of the difference between the two populations related to the monthly distribution of MA RSV cases throughout the season. If an infant was dosed at the beginning of the season in a temperate region (based on observed cases in a South Australian hospital), they would be covered for almost 88% of the annual RSV cases. However, if an infant was dosed at the beginning of the season in a tropical region (based on a northern Queensland hospital), they would only be protected during 78% of the annual RSV cases. Although the submission assigned all births in Queensland and Northern Territory to the Tropical population, it was unclear whether all populations would be exposed to the Tropical distribution of the RSV season (which was based on an observational study in Cairns).. A key driver of the model is the ability to map the RSV season in different jurisdictions, and provide advice about the optimal timing of nirsevimab administration.

6.80 Although the RSV season in the modelled tropical region (21% of the total population) is more dispersed, the evaluation noted that it is still defined. It is unclear whether there are regions in Australia that would have more erratic seasons, or seasons with longer durations, than the distribution from Cairns. Given the impact of a more dispersed RSV season on the ICER (almost 6.5 times higher in tropical vs temperate regions), it is likely that the ICER of nirsevimab vs standard of care in regions without distinct RSV seasons would be considerably higher than either the temperate or tropical populations in the model. An additional concern relates to the advice provided by local health authorities regarding the optimal timing of nirsevimab dosing. In regions that are clearly temperate or clearly tropical, this may be straightforward. However, if the line between tropical and temperate seasonal distribution of RSV does not neatly align with State borders, it may be challenging to provide advice regarding optimal timing if it differs by location within the same State.

6.81 The PSCR stated that administration of nirsevimab, either at or near to the optimal time, could be achieved in practice in the context of frequent GP visits that occur for other immunisations that infants require during the first year of life. The PSCR also noted that the practicality of the timing of nirsevimab administration would be best addressed by Federal and State experts. The ESC noted that timing of administration is a key driver of the model, and the ability to map the RSV season in different jurisdictions, and provide advice about the optimal timing of nirsevimab administration will be critical for achieving cost-effectiveness in clinical practice. The PBAC noted that nirsevimab is likely to be most effective when given shortly after birth for infants born just before or during the RSV season. The PBAC considered that the optimal administration assumed by the model did not reflect the likely use of nirsevimab in clinical practice, and noted the sensitivity analysis which showed that delaying the administration by one month in the model, as may occur if the season begins unpredictably, or if parents/carers were unable to attend a GP at the optimal time, resulted in an increase in the ICER of 78%.

6.82 Results of the stepped economic evaluation for the topical, temperate and aggregated populations are presented in Table 21. The ESC noted that the ICERs for the tropical population ($35,000 to < $45,000 per additional QALY) and the temperate population ($5,000 to < $15,000 per additional QALY) differed considerably.

Table 21 Results of the stepped economic evaluation for the submission base case (including results corrected by the evaluation)

TROPICAL POPULATION (n = [redacted][1])					
Step	**Model output[a]**	**Standard of care**	**Nirsevimab**	**Difference**	**ICER**
1	Costs	$[redacted]	$[redacted]	$[redacted]	
	Corrected	$[redacted]		$[redacted]	
2	RSV cases	[redacted][8]	[redacted][9]	-[redacted][9]	[redacted][2]
	Corrected				[redacted][2]
3	Life years	1,278,928	1,278,929	0.871	[redacted][3]
	Corrected				[redacted][3]
4	QALYs	1,273,964	1,274,132	167	[redacted][4]
	Corrected				[redacted][4]
TEMPERATE POPULATION (n = [redacted][5])					
Step	**Model output**	**Standard of care**	**Nirsevimab**	**Difference**	**ICER**
1	Costs	$[redacted]	$[redacted]	$[redacted]	
	Corrected	$[redacted]		$[redacted]	
2	RSV cases	[redacted][10]	[redacted][8]	-[redacted][11]	[redacted][2]
	Corrected				[redacted][2]
3	Life years	4,728,659	4,728,663	4.025	[redacted][3]
	Corrected				[redacted][3]
4	QALYs	4,710,317	4,711,086	768	[redacted][6]
	Corrected				[redacted][6]
AGGREGATED POPULATION (n = [redacted][7])					
Step	**Model output**	**Standard of care**	**Nirsevimab**	**Difference**	**ICER**
1	Costs	$[redacted]	$[redacted]	$[redacted]	
	Corrected	$[redacted]		$[redacted]	
2	RSV cases	[redacted][12]	[redacted][11]	-[redacted][11]	[redacted][2]
	Corrected				[redacted][2]
3	Life years	6,007,586	6,007,591	4.896	[redacted][3]
	Corrected				[redacted][3]
4	QALYs	5,984,282	5,985,217	936	[redacted][6]
	Corrected				[redacted][6]

Source: Table 3.8.2, of the submission.

ED = Emergency department; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RSV = Respiratory syncytial virus.

[a] Corrected values relate to a referencing error in the model which excluded the emergency department costs for Month 2 infants in the control arm of the model.

The redacted values correspond to the following ranges

1 60,000 to < 70,000
2 Dominant
3 > $1,055,000
4 $35,000 to < $45,000
5 200,000 to < 300,000
6 $5,000 to < $15,000
7 300,000 to < 400,000
8 5,000 to < 10,000
9 500 to < 5,000
10 20,000 to < 30,000
11 10,000 to < 20,000
12 30,000 to < 40,000

6.83 Univariate and multivariate sensitivity analyses were selected to reflect the key uncertainties and the key drivers of the economic model. Sensitivity analyses are numbered as they appeared in the commentary.

Table 22: Sensitivity analyses applied during the evaluation

SA#	Sensitivity analyses	Incremental cost ($)	Incremental QALY	ICER	Change from base case
	Base case	[redacted]	936	[redacted][1]	-
	Corrected base case	[redacted]	936	[redacted][1]	[redacted]%
	Incidence of MA RSV cases (base case = 10.8%)				
3	5% lower and hospitalisations proportionally lower	[redacted]	890	[redacted][2]	[redacted]%
4	5% higher and hospitalisations proportionally higher	[redacted]	981	[redacted][1]	-[redacted]%
	Nirsevimab effectiveness (base case = avoid 79.5% of MA RSV during period of protection)				
6	74.5% effectiveness (ITT from MELODY)	[redacted]	876	[redacted][2]	[redacted]%
6a	62.1% effectiveness (effectiveness for avoiding hospitalisations with RSV, from MELODY)	[redacted]	728	[redacted][3]	[redacted]%
	Timing of nirsevimab dosing (base case = in season dosing)				
8	In season, but delayed by 1 month	[redacted]	882	[redacted][2]	[redacted]%
	Cost of mechanical ventilation (base case = $44,682.02)				
13	Remove mechanical ventilation entirely (costs were already captured in hospitalisation and ICU estimates)	[redacted]	896	[redacted][2]	[redacted]%
	Asthma and recurrent wheezing (base case = costs and QALYs incorporated)				
14	Remove costs and QALY losses associated with both asthma and wheezing	[redacted]	650	[redacted][4]	[redacted]%
	Emergency attendance costs (base case $1907.81)				
15	Reduce by 50% based on NHCDC ratio of hospitalised vs nonhospitalised ED ($953.91)	[redacted]	936	[redacted][2]	[redacted]%
	Hospitalisation costs (base case $10,895.19)				
16	Add ED costs to hospitalisation costs ($12,803)	-[redacted]	936	dominant	n/a
	Subsequent hospitalisations, ED visits and ICU visits (base case = costs include all subsequent (all cause) admissions over 6 months)				
17	Include only the index hospitalisation in the estimate of the hospitalisation costs, ED visit and ICU visit	[redacted]	936	[redacted][3]	[redacted]%
	Disutilities applied to primary care, ED, ICU and hospitalisation RSV health states (base case = applied for a full month)				
18	Disutilities applied to reflect duration of event from Nourbakhsh 2021	[redacted]	630	[redacted][2]	[redacted]%
	Administration cost of nirsevimab (base case = one third of administrations require a GP visit)				
19	All administrations require a GP visit	[redacted]	936	[redacted][2]	[redacted]%
	Case fatality ratio of hospitalised RSV (base case = 0.000033)				
20	CFR calculated during the evaluation (0.002)	$[redacted]	1232	[redacted][1]	-[redacted]%
	Multivariate analyses prepared during evaluation				
MA1	6+13+14+15+16+17+20	[redacted]	850	[redacted][5]	[redacted]%
MA2	MA1 + 19	[redacted]	850	[redacted][6]	[redacted]%
MA3	MA1 + 8 + 19	[redacted]	799	[redacted][6]	[redacted]%
	Multivariate analyses proposed by the ESC				
ESC1	13 + 18	[redacted]	580	[redacted][4]	[redacted]%
ESC2	13 + 18 + 14	[redacted]	295	[redacted][6]	[redacted]%
ESC3	13 + 18 + 14 + 20	[redacted]	592	[redacted][7]	[redacted]%

Source: generated during the evaluation from the Nirsevimab economic evaluation workbook

CFR = case fatality ratio; ED = Emergency department; GP = General practitioner; ICER = incremental cost-effectiveness ratio; ICU = Intensive care unit; MA RSV = Medically attended RSV; NHCDC = National Hospital Cost Data Collection; NNDSS = National Notifiable Diseases Surveillance System; QALY = quality-adjusted life year; RSV = Respiratory syncytial virus, SA# = sensitivity analysis number.
[a]Varying the discount rate alone has almost no impact on the model due to the very small case-fatality ratio applied in the submission's base case. Sensitivity analysis 21 and 22 represent multivariate analysis and incorporate a change to the CFR (SA# 20) and a change to the discount rate. The impact of the discount rate on the model should be compared with SA# 20.
The redacted values correspond to the following ranges
1 $5,000 to < $15,000
2 $15,000 to < $25,000
3 $45,000 to < $55,000
4 $25,000 to < $35,000
5 $55,000 to < $75,000
6 $75,000 to < $95,000
7 $35,000 to < $45,000

6.84 The evaluation considered that the submission's model contained many parameters that were both uncertain and influential on the model results. A multivariate analysis was undertaken by the evaluation (MA1 in Table 22). Changes applied in the multivariate analysis that increase the ICER include: an estimate of effectiveness from the MELODY study, the removal of mechanical ventilation from the model, the removal of asthma and wheezing from the model, the reduction of ED costs for non-hospitalised individuals, and the use of only index hospitalisations relating for the derivation of hospitalisation, ICU and ED costs. Changes that reduce the ICER were the addition of ED costs to hospitalisation costs and the application of a higher case fatality rate.

6.85 The multivariate analysis (MA1 in Table 22) resulted in an ICER of $55,000 to < $75,000 per QALY. The evaluation also calculated that if a unique GP attendance was assumed for each nirsevimab administration, and the timing of nirsevimab administration was delayed in the model by 1 month (to reflect imprecision of timing of dosing in clinical practice), the ICER increased to $75,000 to < $95,000 per QALY (MA3 in Table 22).

6.86 The treatment effect for nirsevimab was applied with a single input, which was a reduction in the number of MA RSV cases. The ESC noted that the difference in the treatment effect of nirsevimab for preventing MA RSV (74.5%) and for preventing hospitalised RSV (62.1%) was not addressed by the submission.

6.87 The ESC considered that there were several key uncertainties which made interpretation of the economic model difficult. The ESC proposed three new multivariate analyses for consideration (Table 22), however still felt that the resultant ICERs were likely to be optimistic. The ESC advised that the amendments proposed could be considered a minimum set of changes that would be informative for decision-making. These included amendments to 1) mechanical ventilation costs; 2) use of updated disutilities; 3) removal of asthma and recurrent wheezing; and 4) adjustment of CFR to 0.002. In addition, the ESC advised that other elements of the economic model were subject to substantial uncertainty. These additional key elements were:

- reduced effectiveness, noting that the estimate of 79.5% from a meta-analysis applied by the submission was substantially higher than estimates from the MELODY trial and further that effectiveness of nirsevimab for preventing MA RSV

hospitalisations was lower than for preventing all MA RSV (62.1% vs 74.5%), and the economic model did not easily allow hospitalisations to be modelled separately (see Table 19).

- timing of nirsevimab administration represents (near) optimal administration, which may not reflect clinical practice (see Table 19).
- the estimate for RSV hospitalisation rate was applied at the highest rate (4.2%) of rates reported in three unpublished studies (see paragraph 6.55 and Table 19).
- reducing the cost of subsequent hospitalisations rather than applying a cost (as per the submission) that represented an aggregation of all hospitalisations over 6 months (see Table 19).

Supplementary (nirsevimab versus palivizumab) and near market (nirsevimab versus RSVpreF maternal immunisation) comparisons

6.88 The submission presented an economic evaluation comparing two additional comparators: maternal vaccination (for the first RSV season) and palivizumab (for high-risk infants in the second RSV season). The economic analysis comparing nirsevimab with the near market comparator, maternal vaccination, was a cost-utility analysis. The supplementary economic analysis comparing nirsevimab and palivizumab was a cost-minimisation analysis.

6.89 The evaluation considered that the comparison of nirsevimab vs maternal vaccination was uncertain. The economic analysis sourced the treatment effect of maternal vaccination from the primary study of maternal vaccination vs placebo presented in the submission[31]. The price assumed for the vaccine was derived from international sources. The PBAC considered the economic analysis was not informative for decision-making.

6.90 The submission presented a comparison of nirsevimab vs palivizumab in a high-risk population entering their second RSV season, which was based on an equi-effective dose of 1 nirsevimab dose to 5 x 1 month palivizumab doses. As palivizumab is not PBS listed, and has previously been rejected by PBAC on the basis of cost-effectiveness (March 2005 PBAC Outcomes), the interpretation of this analysis is unclear. The PBAC considered the evaluation was not informative for decision making.

6.91 The submission did not provide an analysis of the cost-effectiveness of nirsevimab for high-risk infants in their second RSV season comparing nirsevimab with no immunisation. The PBAC considered that this was not appropriate and that no immunisation should be considered the main comparator for the second season, given that palivizumab is not widely available (see paragraph 5.5).

[31] Kampmann B, Madhi SA, Munjal I, Simões EA, Pahud BA, Llapur C, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. New England Journal of Medicine. 2023;388(16):1451-64.

Nirsevimab cost/patient/year

Table 23: Drug cost per patient for proposed drug

	Nirsevimab recommended dose and frequency	Nirsevimab Model	Nirsevimab Financial estimates
Dose	One or two doses [a]	One dose	One or two doses [a]
Frequency	Once a year	Once a year	Once a year
Cost/patient/year	$ [redacted] per dose	$ [redacted] per dose	$ [redacted] per dose

Source: tabulated during evaluation from the "Appendix 7.1 nirsevimab PBAC macro' workbook and the "Appendix 6. Nirsevimab Utilisation and Cost Model' Workbook provided in the submission

[a] One dose for all infants in their first year; second dose for high-risk infants less than 24 months old

Estimated PBS usage & financial implications

6.92 This submission was considered by the DUSC.

6.93 The submission utilised an epidemiological approach to estimate the extent of use and financial impact of listing nirsevimab on the PBS.

6.94 The key inputs utilised in the financial analysis are summarised in Table 24.

Table 24: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible populations			
Population 1: Temperate regions (all infants aged 0-1)			
Incident population	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	Table 1.1, ABS 3301.0, Births, summary, by state	The DUSC considered this was reasonable.
Uptake rate	70%	Assumption	The evaluation considered this uptake rate was uncertain and may be too high. The DUSC considered the uptake rate to be reasonable, noting the introduction of state-based programs offering RSV vaccine for infants and considered that the increased awareness of RSV would lead to a high uptake of nirsevimab if PBS listed. The DUSC noted the immunisation schedule for infants (0, 2 and 4 months) and considered the opportunities for health care practitioners to discuss RSV risk and immunisation with nirsevimab with parents, would also support uptake.
Number immunised	Yr 1: [redacted][2] Yr 2: [redacted][2] Yr 3: [redacted][2] Yr 4: [redacted][2] Yr 5: [redacted][2] Yr 6: [redacted][2]	Estimated by multiplying the number of incident individuals and the uptake rate	The DUSC considered this was reasonable.

Data	Value	Source	Comment
Population 2: Tropical regions (all infants aged 0-1)			
Incident individuals	Yr 1: [redacted]3 Yr 2: [redacted]3 Yr 3: [redacted]3 Yr 4: [redacted]3 Yr 5: [redacted]3 Yr 6: [redacted]3	Table 1.1, ABS 3301.0, Births, summary, by state	The DUSC considered this was reasonable.
Uptake rate	70%	Assumption	As above, the evaluation considered this uptake rate was uncertain and may be too high. The DUSC considered the uptake rate to be reasonable,
Number immunised	Yr 1: [redacted]4 Yr 2: [redacted]4 Yr 3: [redacted]4 Yr 4: [redacted]4 Yr 5: [redacted]4 Yr 6: [redacted]4	Estimated by multiplying the number of incident individuals and the uptake rate	The DUSC considered this was reasonable.
Population 3: infants aged 1-2 years who remain vulnerable			
Incident individuals	Yr 1: [redacted]5 Yr 2: [redacted]5 Yr 3: [redacted]5 Yr 4: [redacted]5 Yr 5: [redacted]5 Yr 6: [redacted]5	ABS 3222.0, Projected population (released in 2013).	The evaluation considered it may have been more reasonable to utilise the most updated ABS population projections. Further, for consistency, it may have been appropriate to utilise the number of live births in the prior year to estimate the number of eligible and treated individuals in this population. The DUSC agreed with the evaluation.
Eligible individuals	4.34%	Births with a gestational age of less than 36 weeks; Table 3.5, National Perinatal Data Collection annual update 2022	The evaluation considered the source was reasonable. However, considered the submission had underestimated the population as it did not account for infants born at 36 weeks or over with bronchopulmonary dysplasia or congenital heart disease. Further it did not estimate the number of indigenous children, who were at high-risk of severe RSV infection. The PSCR stated that bronchopulmonary dysplasia (BPD) is associated with preterm births, with prevalence rates of over 35% for infants with a gestational age of less than 28 weeks. The DUSC noted the discussion in the PSCR and considered that infants born at 36 weeks or over with bronchopulmonary dysplasia were adequately accounted for in the financial estimates. However, DUSC considered that infants with congenital heart disease and Indigenous children were not accounted for in the financial estimates.
Uptake rate	90%	Assumption	The evaluation considered this may be reasonable given that infants in this population are at a high-risk of developing severe RSV infection. The DUSC considered the uptake rate to be reasonable, and noted that it would be important

Data	Value	Source	Comment
			to inform families of high-risk infants of the advice to receive the second dose of nirsevimab.
Number immunised	Yr 1: [redacted][6] Yr 2: [redacted][6] Yr 3: [redacted][6] Yr 4: [redacted][6] Yr 5: [redacted][6] Yr 6: [redacted][6]	Estimated by multiplying the number of incident individuals with the percentage of births with a gestational age of less than 36 weeks and the uptake rate	The DUSC considered that this was an underestimate of the proposed population, given that it did not explicitly account for infants with congenital heart disease and Indigenous children.
Costs			
Nirsevimab 50 mg 100 mg 200 mg	$[redacted] $[redacted] $[redacted]	Requested DPMQs	
Patient copayment	PBS: $7.46 RPBS: $4.53	PBS statistics, all PBS listed items utilisation report between June 2022 and 2023.	The evaluation considered this was reasonable since there is no PBS listed comparator for nirsevimab. Although, since the intended population were infants aged 0-2, it would have been reasonable for the submission to assume that all services would be PBS services (the submission assumed that 3% of services would be RPBS scripts).
MBS costs	MBS item 23: $41.40	The submission estimated an increase in the utilisation of MBS item 23 for nirsevimab administration. • $13.80 (calculated as $41.40 x 4/12, with 80% benefit) was applied to each infant. This assumed in 8 out of 12 months, infants would be treated concurrently with other immunisations or during seasonal catchups (i.e. not require an additional consultation). • The submission also estimated a decrease in primary care visits associated with the use of nirsevimab (due to reduced RSV). This was the full cost of one GP visit (100% benefit) applied to 3.4% of the treated population.	The evaluation considered that an increase in MBS primary care costs associated with administration of nirsevimab, countered by a decrease in MBS primary care costs associated with reduced RSV was reasonable, however the estimates were uncertain. • The proportion of GP visits that would occur for the purpose of nirsevimab administration following listing on the PBS is uncertain, noting that individuals will be required to have a prescription dispensed prior to administration. MBS costs were likely to be higher than an average of $13.80 per patient (also noting that for MBS item 23, the submission incorrectly applied a benefit of 80% when a 100% benefit applies to MBS item 23 - this was corrected in the Commentary.)

Source: tabulated from Table 4.2.3, of the submission.
ABS = Australian Bureau of Statistics; DPMQ = dispensed price for maximum quantity; GP = general practitioner; MBS = Medicare Benefits Scheme; NIP = national immunisation program; NP = nurse practitioner; PBS = pharmaceutical benefits schedule
The redacted values correspond to the following ranges
1 200,000 to < 300,000
2 100,000 to < 200,000
3 60,000 to < 70,000
4 40,000 to < 50,000
5 300,000 to < 400,000
6 10,000 to < 20,000

6.95 The submission estimated the number of infants who were likely to be administered nirsevimab from the projected number of live births in temperate and tropical regions. An average growth rate in the number of live births was calculated and used to project the number of live births between years 2025 and 2030. For population 3 (infants aged 1-2 years who remain vulnerable), the submission estimated that 4.34% of all infants would remain vulnerable to RSV infections in the second season as described in Table 24. The number of infants who were ≥ 12 months and ≤ 24 months old was sourced from ABS population data. The evaluation considered this was reasonable for estimation of premature infants that would be eligible for nirsevimab, but it was noted that the estimates did not consider infants born with bronchopulmonary dysplasia, congenital heart disease or indigenous children who were considered to be at high-risk of severe RSV infection. Further, the submission did not utilise the most recent ABS population projections which use 2022 data as the basis. When the most recent projections were utilised, the overall cost to the PBS decreased. The submission's estimates for the number of individuals likely to be treated with nirsevimab in the first 6 years of listing is presented in Table 25, as well as the revised estimates using the most recent ABS data that were prepared during the evaluation.

6.96 The submission applied uptake rates of 70% across all years in populations 1 and 2 and uptake rates of 90% in population 3. The commentary considered the uptake rates applied to the eligible infants in population 3 to be reasonable as this population is at a high risk of developing severe RSV infection. However, as nirsevimab will require a prescription, the commentary considered the uptake rates applied to populations 1 and 2 appeared too high and were uncertain. The DUSC considered that an assumed uptake of 70% was reasonable for populations 1 and 2, on the basis that increased awareness of RSV would lead to a high uptake of nirsevimab if PBS listed.

Table 25: Estimation of number of treated individuals

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Population 1: temperate regions						
Projected number of live births	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Uptake rate (70%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Population 2: tropical regions						
Projected number of live births	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Uptake rate (70%)	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4
Population 3: infants aged 1-2 years who remain vulnerable to RSV						
Number of infants aged 1-2 years	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5
Eligibility (4.34%)	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
Uptake rate (90%)	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
Revised [a]	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
Treated individuals	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Revised [a]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1

Source: Table 4.3.2, o the submission.

[a] Revised by the evaluation using the most updated ABS population projections (base year 2022)

The redacted values correspond to the following ranges

1 200,000 to < 300,000
2 100,000 to < 200,000
3 60,000 to < 70,000
4 40,000 to < 50,000
5 300,000 to < 400,000
6 10,000 to < 20,000

6.97 The submission applied costs of $[redacted] per immunisation for each infant in the temperate and tropical region populations (population 1 and 2) and a cost of $[redacted] for each infant treated in the high-risk population (population 3). Weighted co-payments for PBS and RPBS services were calculated from the PBS services utilisation data of all PBS listed items between June 2022 and June 2023.

6.98 For each nirsevimab administration, the submission applied MBS service costs of $13.80 (MBS item 23, 80% benefits). The submission assumed that most infants would be immunised along with other immunisation programs or during seasonal catch-ups of immunisation in 8 out of the 12 months in a year. Thus, only the infants who were not immunised in these 8 months would need to visit the GP for nirsevimab administration in the remaining 4 months. As such, the cost of administration per treated infant ($13.80) was calculated as: $41.40 x (4/12). The evaluation considered the proportion of GP visits that would occur for the purpose of nirsevimab administration following listing on the PBS is uncertain, noting that individuals will be required to have a prescription dispensed prior to administration. MBS costs are likely to be higher than an average of $13.80 per patient. Further, the submission erroneously applied the MBS item 23 with 80% benefit (the benefit should be 100%). Revised estimates correcting the benefit applied and applying the full fee to each eligible infant is presented in Table 26.

6.99 The financial implications associated with the proposed listing of nirsevimab are presented in Table 26.

Table 26: Estimated financial implications associated with the listing of nirsevimab

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Treated individuals	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Revised	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total prescriptions[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Revised[b]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of nirsevimab to the PBS/RPBS						
Cost to the PBS/RPBS less copayments	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Revised[b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications for other drugs						
Cost to the PBS/RPBS less copayments	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Revised[b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost to MBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Revised[b,c]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to PBS/RPBS and MBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Revised	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

Source: tabulated during evaluation from the "Appendix 6. Nirsevimab Utilisation and Cost Model' Workbook provided in the submission
Note: revised estimates use the most updated ABS population projections (base year 2022), assume all services will be PBS services and apply the full cost of MBS item 23 ($41.40) to each treated infant.
[a] 1 script per infant in populations 1 and 2; 2 scripts per infant in population 3
[b] Revised by the evaluation using the most updated ABS population projections (base year 2022).
[c] MBS fees for item 23 is adjusted and applied to each infant treated with nirsevimab
The redacted values correspond to the following ranges
1 200,000 to < 300,000
2 $100 million to < $200 million
3 $0 to < $10 million

6.100 The total cost to the PBS of listing nirsevimab was estimated by the submission to be $100 million to < $200 million in Year 6 and a total of $600 million to < $700 million across the first 6 years of listing. The total cost to the MBS was $10 million to < $20 million in the first 6 years of listing. The cost to the PBS decreased to $600 million to < $700 million across the first 6 years of listing when the most recent ABS population projections were utilised to estimate the number of infants treated in population 3, i.e., the infants aged 1-2 who remain vulnerable to RSV infections. Further, when the MBS fees for item 23 were adjusted and applied to each infant treated with nirsevimab, the total cost to the MBS increased to $50 million to < $60 million across the first 6 years of listing.

6.101 Overall, the DUSC considered the estimates presented in the submission for populations 1 and 2 were reasonable noting that a 70% uptake rate was assumed (see paragraph 6.96). The DUSC considered this was appropriate given increasing awareness of RSV in the community and prescriber familiarity associated with state-based programs. The DUSC also noted high uptake rates of nirsevimab internationally.

6.102 In regard to population 3 (infants aged 1-2 who remain vulnerable to RSV infections after their first RSV season), the DUSC considered that the submission underestimated the number of eligible individuals. Specifically, DUSC considered children with

haemodynamically significant congenital heart disease and Aboriginal and Torres Strait Islander population children should be explicitly included in the financial estimates. DUSC considered children with BPD had been accounted for as part of the eligible population.

6.103 The pre-PBAC response stated that bronchopulmonary dysplasia (BPD) is linked to preterm births and decreased gestational age, with prevalence rates of over 35% for infants with a gestational age <28 weeks. According to the National Perinatal Data Collection, 0.41% of all live births had a gestational age <28 weeks. Using these values, this equates to approximately < 500 births with BPD. Congenital heart disease affects an estimated 500 to < 5,000 infants affected in Australia each year[32]. The latest update from the National Perinatal Data Collection reported 10,000 to < 20,000 First Nations live births. The pre-PBAC response estimated the total number of high-risk children during their second RSV season to be 10,000 to < 20,000 (i.e., < 500 + 500 to < 5,000 + 10,000 to < 20,000).

Quality Use of Medicines

6.104 The submission stated that the sponsor will work collaboratively with health care providers to ensure that nirsevimab is used appropriately and in line with the available clinical evidence and TGA restrictions. The submission outlined a strategy that aimed to address any potential issues that may arise with the implementation of the nirsevimab program on the PBS; proposed patients access pathways and the processes necessary for monitoring of patient outcomes and adverse events following treatment with nirsevimab. The strategy consisted of 9 stages: decision, order, review, issue, supply, distribution, administration, monitoring and data collection. This would ensure that all eligible infants were correctly identified and that nirsevimab administration would consider gestational and chronological age of the infants and the time of the year relative to the RSV season.

6.105 The submission identified the following QUM issues: maternal vaccination status prior to treatment with palivizumab and nirsevimab; impact of weight on dosing; seasonality of RSV on timing of immunisation; uptake of nirsevimab given that it will not be listed on the NIP; coordination of issue of prescription with supply and administration. The submission did not consider that it may be difficult for clinicians to accurately monitor and predict the start of the RSV season. The evaluation noted an additional risk, that infants may be given the lower dose of nirsevimab in error, if there was a delay in administration following a prescription for nirsevimab and the infant's weight exceeded 5 kg in that time. No further QUM issues were identified during the evaluation.

6.106 The DUSC considered that as nirsevimab is a new health technology (prophylactic antibody treatment against RSV), there is opportunity to educate and improve the health literacy of consumers. The DUSC considered the importance of informing

[32] AIHW, Congenital heart disease in Australia. 2019.

families of high-risk infants to receive the second dose of nirsevimab (population 3). The DUSC also noted the complexities of optimising the timing of doses given variation in the onset of the RSV season.

Financial Management – Risk Sharing Arrangements

6.107 The submission did not propose a risk-sharing arrangement.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the General Schedule Restricted Benefit PBS listing of nirsevimab for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease (LRTD) 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. The PBAC considered that nirsevimab was superior in terms of effectiveness compared to no immunisation, with an acceptable safety profile in the first RSV season. However, the PBAC considered the incremental cost-effectiveness ratio for nirsevimab for the first RSV season to be substantially underestimated and highly uncertain. The PBAC did not accept palivizumab as the main comparator for the second season, and noted there was limited clinical evidence to support the proposed listing of nirsevimab in the second season.

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

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

7.4 The PBAC noted that nirsevimab is a recombinant human IgG1 kappa monoclonal antibody that binds to the prefusion conformation of the RSV F protein to block viral entry into the host cell. Nirsevimab provides protection for at least 5 months via passive immunisation of the infant or young child and works immediately after injection.

7.5 The PBAC considered there is a high clinical need for vaccines, or other interventions such as nirsevimab, 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 listing for nirsevimab was supported by the consumer comments received for this submission.

7.6 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.

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

7.8 In the absence of any immunisation for RSV (vaccine or monoclonal antibody) being currently available on the PBS or NIP in Australia, the PBAC accepted the proposed clinical place for nirsevimab for 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.

7.9 The PBAC noted that the Australian Immunisation Handbook (AIH) includes recommendations for use of vaccines and monoclonal antibodies for prophylaxis of RSV disease (paragraph 3.9), and that a resubmission should consider these recommendations when specifying proposed PBS restrictions, especially in relation to instances where it may be appropriate to administer nirsevimab to an infant after maternal vaccination has occurred, and additional considerations in regard to eligibility for nirsevimab in high-risk infants.

7.10 The proposed restriction stated that for neonates and infants born during or entering their first RSV season, a patient's mother must not have received immunisation against RSV while pregnant, and the patient must not have received a prophylactic antibody treatment against RSV. The PBAC considered that additional benefits of maternal vaccination plus nirsevimab would be difficult to assess due to limited data; however, it considered that there may be a small number of instances where it may be clinically appropriate for an infant to receive nirsevimab after the mother had been vaccinated. Examples of these instances as stated in the Australian Immunisation Handbook are: (i) Infants born within 2 weeks of the mother receiving RSV vaccine during pregnancy ii) Infants with risk conditions for severe RSV disease regardless of maternal vaccination iii) Infants born to mothers with severe immunosuppression and iv) Infants whose mothers have received RSV vaccine in pregnancy but have subsequently undergone a treatment that has led to loss of maternal antibodies). The PBAC considered, that if clinically justified, these infants should not be precluded from accessing nirsevimab by the restriction, as outlined in the ATAGI's advice to the PBAC. In regard to the restriction that proposed access for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, the PBAC considered that the definition of the high-risk group needed refinement to ensure that current ATAGI advice is incorporated.

7.11 The PBAC considered the submission's nomination of no immunisation as the main comparator, and RSVpreF maternal vaccine as the near market comparator in Season 1 was appropriate. However the PBAC considered that no immunisation should be considered as the main comparator for Season 2, rather than palivizumab as proposed

by the submission, on the basis that palivizumab is not widely used. The PBAC considered that the cost-effective price of palivizumab was unknown, noting that palivizumab was not recommended for PBS listing when it was considered in 2005 (paragraph 5.2).

7.12 The PBAC considered that the uptake rates remained uncertain but that high uptake in the first year of life should be the goal for the proposed listing, in order to maximise clinical benefits for infants. In regard to the utilisation estimates, the PBAC also considered that uptake may be reduced due to the need for prescriptions and co-payments in comparison with a listing on the NIP, and that a resubmission would need to provide further justification for the assumed uptake rate in each population which considered the setting of administration and prescription requirements. The PBAC noted that the submission's estimates of population 3 were based solely on estimation of the number of births with a gestational age of less than 36 weeks, and considered that the estimate should individually quantify infants with BPD or CHD, and indigenous children, and take into account the corrections made during the evaluation, and the advice from the DUSC.

7.13 The PBAC noted that the timing of RSV outbreaks varies with the climate across different regions of Australia and that the timing of administration of nirsevimab in relation to the RSV season, was a key driver of the economic model. The nirsevimab model contained two populations based on their climate, either tropical or temperate, to permit the simulation of different timing and duration of the RSV season. The submission assumed that the use of nirsevimab at the beginning of the season in temperate climates would protect against almost 90% of the yearly cases of RSV. In tropical climates, where the RSV season is more dispersed, it was assumed that nirsevimab administered at the beginning of the season provided protection against almost 80% of all yearly cases of RSV. However, this would require the provision of accurate advice about the optimal timing of nirsevimab administration for different jurisdictions, and for this advice to be precisely followed. The PBAC noted that the duration of protection of nirsevimab is five months, however the proposed use of nirsevimab, aimed to allow the timing of administration to infants to be targeted to maximise protection over the duration of RSV season. This differed from the RSVpreF maternal vaccine considered by the PBAC in March and May 2024 (paragraph 5.3). The PBAC noted the ATAGI's advice for RSVpreF 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. The PBAC noted that a year-round program for RSVpreF would allow access to the vaccine through routine antenatal care (Paragraph 4.6, RSVPreF Public Summary Document, March 2024 PBAC Meeting).

7.14 The PBAC considered that a claim of superior comparative effectiveness was reasonable for the main comparison between nirsevimab and no immunisation in Season 1, as supported by the relative risk reduction in MA RSV LRTI for nirsevimab patients compared with placebo in the MELODY and Phase IIb studies. The PBAC was

also satisfied that the claim of non-inferior safety was reasonable based on the similar rates of AEs observed in the nirsevimab and placebo arms of both studies.

7.15 The PBAC did not support a conclusion of non-inferiority between nirsevimab and the supplementary comparator palivizumab for high-risk infants in both Seasons 1 and 2. While the MEDLEY trial did not show any material difference between the treatment arms with respect to efficacy or safety, the trial was not sufficiently powered to detect a difference, making any clinical conclusions uncertain. The PBAC considered that this clinical comparison was of limited relevance and that no immunisation should be considered the main comparator for Seasons 1 and 2.

7.16 The PBAC considered that RSVpreF maternal vaccine was a relevant comparator for nirsevimab in Season 1. However, the PBAC considered the clinical evidence did not support a conclusion of superiority between nirsevimab and the near-market comparator RSVpreF maternal vaccine in Season 1, due to substantial transitivity issues between the nirsevimab trials and the RSVpreF MATISSE trial.

7.17 The submission presented a cost-utility analysis based on a meta-analysis of the MELODY trial and a subgroup of the Phase IIb study (Simões et al (2023)). The PBAC noted that the base case ICER in the submission was $5,000 to < $15,000 /QALY (after correction during evaluation); however, considered the results of the economic evaluation uncertain because the model was highly sensitive to small variations in several inputs (Table 22). The PBAC noted that the ICERs for the tropical population and the temperate population differed considerably ($35,000 to < $45,000/QALY and $5,000 to < $15,000 /QALY, respectively in the submission base case; Table 21).

7.18 The PBAC agreed with the amendments to the economic model proposed by the ESC as a minimum set of changes to be considered, which resulted in an ICER of $35,000 to < $45,000/QALY. Further, the PBAC agreed with the ESC's advice that additional amendments should be considered to address the issues outlined in paragraph 6.87. The PBAC noted that these issues were considered in a MSA prepared during the evaluation which resulted in an ICER of $75,000 to < $95,000/QALY (MA3, which attempted to address as many of the identified concerns as possible within the framework of the model provided). The PBAC noted advice from the ATAGI in relation to hospitalisation rate (paragraph 6.55) and removal of asthma and recurrent wheezing (paragraph 6.61).

7.19 The PBAC noted that an ICER between $35,000 to < $45,000/QALY and $75,000 to < $95,000/QALY was estimated for the proposed listing in season 1, based on multivariate sensitivity analyses. However, the PBAC noted that limitations of the model structure, such as the use of a single measure of treatment effect to drive the model rather than a range of endpoints collected in the trial (see paragraph 6.86) and other issues related to the estimation of cost-effectiveness in the proposed circumstances of use remained and would require further consideration in a resubmission (see below).

7.20 The PBAC noted that the cost-effectiveness of nirsevimab in clinical practice will

depend on many factors, such as annual variations in RSV incidence and severity, and the potential impact of seasonal changes from year to year which may impact the optimal timing of administration of nirsevimab and reduce cost-effectiveness (paragraph 6.81). Some of these concerns were partially explored in sensitivity analyses, however the model design made it difficult to assess them fully. In addition, the PBAC considered that administration of nirsevimab to infants of mothers that received the maternal vaccination may occur in practice, in clinically relevant situations, guided by the advice set out in the AIH as described in paragraph 7.9. A scenario analysis could be informative to examine this usage.

7.21 The PBAC further considered that the cost-effectiveness of nirsevimab would be reduced in the event of a prolonged RSV season, noting that the key driver of the difference in ICERs between the two modelled regions was the monthly distribution of cases assumed throughout the season (paragraph 6.79). The PBAC also considered that nirsevimab may provide higher clinical value for high-risk infants in the first RSV season, however this had not been assessed in the submission. The PBAC considered that an economic model (or subgroup analysis) to assess the cost-effectiveness of nirsevimab in a high-risk population would be informative in a resubmission, noting this was consistent with advice received from the ATAGI. The PBAC also considered that an economic evaluation comparing a second dose of nirsevimab with no immunisation was necessary to assess the cost-effectiveness of the proposed listing in the second RSV season for high-risk infants. The PBAC suggested this could be combined with the subgroup analysis for high-risk infants in the first season.

7.22 The PBAC considered that a number of updates should be considered in a resubmission in relation to the financial estimates, including updates to the proposed eligible population (paragraphs 7.9 and 7.10). The PBAC considered that the assumed uptake rates in season 1 required further consideration and justification (paragraph 6.96, and further clarification of the estimated population of high-risk children in season 2 was required (paragraph 7.12).

7.23 The PBAC considered that a resubmission for nirsevimab should address the issues raised in these minutes. The PBAC considered that clarification of the eligible population was required, and that data for the overall infant population and for the high-risk subgroup should be presented separately throughout the resubmission, consistent with the ATAGI advice. The PBAC advised that the economic evaluation and financial estimates should be provided separately for the overall infant population and for the high-risk subgroup and that revisions to the economic model and financial estimates for season 1 would be required as described in these minutes. The PBAC considered that the clinical comparison of nirsevimab versus RSVpreF maternal vaccination would remain relevant in a resubmission as a near market comparator in the first RSV season, noting that the claim of superior effectiveness was not accepted. In relation to season 2, the PBAC considered that no immunisation should be the main comparator, and that the submission would need to present corresponding clinical

and economic evidence to support this proposed listing, and corresponding financial estimates.

7.24 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.25 The PBAC noted that this submission is eligible for an Independent Review.

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

While Sanofi is disappointed with this outcome, we welcome the Committee's recognition of the effectiveness and safety of nirsevimab for RSV prevention and remain committed to working with the PBAC to enable timely and equitable access of nirsevimab to protect all Australian infants from RSV.