Technology Guidance

Nirsevimab

for prevention of respiratory syncytial virus-associated lower respiratory tract disease in infants during their first RSV season

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended nirsevimab for inclusion on the MOH Subsidised Vaccine List (SVL) for prevention of respiratory syncytial virus (RSV)-associated lower respiratory tract disease in infants during their first RSV season. The decision was based on the unfavourable cost effectiveness of nirsevimab compared with no immunisation, and the unacceptable price-volume agreement proposed by the company.

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Technology Evaluation

1.1. At the April 2026 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of nirsevimab for the prevention of respiratory syncytial virus (RSV)-associated lower respiratory tract disease (LRTD) in infants during their first RSV season. The evaluation considered the evidence submission by Sanofi for nirsevimab (Beyfortus), and a review conducted by one of ACE's evidence review centres. The use of nirsevimab for the prevention of RSV-associated LRTD in children during their second RSV season was outside the scope of this evaluation.

1.2. Expert opinion from clinicians at public healthcare institutions (PHIs) and the Expert Committee on Immunisation (ECI) helped ACE ascertain the clinical value of nirsevimab.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. RSV is a common cause of respiratory illness in infants and young children in Singapore, particularly those under two years of age. Infants not previously exposed to RSV and those in high-risk subgroups are particularly susceptible to poor outcomes due to RSV-LRTD, including hospitalisation and death. Infants at high risk of severe RSV disease include those born preterm, or with chronic lung disease, congenital heart disease, neuromuscular disorders, or who are immunocompromised. Local clinical experts agreed that there is no clearly defined RSV season in Singapore, hence the first RSV season refers to an infant's first year of life.

2.2. Currently, RSV immunisation is not routine practice for the general infant population, and no immunisation products are included on the MOH Subsidised Vaccine List (SVL). Nirsevimab is a long-acting monoclonal antibody (mAb) administered directly to infants that provides passive immunisation against RSV. Other HSA-approved RSV prevention options for infants in their first RSV season include clesrovimab, another long-acting mAb, and the RSV prefusion F protein maternal vaccine (RSVpreF), which relies on the transfer of protective maternal antibodies during pregnancy. For high-risk subgroups, palivizumab remains a short-acting mAb option, although it was not recommended for funding in 2022 as it did not represent a cost-effective use of healthcare resources.

2.3. The Committee acknowledged the clinical need for a safe and effective immunisation to prevent RSV infection in infants, particularly those at high risk of severe RSV disease. They heard that local clinical experts expect nirsevimab to be administered at birth or before hospital discharge for most infants who receive it.

2.4. The Committee also acknowledged local clinical experts' advice that infant RSV immunisation after prior maternal vaccination with RSVpreF may still be needed for:

- Infants at high-risk of severe RSV disease;
- Infants whose mothers are immunocompromised with poor immune response to vaccination;
- Infants with loss of maternal antibodies e.g. following bypass or extracorporeal membrane oxygenation; and
- Infants born less than 14 days after their mothers were vaccinated (before neutralising antibodies have had time to form).

Clinical effectiveness and safety

Nirsevimab versus no immunisation

3.1. The Committee reviewed the clinical evidence in the company submission from three randomised controlled trials (RCT; Phase 2b, MELODY and HARMONIE), which compared nirsevimab to no immunisation across different healthy infant populations born at ≥29 weeks' gestational age.

3.2. The three RCTs showed that nirsevimab generally led to statistically significant relative risk reductions (RRRs) for medically attended RSV lower respiratory tract infection (MA RSV-LRTI) at 150 days and RSV-LRTI hospitalisation at 150 or 180 days in healthy infants, compared with no immunisation (Table 1). The absolute risk reductions corresponded with a number needed to immunise of 15 to 27 for MA RSV-LRTI at 150 days, and 31 to 82 for RSV-LRTI hospitalisation at 150 or 180 days.

3.3. The Committee noted there was a lack of comparative RCT evidence between nirsevimab and no immunisation in high-risk infants, and for the sequential use of nirsevimab in infants following maternal vaccination.

Table 1: Results of MA RSV-LRTI at 150 days and RSV-LRTI hospitalisations at 150 and 180 days from the nirsevimab trials

Trial	Nirsevimab, n/N (%)	Placebo/SOC, n/N (%)	RRR, % (95% CI)	p-value
MA RSV-LRTI at 150 days				
Phase 2b	25/969 (2.6)	46/484 (9.5)	70.1 (52.3 to 81.2)	<0.0001
MELODY (primary analysis; 11 March 2021 data cut-off)	12/994 (1.2)	25/496 (5.0)	74.5 (49.6 to 87.1)	<0.001
MELODY (all subjects; 31 March 2022 data cut-off, final analysis)	24/2009 (1.2)	54/1003 (5.4)	76.4 (62.3 to 85.2)	<0.0001*
RSV-LRTI hospitalisations at 150 days				
Phase 2b	8/969 (0.8)	20/484 (4.1)	78.4 (51.9 to 90.3)	0.0002
MELODY (primary analysis; 11 March 2021 data cut-off)	6/994 (0.6)	8/496 (1.6)	62.1 (-8.6 to 86.8)	0.07
MELODY (all subjects; 31 March 2022 data cut-off, final analysis)	9/2009 (0.4)	20/1003 (2.0)	76.8 (49.4 to 89.4)	0.0002*
HARMONIE (28 February 2023 data cut-off)^	11/4037 (0.3)	60/4021 (1.5)	83.2 (67.8 to 92.0)	<0.0001
RSV-LRTI hospitalisations at 180 days				
HARMONIE (7 April 2023 data cut-off)	12/4038 (0.3)	68/4019 (1.7)	82.7 (67.8 to 91.5)	<0.0001

Abbreviations: CI: confidence interval; LRTI: lower respiratory tract infection; MA: medically attended; n: number of participants with event; N: total participants in group; RRR: relative risk reduction; RSV: respiratory syncytial virus; SOC: standard of care.

*The final analysis was not controlled for multiplicity. Hence, p-values are nominal.

^Results for the primary endpoint of HARMONIE of overall incidence of RSV hospitalisation *through the RSV season,* where patients were followed up from the time of randomisation during the recruitment period (8 Aug 2022 to 28 Feb 2023) to the end of the RSV season (28 Feb 2023). Median follow-up time was 2.3 months in the nirsevimab group and 2.0 months in the SOC group.

3.4. In terms of safety, the adverse event (AE) rates were largely similar across arms. While nirsevimab was associated with slightly higher incidences of certain AEs compared to no immunisation, including upper respiratory tract infection, diaper dermatitis and nasal congestion, the Committee considered them manageable. The most frequently reported AEs with nirsevimab included upper respiratory tract infections, nasopharyngitis and pyrexia.

3.5. Based on the available evidence, the Committee concluded that the submission's claim of superior efficacy of nirsevimab versus no immunisation in all infants was considered adequately supported. However, its magnitude of efficacy in high-risk infants remained uncertain. In terms of safety, the Committee considered the submission's claim that nirsevimab was associated with a higher incidence of mild AEs versus no immunisation to be reasonable.

Nirsevimab versus RSVpreF maternal vaccination

3.6. In the absence of head-to-head trials, the Committee reviewed indirect treatment comparisons (ITCs) presented in the submission, based on RCTs for RSVpreF (Phase 2b, MATISSE) that compared RSVpreF and no immunisation in women at 24 to 36 weeks of gestation.

3.7. Although the results of ITCs for MA RSV-LRTI and RSV-LRTI hospitalisations at 150 and 180 days favoured nirsevimab, they were unlikely reliable due to the lack of exchangeability between the nirsevimab and RSVpreF trials, including different proportions of premature infants, timing of administration and timing of endpoint assessment. The ITCs were further limited by insufficient description and inconsistent application of methodology.

3.8. Based on the evidence submitted, the Committee concluded that the submission's claim of superior efficacy of nirsevimab compared with RSVpreF in all infants was not adequately supported. In terms of safety, the submission's claim of a different safety profile may be plausible given the different AEs observed in the infant populations for nirsevimab (upper respiratory tract infections, nasopharyngitis and pyrexia) versus RSVpreF (premature birth and low birth weight).

Nirsevimab versus palivizumab

3.9. The Committee considered direct evidence from the MEDLEY RCT that studied nirsevimab versus palivizumab in high-risk infants. While MEDLEY showed numerically comparable event rates across efficacy outcomes for both treatment arms, the trial was not powered to detect statistical significance for efficacy outcomes, and event rates were low.

3.10. An ITC between the nirsevimab Phase 2b trial and an RCT (IMpact-RSV) that compared palivizumab and no immunisation in high-risk infants showed no statistically significant difference for RSV-LRTI hospitalisation at 150 days. However, the ITC was limited by the lack of exchangeability between both trials.

3.11. Overall, the Committee concluded that the submission's claim of comparable efficacy of nirsevimab compared with palivizumab in high-risk infants was not adequately supported. The submission's claim that nirsevimab was no worse in terms of safety than palivizumab in high-risk infants was considered plausible given the rates of AEs were balanced across study arms in MEDLEY, though not well supported due to limitations with the MEDLEY trial.

3.12. While clesrovimab was considered a potential near-market comparator, published trial data were unavailable at the time of submission and formal comparisons with clesrovimab were not included.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis (CUA) that compared nirsevimab with no immunisation for the prevention of RSV in infants during their first season. Key components of the base-case economic evaluation provided in the submission are summarised in Table 2.

Table 2: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Resident infant population in Singapore during their first RSV season (age 0-12 months) • Healthy infants born at ≥35 wGA (94.65%) • Healthy infants born from 29 to <35 wGA (2.07%) • High-risk infants born at ≤28 wGA, or with CLD or CHD (3.28%)
Intervention	Nirsevimab administered at birth
Outcomes	Total and incremental direct medical costs; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Static decision tree model
Time horizon	1 year, based on outcomes reported at 5 to 6 months in the trials
Health events	• RSV MA-LRTIs, including primary care visits, ED attendance, hospitalisations, ICU admissions, ICU admissions with MV • RSV-related deaths
Incidence of health events	• Per patient risk of primary care visit, ED attendance, hospitalisation, ICU admission and ICU with MV was stratified by the infant's age at the time of infection. • Per patient risk of hospitalisation, ICU admission and ICU with MV was further stratified by infant subpopulation.
Clinical effectiveness	• Healthy infants born at ≥35 wGA: ○ RRR for MA RSV-LRTI at 150 days (MELODY): 74.5% ○ RRR for RSV-LRTI hospitalisations at 180 days (HARMONIE): 82.7% • Healthy infants born from 29 to <35 wGA: ○ RRR for MA-RSV-LRTI for infants <5kg (Phase 2b trial): 86.2% ○ RRR for RSV-LRTI hospitalisations at 180 days (HARMONIE):82.7% • High-risk infants: ○ RRR for MA-RSV-LRTI and RSV-LRTI hospitalisation (systematic review of palivizumab trials): 56.0% Efficacy inputs against RSV was applied for the first 6 months, followed by efficacy waning linearly from the 7th to the 12th month.
Health-related quality of life	• Disutility for hospitalisation, ICU admission and ICU admission with MV: 0.01014 (Mao et al. 2023) • Disutility for primary care visit and ED attendance: 0.0063 (Mao et al. 2023) • The EQ-5D population norms from the UK (Janssen et al. 2014) and the average life expectancy in Singapore were used to derive the QALY loss due to RSV-associated premature death
Types of healthcare resources included	• Drug and administration cost • Disease management cost

Abbreviation: CHD, congenital heart disease; CLD, chronic lung disease; ED, emergency department; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LRTI, lower respiratory tract infection; MA, medically attended; MV, mechanical ventilation; QALY, quality-adjusted life year; RRR, relative risk reduction; RSV, respiratory syncytial virus; wGA, weeks' gestational age.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$45,000 and SG$75,000 per quality-adjusted life year (QALY) gained for nirsevimab compared with no immunisation in the all-infant population. However, the Committee considered the ICER to be highly uncertain and likely underestimated given:

- There was insufficient clinical evidence for high-risk infants, and the submission assumed nirsevimab's efficacy to be equivalent to palivizumab, introducing substantial uncertainty in the cost-effectiveness results in this population.

- There was selective use of efficacy inputs from different trials for healthy infants, favouring nirsevimab. Furthermore, the duration of protection for nirsevimab before efficacy waning was uncertain.

- The incidence rates for RSV-related health events were likely overestimated and highly uncertain.
  - Hospitalisation rates were based on multiple sources and likely overestimated.
  - The proportions of hospitalisations requiring intensive care unit (ICU) and mechanical ventilation (MV) events were modelled as separate health events and are likely double-counted, as MV is often administered in an ICU setting.
  - The emergency department attendance rates were uncertain and assumed, without sufficient justification, to be double those reported in the US.
  - The primary care visit rates were derived by applying a ratio (from a published systematic review) to local hospitalisation rates, despite the availability of local published data.

- The submission applied inaccurate immunisation cost and administration charges for nirsevimab.

4.3. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes to the economic model included presenting a revised base case for healthy infants only, using efficacy inputs from Phase 2b and MELODY trials, revising incidence rates for health events (including removing the double-counting of MV and using local data where available), and updating cost inputs. These changes substantially increased the ICER to between SG$245,000 and SG$285,000 per QALY gained.

4.4. When model parameters were varied across the range of possible values, the ICER remained unacceptably high. The Committee noted that the results were most sensitive to the timing of nirsevimab administration. Delaying this timing by six months increased the ICER substantially to more than SG$365,000 per QALY gained.

4.5. The Committee also noted that the submission included a scenario analysis

comparing nirsevimab to a combined vaccination strategy with palivizumab and RSVpreF. However, given the uncertain comparative efficacy and safety data in the available clinical evidence, a revised base case for this comparison was not conducted.

4.6. Overall, the Committee considered that, at the price proposed by the company, nirsevimab did not represent a cost-effective use of healthcare resources for prevention of RSV-associated LRTD in infants during their first RSV season.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the healthcare system (including PHIs and Community Health Assist Scheme [CHAS] clinics) would be between SG$1 million and SG$3 million in the first year, and between SG$5 million and SG$10 million in the fifth year of listing nirsevimab on the MOH Subsidised Vaccine List for prevention of RSV-associated LRTD in infants during their first RSV season.

5.2. The Committee considered that the submission estimates were uncertain, due to the assumption that all infants receiving nirsevimab would receive it in PHIs or CHAS clinics when listed, even though about half of all births are in private hospitals. Based on the revised budget impact model, the annual cost impact to the healthcare system was estimated to be between SG$5 million and SG$10 million in the first year, decreasing to between SG$3 million and SG$5 million in the fifth year of listing. The Committee also considered that the submission's price-volume agreement (PVA) caps were unacceptably high and inadequate to provide budget certainty.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing nirsevimab on the MOH Subsidised Vaccine List for prevention of RSV-associated LRTD in infants during their first RSV season. The decision was based on the unfavourable cost effectiveness of nirsevimab compared with no immunisation, and the unacceptable PVA proposed by the company.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at https://www.ace-hta.gov.sg/about-us/

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