Canada's Drug and
Health Technology Agency

CADTH Health Technology Review

Nirsevimab (Beyfortus)

Sponsor: Sanofi

Indication: For the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season, and in children up to 24 months of age who remain vulnerable to severe disease through their second RSV season

Implementation Advice

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What Is the Unmet Need for Prevention of RSV?

Respiratory syncytial virus (RSV) is a common, contagious viral pathogen transmitted by contact with respiratory droplets and secretions from an infected person. Although RSV typically causes mild illness with upper respiratory tract symptoms, it can also present with serious acute lower respiratory tract infection (LRTI) illness, typically bronchiolitis and pneumonia, leading to hospitalization in young children.[1] The most commonly recognized risk factors for severe outcomes from RSV infection in children are younger age, prematurity, chronic lung disease (CLD), congenital heart disease (CHD), and compromised immune system.[2] Children living in remote communities in the far north are also at increased risk of RSV hospitalization.[3] The higher burden, explained by several social determinants of health and compounded by limited access to health care, could lead this particular population to worse clinical outcomes.

In the 2022 to 2023 RSV season, reduced exposure to RSV during the COVID-19 pandemic and the subsequent end of public health measures such as social distancing and mask wearing contributed to a large spike in RSV infections, stretching health care resources and overwhelming pediatric hospitals.[4] At the time of this review, the only prophylactic intervention against RSV-associated illness is passive protection with the monoclonal antibody palivizumab (Synagis). Used in infants and children at high risk of severe RSV disease since 2002, it is administered through intramuscular (IM) injection once monthly for up to 5 months during the RSV season. However, it may not be easily accessible for all patients, especially those living in remote geographical locations. Health Canada is currently reviewing a submission for an RSV vaccine to be used in pregnant people, which may provide protection for their infant(s) upon delivery.

What Is Nirsevimab?

Nirsevimab (Beyfortus) is a humanized monoclonal antibody with an extended half-life that binds specifically to the RSV prefusion conformation of the RSV fusion protein, thus preventing a key component of human cell infection by the virus.[5]

Nirsevimab has had a Health Canada indication since April 19, 2023, for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season, and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.[5] The recommended dose of nirsevimab is a single IM injection of 50 mg for infants with a body weight lower than 5 kg, and a single IM injection of 100 mg for infants with a body weight of 5 kg or more. For children who remain vulnerable to severe RSV disease entering their second RSV season, the recommended dose of nirsevimab is 200 mg, given as 2 IM injections of 100 mg.[5]

How Did CADTH Approach This Review?

The National Advisory Committee on Immunization (NACI) will conduct a comprehensive comparative review of all authorized RSV preventive options for infant protection, including nirsevimab, the results of which are anticipated in 2024. Therefore, the aim of this CADTH review is to inform decision-making on the optimal

use of nirsevimab for the upcoming 2023 to 2024 RSV season, before NACI's final recommendation on nirsevimab is available to Canadian jurisdictions.

CADTH convened an implementation advice panel (the "panel") whose members spanned various disciplines and clinical settings with geographical representation across Canada. The panel captured expert advice through consensus and prioritized patient populations that are most likely to benefit from nirsevimab RSV prevention in a tiered-risk group approach.

What Is the Implementation Advice?

The panel suggests prioritizing infants at highest risk for severe RSV disease entering their first RSV season into 3 groups, the use of which depends on the implementation challenges that jurisdictions may face during the upcoming 2023 to 2024 RSV season. Implementation challenges may include, but are not limited to, procurement, budget constraints, administration programs for the 2023 to 2024 season, and distribution to remote locations. The tiered-risk groups are based on the following infant's individual characteristics: high risk for severe RSV disease, limited access to health care due to remoteness, and likeliness to benefit most from the drug and from its single-dose administration.

The risk groups were identified based on evidence available at the time of the review, which included 3 manufacturer-sponsored studies evaluating the use of nirsevimab for RSV prevention in infants with varying levels of risk for RSV disease. Important gaps in the available evidence led the panel to also use findings from epidemiological studies, health care utilization data related to RSV, and expert opinion to inform decision-making. The overall clinical evidence was deemed insufficient to inform on the comparative effectiveness between nirsevimab and palivizumab; therefore, the panel was unable to provide considerations for decision-making between nirsevimab and palivizumab in infants eligible for either prophylactic option.

In light of the challenges observed from the past 2022 to 2023 RSV season, there is a need for early guidance on the optimal use of nirsevimab. The RSV landscape is, however, expected to evolve in the near future, especially with another preventive option currently under review for infant protection (i.e., maternal immunization). Therefore, the panel's deliberations focused on the use of nirsevimab within the context of public health priority, and also within the current RSV landscape, for the 2023 to 2024 RSV season.

What Are the Limitations of the Review?

There were important gaps in the evidence from the clinical trials. The MEDLEY and MELODY trials and Study 3 did not inform on the efficacy of nirsevimab for all subgroups of infants considered by the panel to be at high risk of severe RSV disease. Therefore, the panel relied on epidemiological evidence and expert opinion to bridge the evidence gaps and proceed with prioritization of infant populations that may benefit the most from prophylaxis with nirsevimab.

The overall evidence available included interim analyses with some level of uncertainty; as a result, additional exposure and follow-up data in larger patient populations are needed to fully characterize the safety profile of nirsevimab. As MEDLEY is an ongoing safety study, it did not statistically compare the efficacy of nirsevimab versus palivizumab; therefore, it is unknown whether these drugs are similar in preventing severe RSV disease.

Table 1: Prioritization of Infants to Receive Nirsevimab for RSV Prophylaxis Based on a Tiered-Risk Group Approach

Tier	Risk group

1	Infants at highest risk for severe RSV disease entering their first RSV season, defined as those who have limited access to health care, such as those living in rural or remote settings who would require air transport for hospitalization, and:
	• infants < 33 weeks, 0 days, gestational age, or
	• infants presenting with at least 1 of the following clinical risk factors:
	  ○ chronic lung disease of prematurity or severe chronic lung disease of other etiology, or
	  ○ hemodynamically significant heart disease, or
	  ○ moderately to severely immunocompromised.[a]

2	Infants at high risk for severe RSV disease entering their first RSV season, defined as having **at least** 1 of the following:
	• infants < 37 weeks, 0 days, gestational age who have limited access to health care, such as those living in rural or remote settings who would require air transport for hospitalization, or
	• infants < 33 weeks, 0 days, gestational age, or
	• infants presenting with at least 1 of the following clinical risk factors:
	  ○ chronic lung disease of prematurity or severe chronic lung disease of other etiology, or
	  ○ hemodynamically significant heart disease, or
	  ○ moderately to severely immunocompromised.[a]

3	Infants entering their first RSV season who have limited access to health care, such as those living in rural or remote settings who would require air transport for hospitalization.

RSV = respiratory syncytial virus.

[a]Moderately to severely immunocompromised includes infants with absolute lymphocyte counts of fewer than 100/mm^3, who may be at higher risk of severe RSV disease.[6]

Rationale for Decision-Making

Randomized Controlled Trial Evidence

Results from 2 randomized controlled trials (RCTs), MELODY and Study 3, demonstrated that nirsevimab was superior to placebo in reducing the risk of experiencing medically attended RSV LRTI with or without hospitalization in healthy term and preterm infants born 29 weeks, 0 days, or more of gestational age entering their first RSV season. The panel concluded that the findings available at the time of the review were supportive of the use of nirsevimab in clinical practice.

However, in the context that there might be challenges related to implementation for the upcoming 2023 to 2024 RSV season, the panel suggested prioritization of infant populations according to risk for severe

RSV-associated illness and worse clinical outcomes, as well as access to health care resources, to guide the optimal use of nirsevimab in infants who have the greatest unmet needs. To do so, evidence considered included findings from epidemiological studies that identified factors that are likely to put an infant at risk of severe RSV disease, as well as health care utilization data related to RSV.

The use of nirsevimab in a larger population (e.g., healthy term and preterm infants) will be assessed by NACI in an upcoming comprehensive comparative review of all authorized RSV preventive options. The panel acknowledged that cost-effectiveness of nirsevimab will be assessed as part of the NACI review.

Epidemiological Evidence and Expert Opinion

The panel used an existing comprehensive review performed by NACI that documented the burden of RSV disease to inform on the optimal use of prophylaxis.[3] Specific high-risk populations included preterm infants; infants with CLD of prematurity and other chronic lung diseases, CHD, and other hemodynamically significant chronic cardiopathies, as well as severely immunocompromised infants (i.e., absolute lymphocyte counts of < 100/mm^3); and infants residing in remote communities who would require air transport for hospitalization or remote communities with documented high rates of hospitalization for RSV.[2]

The panel used expert opinion to bridge evidence gaps and inform decision-making. The panel concluded that there was epidemiological evidence to support prioritization of infants presenting with the aforementioned commonly recognized risk factors for severe outcomes of RSV to receive nirsevimab prophylaxis, with the primary goal of therapy being to prevent RSV-associated hospitalizations. The panel recognized that the effectiveness of nirsevimab may differ from what was observed in clinical trials, considering that the trials' selection criteria excluded some of these categories of patients.

The panel also emphasized the clinically meaningful benefits associated with the single-dose administration of nirsevimab, including reduced burden on infants, on caregivers, and on the health care system, as well as full treatment completion. This was especially the case for infants living in remote communities who would require air transport for hospitalization, which in itself can increase the risk of adverse outcomes and would disproportionately increase the burden on caregivers and the health care system.

Panel Deliberation

The panel, comprising 10 members representing primary care and family medicine, infectious disease, emergency medicine, internal medicine and critical care medicine, pediatrics, geriatrics, ethics, pharmacy, and nursing from urban and rural clinical settings across Canada, met on June 8, 2023. The aim was to inform decision-making on the optimal use of nirsevimab for RSV prophylaxis. Particularly, CADTH was seeking feedback from the panel regarding the prioritization of patient populations to receive nirsevimab in situations where there might be implementation challenges. Prioritization would be based on the:

- patient populations that are most likely to achieve therapy goals of preventing RSV hospitalizations
- patient populations that are most likely to benefit from nirsevimab and the use of a single-dose drug
- patient populations that demonstrate the greatest unmet need for an RSV preventive option

- patient populations that are less likely to benefit from nirsevimab, or who are less likely to achieve treatment goals due their lower level of risk of experiencing poor outcomes from severe RSV disease.

Considerations for special populations and communities, as well as considerations associated with administration and treatment course (i.e., prescribing advice), were discussed.

The clinical value of nirsevimab was deliberated on in the context of the RSV public health priority. The advice reflects the panel's consensus based on the best available evidence for RSV prophylaxis with nirsevimab and based on their clinical expertise in the diagnosis and management of RSV. The panel also discussed ethical considerations for the judicious use of nirsevimab during the 2023 to 2024 RSV season, particularly in scenarios of high demand for prophylaxis combined with implementation challenges. Economic evidence and consideration were not within the scope of this review, per the *Procedures for CADTH Review of Nationally Procured Drug Products*.[7]

Place in Therapy

Goals of Therapy

The panel concluded that the primary goal of therapy with nirsevimab is the prevention of RSV-associated hospitalizations. Panel members noted that, according to expert opinion, preventing hospitalization would likely also result in preventing admission to the intensive care unit, the requirement for mechanical ventilation, and potentially death.

A secondary goal of therapy discussed by the panel is a reduction in medically attended RSV infections. Together with the prevention of hospitalizations, panel members indicated that this would help reduce the burden of RSV infections on patients and caregivers, as well as on the health care system.

As RSV epidemiology evolves (particularly the incidence, seasonality, and age distribution of medically attended RSV-associated illness) and immunologic evidence emerges, additional goals of therapy related to RSV may be considered, especially in a scenario similar to the last 2022 to 2023 RSV season, where a large spike in RSV infections posed a substantial burden on infants and caregivers, overwhelming pediatric hospitals and stretching health care resources.

Unmet Needs

The panel members agreed that the greatest unmet needs are in infants in their first RSV season who are part of either or both of the following populations:

- infants with clinical factors putting them at high risk of experiencing poor outcomes from RSV disease
- infants with situational factors related to remote geographic locations and limited access to health care who sustain a higher risk of complications and for whom such complications would result in a higher-than-average burden on infants, caregivers, and health care resource use.

Special consideration should be given to vulnerable populations that may also be at increased risk of poor outcomes from RSV disease despite not being within the highest risk category, such as infants with Down syndrome, cystic fibrosis, and neuromuscular conditions affecting ability to clear airway secretions.

Prescribing Advice

- The panel advised that the balance between benefits and potential harms must be assessed for each infant in relation to their risk of severe RSV disease, and that these must be discussed with caregivers. At the time of this review, the efficacy and safety of nirsevimab is being supported in part by data from interim analyses of ongoing trials; therefore, uncertainty around the safety profile of the drug cannot be excluded until follow-up data in larger populations are available.
- The proportions of patients who died throughout the first RSV season, assessed as harms outcomes in the studies reviewed by CADTH, were small and considered unrelated to the study treatment; however, they were numerically higher in patients receiving nirsevimab compared to patients receiving palivizumab or placebo in the comparator group (in the 2 ongoing studies with results from interim analyses). Again, follow-up data in larger populations are required to fully characterize the safety profile of the drug.
- Other considerations for choice of preventive therapy may be given to the single-dose administration of nirsevimab to reduce the burden on infants and caregivers, and to maximize treatment completion and protection against RSV, especially in infants living in remote communities who may have limited access to palivizumab clinics. A single-dose administration may also present benefits for program delivery and health care resources.
- The panel ascertained the need to involve remote northern Canadian communities and their health care workers as partners in the implementation of RSV prophylaxis programs. The panel discussed lessons learned from a past prophylaxis program and highlighted the need for communication and collaboration between local partners, which are essential to promote feasibility and social acceptability.[8]
- The panel advised that RSV prophylaxis with nirsevimab does not replace basic public health and infection prevention measures to reduce RSV transmission, including, but not limited to, hand washing, masking, and sanitization.

Other Discussion Points

The panel noted the following:

- There may be several potential barriers for implementation of this guidance, such as the lack of time to prepare and roll out administration programs. Where it is not feasible to implement a particular tier, subsequent tiers can be considered, depending on implementation challenges.
- There are no efficacy and safety data to inform on the use of nirsevimab in infants who had any prior RSV infection, infants with current symptoms that are consistent with RSV infection, and infants who received any prior monoclonal antibody for RSV specifically or for any other indication, including an incomplete series of doses of palivizumab prophylaxis.
- Nirsevimab is approved for RSV prophylaxis; the efficacy and safety of the drug has not been evaluated in the treatment of RSV disease.

- Evolutionary changes in the genes encoding the RSV fusion protein, to which monoclonal antibodies bind, may impact the clinical effectiveness of nirsevimab. Therefore, epidemiological and molecular viral surveillance is important.
- Additional treatment goals should be considered in future research for RSV preventive options, including reduction of virus transmission, as well as prevention of asthma. At this time, further data are required to inform these goals.

Background

An overview of the details for the drug under review is provided in Table 2.

Table 2: Review Details

Item	Description
Drug product	Nirsevimab (Beyfortus); solution for IM injection
Health Canada indication	For the prevention of RSV lower respiratory tract disease in: • neonates and infants during their first RSV season • children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, which may include but is not limited to children with: ◦ chronic lung disease of prematurity ◦ hemodynamically significant congenital heart disease ◦ immunocompromised states ◦ Down syndrome ◦ cystic fibrosis ◦ neuromuscular disease ◦ congenital airway anomalies.
Health Canada approval status	Approved
NOC date	April 19, 2023
Sponsor	AstraZeneca

NOC = Notice of Compliance; RSV = respiratory syncytial virus.

Respiratory Syncytial Virus

RSV is an enveloped ribonucleic acid (RNA) virus and a common, contagious viral pathogen transmitted by contact with respiratory droplets and secretions from an infected person that causes a wide variety of respiratory illness. By the age of 2, most children will have experienced an RSV infection.[6] Reinfections with RSV are common, but illness is usually milder with subsequent infections. RSV typically causes mild illness with coldlike symptoms; most infections are upper respiratory tract infections that present as nasal congestion, cough, low grade fever, and loss of appetite and last approximately 1 to 2 weeks.[1] However, it can present with more serious complications. RSV is the most common cause of acute LRTI in young children,[1] estimated to account for 28% of all episodes of acute LRTI (i.e., bronchiolitis and pneumonia).[6]

The risk of severe outcomes from RSV infection is higher among infants and young children under the age of 2, and children with CLD, CHD, compromised immune systems, or neuromuscular disorders.[2] In severe cases, RSV requires hospitalization and may be life-threatening. However, most children under 2 years of age hospitalized with RSV infection have no comorbidities.[9] Hospitalization rates are highest among children under 1 year old, and highest within the first 2 months of life.[2] In Canada, approximately 1% of all infants are hospitalized with RSV in their first year of life.[2] Hospitalization rates in Canada are reported to be 20, 10.2, and 4.8 per 1,000 per year for children aged younger than 6 months, younger than 1 year, and 1 to 3 years, respectively.[9-11] In Ontario, 9% of annual hospital admissions for children under 1 year of age were due to RSV.[9] Infants with CLD, CHD, or other chronic conditions such as cystic fibrosis have higher rates and duration of hospitalization and are more likely to be admitted to intensive care units.[9,12,13] Premature birth is also a notable risk factor for RSV hospitalization; infants born at fewer than 30 weeks gestation have higher RSV hospitalization rates.[2] Children living in remote communities in the far north may also be at increased risk of RSV disease.[3] In some communities, RSV hospitalization rates have been as high as 20% to 50% of all live births.[2] The higher burden, explained by several social determinants of health and compounded by limited access to health care, could lead this particular population to worse clinical outcomes. Mortality is rare among children receiving supportive care. The overall case-fatality rate of children hospitalized with RSV is estimated to be less than 0.5%, with most deaths occurring in children with underlying risk factors to severe RSV disease.[2] One Canadian study reported that 82% of deaths from RSV illness were in children with underlying risk factors.[14]

RSV follows an annual seasonal pattern. In Canada, the RSV season usually begins in October or November and lasts until April or May, with peaks in December through March. In the 2022 to 2023 RSV season, reduced exposure to RSV during the COVID-19 pandemic and the subsequent end of public health measures such as social distancing and mask wearing contributed to a large spike in RSV infections, stretching health care resources and overwhelming pediatric hospitals.[4] In Health Canada's Respiratory Virus Report, levels of activity for RSV were above expected with an average national positivity rate of 7.0% and 6.9% for the last week of October and November, respectively.[15] Given the resurgence of RSV cases that may continue into future RSV seasons, timely RSV prevention programs may help curve the number of severe RSV infections, hospitalizations and medically attended LRTIs, bronchitis, and pneumonia.

At the time of this review, the only prophylactic intervention against RSV-associated illness is passive protection with the monoclonal antibody palivizumab (Synagis). Health Canada approved palivizumab in June 2002 for use in infants and young children younger than 24 months of age who are at high risk of severe RSV disease.[2] The efficacy and safety of palivizumab were established in infants with bronchopulmonary dysplasia, infants with a history of prematurity (less than 35 weeks gestational age), and children with hemodynamically significant CHD. Palivizumab is administered through IM injection once monthly for up to 5 months during the RSV season. It is approximately 40% to 80% effective in preventing hospitalization, depending on age and underlying health conditions.[2] Health Canada is currently reviewing 2 vaccine submissions for RSV; a submission from GlaxoSmithKline (November 2022) for an RSV vaccine to be used in adults 60 years of age and older, and a submission from Pfizer (March 2023) for an RSV vaccine to be used in pregnant people to protect their infants and for adults 60 years of age and older.

The objective of this CADTH review is to identify, through a tiered-risk group approach, patient populations that may gain the most benefit from nirsevimab therapy for the upcoming 2023 to 2024 RSV season.

Nirsevimab (Beyfortus)

Nirsevimab (Beyfortus) is a humanized, immunoglobulin G1 monoclonal antibody with an extended half-life that has been developed as an RSV immunizing drug for RSV prophylaxis in infants and children. Nirsevimab was approved by Health Canada (April 19, 2023) "for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season, and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, which may include but is not limited to children with CLD of prematurity, hemodynamically significant CHD, immunocompromised states, Down syndrome, cystic fibrosis, neuromuscular disease, and congenital airway anomalies."[5]

The recommended dose of nirsevimab is a single fixed dose of 50 mg for infants with a body weight of less than 5 kg and a single fixed dose of 100 mg for infants with a body weight of 5 kg or greater, given as a single IM injection. Dosing in infants with a body weight between 1.0 kg and 1.6 kg is based on extrapolation. Nirsevimab should be administered from birth for infants born during the RSV season, and for infants born outside the season, it should be administered before the RSV season.[5] For children who remain vulnerable to severe RSV disease entering their second RSV season, the recommended dose of nirsevimab is a single dose of 200 mg given as 2 IM injections (2 doses of 100 mg).[5] Additional dosing consideration may be required to individuals undergoing cardiac surgery with cardiopulmonary bypass.

Nirsevimab was recently approved (October 31, 2022) by the Medicines and HealthCare products Regulatory Agency in the UK and by the European Commission for prevention of RSV LRTI in newborns and children during their first RSV season.[16] The US FDA has not yet approved nirsevimab for the prevention of RSV LRTI in newborns and infants, and a regulatory decision is expected in the third quarter of 2023.[17]

In Canada, NACI will conduct a comprehensive comparative review of all authorized RSV preventive options for infants, including nirsevimab, the results of which are anticipated in 2024.

Summary of Evidence

Description of Studies

Three manufacturer-sponsored, multicentre, double-blind RCTs were used as the primary source of evidence to assess the efficacy and safety of nirsevimab for RSV prevention in infants with varying levels of risk for RSV disease. These were MEDLEY,[18] MELODY,[19] and Study 3;[20] the details of each study are presented in Table 3.

- MEDLEY (n = 925) is an ongoing phase III, active-controlled RCT comparing nirsevimab to palivizumab through descriptive analyses in infants younger than 1 year of age entering their first RSV season. The MEDLEY trial was mainly designed as a descriptive safety study. Patients were either in the preterm cohort (i.e., born ≤ 35 weeks, 0 days, of gestational age with no CLD or

hemodynamically significant CHD and eligible to receive palivizumab) or in the CLD and CHD cohort (i.e., with CLD of prematurity requiring medical intervention or management within prior 6 months, or with hemodynamically significant CHD that is unoperated or partially corrected). The study plans to evaluate nirsevimab throughout a second RSV season in patients from the CLD and CHD cohort; however, results for the second RSV season are not available at the time of this review.

- MELODY (n = 1,490; primary efficacy cohort) is an ongoing phase III RCT evaluating the superiority of nirsevimab compared with placebo in healthy infants younger than 1 year of age, born 35 weeks, 0 days, or more of gestational age and entering their first RSV season who do not meet national or local criteria to receive palivizumab. Detailed results are available for the primary efficacy cohort. Follow-up of a larger full complementary safety cohort is ongoing at the time of this review; however, some preliminary results have been made available through a published correspondence.
- Study 3 (n = 1,453), which was a phase II study labelled NCT02878330, also evaluated the superiority of nirsevimab compared with placebo in healthy infants younger than 1 year of age entering their first RSV season and not meeting national or local criteria to receive palivizumab, but who were born between 29 weeks, 0 days, and 34 weeks, 6 days, of gestational age. The results of this phase II study were pooled with the results of the MELODY trial in the primary efficacy cohort for evaluation of nirsevimab in preterm infants born 29 weeks, 0 days, or more of gestational age who are not eligible to receive prophylaxis with palivizumab.

Intervention

In the MEDLEY and MELODY trials, nirsevimab was administered at the dosage recommended in the product monograph (i.e., 1 single IM dose of 50 mg [if < 5 kg] or 100 mg [if ≥ 5 kg]).[21] In Study 3, all patients received 1 single IM dose of 50 mg regardless of body weight. Patients were allowed to receive concomitant medications or treatments necessary to provide supportive care, including routine vitamins and iron.

Outcome Measures

The 3 RCTs shared the same primary outcome of medically attended RSV LRTI (which was a protocol-defined end point) over a minimum follow-up duration of 150 days. The criteria for meeting the prespecified end point were:

- confirmed RSV-positive test result by central laboratory reverse transcriptase-polymerase chain reaction assay
- LRTI documented by physical examination findings of rhonchi, rales, crackles, or wheeze localizing to lower respiratory tract, and
- at least 1 of the following objective measures of clinical severity:
  - increased respiratory rate at rest (< 2 months = ≥ 60 breaths/minute; 2 to 6 months = ≥ 50 breaths/minute; > 6 months = ≥ 40 breaths/minute), or
  - hypoxemia (in room air oxygen saturation of < 95% at altitudes of ≤ 1,800 m or < 92% at altitudes of > 1,800 m), or

    - clinical signs of severe respiratory disease such as acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, retractions (intercostal, subcostal, or supraclavicular), grunting or dehydration secondary to inadequate oral intake due to respiratory distress (need for IV fluid).
- For patients in the MEDLEY CLD and CHD cohort, an additional measure of clinical severity included the prescription of a new medication or increased doses of medications compared to baseline, including bronchodilators, steroids, diuretics, and cardiac medication.

Patient Populations

Although the RCTs evaluated patient populations with different levels of risk for RSV disease, they shared some similarities in selection criteria. As such, patients were not eligible for any of the trials if they had recent fever or acute illness (including any history of LRTI) or were receiving or expecting to receive any regular drug therapy (including immunosuppressive therapy and blood product) or mechanical respiratory or cardiac support.

Key exclusion criteria also included renal impairment or hepatic dysfunction, clinically significant congenital anomaly of the respiratory tract, chronic seizure or evolving or unstable neurologic disorder, prior or acute life-threatening event, known immunodeficiency (including HIV), and prior or acute life-threatening event. The MELODY trial and Study 3 also excluded patients with a history of bronchopulmonary dysplasia or CLD, as well as patients with congenital heart disease, except for those with uncomplicated CHD.

The selection criteria of all studies specified that patients had no history of RSV, did not receive any prior monoclonal antibody (including palivizumab) for RSV or any other indication, and did not receive any RSV vaccination, including a maternal RSV vaccination.

Table 3: Details of Nirsevimab Studies for RSV Prophylaxis

Detail	MEDLEY	MELODY	Study 3
Study design	Phase III DB active-controlled descriptive RCT	Phase III DB placebo-controlled RCT	Phase II DB placebo-controlled RCT
Locations	Multicentre study (126 centres in 25 countries): US, Canada (n = 3 patients), UK, Europe, South Africa, Japan	Multicentre study (211 centres in 31 countries): US, Canada (n = 8 patients), UK, Europe, South Africa, Japan	Multicentre study (194 centres in 23 countries): US, Canada (number of patients not reported), UK, Europe, South America, South Africa
Patient enrolment dates	July 30, 2019, to ongoing Data cut-off date: 03 May 2021 Primary analysis DCO: All randomized patients, RSV season 1	July 30, 2019, to ongoing Data cut-off date: March 11, 2021 Primary analysis DCO: All randomized patients, primary efficacy cohort	Date of study start: November 3, 2016 Date of last patient last visit: December 6, 2018
Randomized (2:1 ratio)	N = 925 patients, RSV season 1 N = 262 patients, RSV season 2	N = 1,490 patients, primary efficacy cohort N = 3,012 patients, full safety cohort	N = 1,453 patients

Detail	MEDLEY	MELODY	Study 3
Relevant inclusion criteria	Infants (< 1 year) entering first RSV season **Cohort 1 (preterm):** • Preterm infants born ≤ 35 weeks, 0 days, GA • No CLD or hemodynamically significant CHD • Eligible to receive palivizumab[a] **Cohort 2 (CLD/CHD):** • Infants with CLD of prematurity or hemodynamically significant CHD[b]	• Healthy infants in the first year of life and born ≥ 35 weeks 0 days of GA • Entering their first RSV season • Patients with underlying illness with no other risk factors were eligible for inclusion • Must not meet national or other local criteria to receive palivizumab	• Healthy infants • Born between 29 weeks, 0 days, and 34 weeks, 6 days, of GA • Entering their first RSV season (and ≤ 8 months of age for patients in Europe) • Must not meet AAP or other local criteria to receive palivizumab
Relevant exclusion criteria	• Fever (≥ 38.0°C), acute illness within 7 days • Any LRTI or RSV, history or active • Hospitalization with > 7 days remaining • Requirement for mechanical respiratory or cardiac support • Anticipated cardiac surgery within 2 weeks • Anticipated survival of less than 6 months • Renal impairment or hepatic dysfunction, including active or chronic hepatitis infection • Clinically significant congenital anomaly of respiratory tract • Chronic seizures; evolving or unstable neurologic disorder • Prior or acute life-threatening event • Known immunodeficiency (including HIV) • Known allergy or history of allergic reaction • Prior or expected use of monoclonal antibody • RSV vaccine, including maternal vaccination	• Fever (≥ 38.0°C), acute illness, drug therapy within 7 days • Any LRTI or RSV, history or active • Current or expected immunosuppressive therapy (including steroids) • History of transfusion or expected transfusion • Renal impairment or hepatic dysfunction, including active or chronic hepatitis infection • History of bronchopulmonary dysplasia, CLD • Clinically significant congenital anomaly of the respiratory tract or congenital heart disease • Chronic seizure or evolving or unstable neurologic disorder • Prior or acute life-threatening event • Known immunodeficiency (including HIV) • Known allergy or history of allergic reaction • Prior or expected use of monoclonal antibody • RSV vaccine, including maternal vaccination	• Fever (≥ 38.0°C), lower respiratory illness, drug therapy within 7 days • Any current acute illness • Any RSV, history or active • Current or expected immunosuppressive therapy (including steroids) • History of, or expected transfusion • Renal impairment or hepatic dysfunction, including active or chronic hepatitis infection • History of bronchopulmonary dysplasia, CLD • Clinically significant congenital anomaly of the respiratory tract or congenital heart disease • Chronic seizure or evolving or unstable neurologic disorder • Prior or acute life-threatening event • Known immunodeficiency (including HIV) • Known allergy or history of allergic reaction • Prior or expected use of monoclonal antibody • RSV vaccine, including maternal vaccination
Intervention	**Season 1 (cohorts 1 and 2):** Nirsevimab single dose administered IM: 50 mg (if < 5 kg) or 100 mg (if ≥ 5 kg), then 4 once-monthly IM doses of placebo	Nirsevimab single dose administered IM according to body weight:	Nirsevimab 50 mg single dose administered IM

Detail	MEDLEY	MELODY	Study 3
	Season 2 (cohort 2 only): One single dose of nirsevimab 200 mg IM, then 4 once-monthly IM doses of placebo	• 50 mg (if < 5 kg) • 100 mg (if ≥ 5 kg)	
Comparator	**Season 1 (cohorts 1 and 2):** Palivizumab 15 mg/kg IM once monthly for 5 months **Season 2 (cohort 2 only):** Rerandomization to intervention or palivizumab 15 mg/kg IM once monthly for 5 months	One single dose of placebo administered IM	One single dose of placebo administered IM
Concomitant intervention(s)	Concomitant medications or treatments necessary to provide supportive care, including routine vitamins and iron, as well as transfusions of blood and blood products, treatment with antibiotics, antiemetics, antidiarrheals, and analgesics	Efficacy cohort: Routine vitamin and iron only, from day 1 to day 15 postdose; other medications in consultation with investigators Safety cohort: Concomitant medications allowed; routine childhood vaccines specifically encouraged	Concomitant medications or treatments necessary to provide supportive care, including routine vitamins and iron
Efficacy and safety follow-up	150 days and 360 days	150 days and 360 days	150 days and 360 days
Primary end point	Efficacy: Medically attended RSV LRTI, descriptive analysis (protocol-defined end point)	Efficacy: Medically attended RSV LRTI (protocol-defined end point)	Efficacy: Medically attended RSV LRTI (protocol-defined end point)
Key secondary end point	Efficacy: Medically attended RSV LRTI with hospitalization (protocol-defined end point) Safety: AEs, SAEs, AEs of special interest	Efficacy: Medically attended RSV LRTI with hospitalization (protocol-defined end point) Safety: AEs, SAEs, AEs of special interest	Efficacy: Medically attended RSV LRTI with hospitalization (protocol-defined end point) Safety: AEs, SAEs, AEs of special interest
Other main secondary end points	All medically attended RSV and non-RSV LRTI, with and without hospitalization	All medically attended RSV and non-RSV LRTI or respiratory illness, with and without hospitalization; medically attended RSV LRTI (very severe)	All medically attended RSV and non-RSV LRTI or respiratory illness, with and without hospitalization; medically attended RSV LRTI (very severe); health care utilization data
Main publications	Domachowske et al. (2022)[22]	Hammitt et al. (2022)[23] Muller et al. (2023)[24]	Griffin et al. (2022)[25]

AAP = American Academy of Pediatrics; AE = adverse event; DB = double-blind; CHD = congenital heart disease; CLD = chronic lung disease; DCO = data cut-off; GA = gestational age; IM = intramuscular; LRTI = lower respiratory tract infection; RCT = randomized controlled trial; RSV = respiratory syncytial virus; SAE = serious adverse event.

[a]Includes patients with uncomplicated small atrial or ventricular septal defects or patent ductus arteriosus; or aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone.

[b]Includes acyanotic cardiac lesions with pulmonary hypertension (≥ 40 mm Hg) or pharmacological management.

Sources: Interim Clinical Study Reports for the MEDLEY[18] and MELODY trials.[19] Final Clinical Study Report for Study 3.[20]

Statistical Analyses

The MEDLEY Trial

The MEDLEY trial had no hypothesis testing. In terms of efficacy, a noninferiority margin could not be established according to the sponsor due to the lack of historical efficacy data for the primary outcome in patients treated with palivizumab. There was also additional uncertainty surrounding the event rates, considering the reduced incidence of RSV disease following the introduction of palivizumab, as well as the reduced RSV circulation attributable to the COVID-19 pandemic-related measures.

Three analyses were planned; at the time of this review, only results from the primary analysis were available. The primary analysis was conducted after all randomized patients had completed follow-up through the first RSV season (150 days) and included all season 1 safety, efficacy, pharmacokinetic, and antidrug antibody data that were available at the time of data cut-off. Planned additional analyses include the season 2 analysis and the final analysis.

Two stratification factors were used in the study design and analysis: age group at randomization and Northern and Southern hemisphere. Categorical data were summarized by number and percentage of patients in each category, while continuous variables were summarized by mean, median, standard deviation, and minimum and maximum.

The sample size of 600 patients exposed to nirsevimab in season 1 was determined for safety consideration; the study had a 95% probability of observing at least 1 adverse event (AE), assuming that the true event rate was 0.5%. As for efficacy, it was anticipated that 600 patients exposed to nirsevimab and 300 patients exposed to palivizumab in season 1 would allow observation of numerically similar efficacy for both monoclonal antibodies.

The MELODY Trial and Study 3

The MELODY trial was originally designed with 3,000 patients. However, COVID-19 resulted in reduced RSV circulation in the population during the pandemic, which impacted the study's conduct. Therefore, there was a protocol amendment in consultation with regulatory authorities to analyze the first 1,500 patients enrolled for efficacy (primary efficacy cohort) and to complete study enrolment for safety and analyze with these patients separately (full complementary safety cohort). At the time of the CADTH review, only the results from the primary analysis performed in the primary efficacy cohort were fully available. Some results for the full complementary safety cohort have also been made available through a published correspondence.[24]

The primary analysis in the MELODY trial and Study 3 was conducted after all randomized patients had completed follow-up through the first RSV season. The primary efficacy outcome was based on patients in the intent-to-treat population (i.e., all patients randomized in season 1 analyzed according to their randomized treatment group). A Poisson regression model with robust variance was used as the primary efficacy analysis model to estimate relative risk based on the incidence of medically attended RSV LRTI between the nirsevimab and placebo groups. The model included the term of the treatment group and patients' age at randomization stratum as covariates. As supporting analysis, the same primary analysis was repeated, this time also adjusting for log (follow-up time) as an offset. In addition, the stratified Cochran-

Mantel-Haenszel test was used as the secondary efficacy analysis of the primary end point to test the treatment effect between groups. The secondary outcome was medically attended RSV LRTI, a subset of the primary outcome. A hierarchical testing strategy was implemented to control for multiplicity.

The relative risk reduction (RRR), defined as 1-RR, and its corresponding 2-sided 95% confidence interval (CI), were estimated from the model. In addition, the 2-sided P value testing the null hypothesis that the incidence of medically attended RSV LRTI between the nirsevimab and placebo groups are the same was obtained from the model. Statistical significance was achieved if the 2-sided P value was 0.05 or less. Patients who did not have a primary outcome event and who were not followed through 150 days had their event status imputed using the prespecified multiple imputation approach assuming the observed placebo primary outcome event rate, conditional on stratification factor. Additional missing data imputation techniques were used as sensitivity analyses.

Other analyses for the primary outcome in the MELODY trial and Study 3 included a Kaplan-Meier curve for time-to-first medically attended RSV LRTI, which was generated based on observed events. Treatment group differences in time-to-first medically attended RSV LRTI were compared using the stratified log-rank test with the stratification factor age at randomization as the strata. In addition, hazard ratios and the corresponding 95% CIs were obtained from the stratified proportional hazard model with the stratification factor age at randomization stratum as the strata. Various subgroup analyses were also performed in the 2 studies for the primary efficacy end point.

Sample sizes in both studies were determined for safety consideration. In the MELODY trial, the full complementary safety cohort of 3,000 patients, of whom 2,000 would be exposed to nirsevimab, had a greater than 99% probability of observing at least 1 AE assuming a true event rate of 0.3%. In Study 3, a sample size of 1,000 patients exposed to nirsevimab had a 90% probability of observing at least 1 AE assuming a true event rate of 0.2%. As for efficacy, the MELODY primary efficacy cohort and the overall population in Study 3 both had at least 99% power to detect a 70% RRR, assuming an 8% incidence of medically attended RSV LRTI in the placebo group. Power calculations were based on a Poisson regression model with robust variance comparing nirsevimab versus placebo using a 2-sided alpha of 0.05.

Pooled Analyses

A pooled analysis was also conducted to assess the overall efficacy of nirsevimab on RSV hospitalization, as there was the risk that the incidence of RSV hospitalization in the MELODY study population of healthy late-preterm and term infants may have been too low (it was expected to be approximately 1% in the placebo group) for this secondary efficacy analysis to reach statistical significance ($P \leq 0.05$) within the MELODY study alone. The pooled analyses consisted of patients from the MELODY primary efficacy cohort and patients in Study 3 (all patients analysis and patients weighing < 5 kg analysis). Combining these patients for analysis was justified according to the sponsor based on the similar study designs and populations of the trials.

For the pooled analyses, a Poisson regression model with robust variance was used to assess the treatment effect on the incidence of medically attended RSV LRTI with hospitalization between the nirsevimab and

placebo groups in the pooled intent-to-treat population. In addition to the treatment group, the variable study (which identifies the enrolled study for each patient) was used as a covariate to adjust for potential differences between the studies. The RRR and its corresponding 95% CI were estimated from the model implemented by PROC GENMOD. Due to the expected low event rate and correspondingly high likelihood of empty cells by strata, the stratification factors were not used during the repeated imputation step to avoid potential convergence issues.

Study Populations

Overall, 925 patients were randomized in the MEDLEY trial, 1,490 patients were randomized in the MELODY trial, and 1,453 patients were randomized in Study 3 in a 2:1 ratio. Details on patients' disposition are presented in Table 4 and Table 5. The proportions of patients who discontinued the study were similar between treatment groups within each study and were also consistent across studies (≤ 8%). The most frequent reason for discontinuation was withdrawal by patient.

Table 4: Patients Disposition — MEDLEY Trial, Through Day 150

	Overall		Cohort 1 — Preterm		Cohort 2 — CLD/CHD	
Category	Nirsevimab	Palivizumab	Nirsevimab	Nirsevimab	Palivizumab	Nirsevimab
Screened, N	960					
Total randomized, N	925		615		310	
Randomized by group, n	616	309	407	208	209	101
Received treatment, n	614	304	406	206	208	98
Completed follow-up, n (%)	**593 (96)**	**293 (95)**	**389 (96)**	**198 (95)**	**204 (98)**	**95 (94)**
Discontinued from study, n (%)	**44 (7)**	**25 (8)**	**29 (7)**	**17 (8)**	**15 (7)**	**8 (8)**
Withdrawal	28 (5)	17 (6)	19 (5)	13 (6)	9 (4)	4 (4)
Lost to follow-up	7 (1)	1 (< 1)	4 (1)	0	3 (1)	1 (1)
Death	5 (< 1)	1 (< 1)	2 (< 1)	0	3 (1)	1 (1)
COVID-19	0	2 (< 1)	0	2 (1)	0	0
Other	4 (< 1)	4 (< 1)	4 (1)	2 (1)	0	2 (2)
ITT,[a] N	616	309	407	208	209	101
Safety analysis set,[b] N	614	304	406	206	208	98

ITT = intent to treat.

[a]Randomized and received the study drug; full analysis set.

[b]All patients who received the study drug.

Source: Interim Clinical Study Report for the MEDLEY trial.[18]

Table 5: Patients Disposition — MELODY Trial Primary Efficacy Cohort; Study 3, Through Day 150

Category	MELODY		Study 3	
	Nirsevimab	Placebo	Nirsevimab	Placebo
Screened, N	1,626		1,540	
Total randomized, N	1,490		1,453	
Randomized by group, N	994	496	969	484
Received treatment, N	987	491	966	481
Completed follow-up in MELODY; completed Study 3, n (%)	**977 (98)**	**488 (98)**	**913 (94)**	**454 (94)**
Discontinued from study, n (%)	**40 (4)**	**21 (4)**	**56 (6)**	**30 (6)**
Withdrawal	20 (2)	14 (3)	21 (2)	11 (2)
Lost to follow-up	9 (< 1)	3 (< 1)	26 (3)	11 (2)
Death	4 (< 1)	0	2 (< 1)	4 (< 1)
COVID-19	3 (< 1)	1 (< 1)	0	0
Other	4 (< 1)	3 (< 1)	7 (< 1)	4 (< 1)
ITT,[a] N	994	496	969	484
Safety analysis set,[b] N	987	491	968	479

ITT = intent to treat.

Note: In the MELODY trial's full complementary safety cohort, 114 patients (6%) discontinued the study in the nirsevimab group (N = 2,009) and 61 patients (6%) discontinued the study in the placebo group (N = 1,003).[24]

[a]Randomized and received the study drug; full analysis set.

[b]All patients who received the study drug.

Sources: Interim Clinical Study Report for the MELODY trial.[19] Final Clinical Study Report for Study 3.[20]

Baseline characteristics were overall similar between treatment groups within each study. Details on patient characteristics are presented in Table 6 and Table 7. Most of the trials' patients were white, with participants who were Black being the second most common. Down syndrome or cystic fibrosis were reported in less than 2% of patients in the studies.

In the MEDLEY trial, 45% of patients were 3 months of age or younger, 34% were older than 3 months but 6 months or younger, and 21% were older than 6 months. In the preterm cohort, 13% of patients were born at fewer than 29 weeks of gestational age, 24% were born at 29 or more weeks but fewer than 32 weeks, 57% were born at 32 weeks or more but fewer than 35 weeks, and 6% were born at 35 weeks or later. In this cohort, 94% of patients had a birth weight 2.5 kg or less and no patient reported any CLD or CHD. In the CLD and CHD cohort, 40% of patients were born at fewer than 29 weeks of gestational age, 16% were born 29 or more to fewer than 32 weeks, 13% were born at 32 or more but fewer than 35 weeks, and 32% were born at 35 weeks or more. In this cohort, 70% of patients had underlying and/or chronic lung disease and 34% of patients had CHD.

A total of 58% of patients included in MELODY were 3 months of age or younger; a proportion that was 53% in Study 3. The proportion of patients older than 3 months but 6 months of age or younger was 32% in the MELODY study and 33% in Study 3. Patients older than 6 months of age accounted for 10% of the population in the MELODY trial and 14% of the population in Study 3. In terms of gestational age, 86% of patients in the MELODY trial were born at 37 weeks or more; the remaining 14% of the population was born between 35 and fewer than 37 weeks. In Study 3, the mean gestational age was 32.7 weeks. The latest published results for the full complementary safety cohort in the MELODY trial[24] showed that baseline characteristics for the overall population were consistent with those reported here for the primary efficacy cohort.

Table 6: Baseline Characteristics — MEDLEY Trial for First RSV Season (ITT Population)

	Overall		Cohort 1 — Preterm		Cohort 2 — CLD or CHD	
Patient characteristic	Nirsevimab N = 616	Palivizumab N = 309	Nirsevimab N = 407	Palivizumab N = 208	Nirsevimab N = 209	Palivizumab N = 101
Age, mean (SD), months	3.9 (2.55)	3.8 (2.46)	3.5 (2.37)	3.5 (2.39)	4.8 (2.66)	4.5 (2.46)
≤ 3 months, n (%)	274 (44.5)	144 (46.6)	214 (52.6)	113 (54.3)	60 (28.7)	31 (30.7)
> 3 to ≤ 6 months, n (%)	210 (34.1)	101 (32.7)	126 (31.0)	59 (28.4)	84 (40.2)	42 (41.6)
> 6 months, n (%)	132 (21.4)	64 (20.7)	67 (16.5)	36 (17.3)	65 (31.1)	28 (27.7)
Sex, n (%)						
Female	297 (48.2)	133 (43.0)	201 (49.4)	93 (44.7)	96 (45.9)	40 (39.6)
Male	319 (51.8)	176 (57.0)	206 (50.6)	115 (55.3)	113 (54.1)	61 (60.4)
Race, n (%)						
White	483 (78.4)	249 (80.8)	305 (74.9)	160 (77.3)	178 (85.2)	89 (88.1)
Black or African American	59 (9.6)	29 (9.4)	49 (12.0)	24 (11.6)	10 (4.8)	5 (5.0)
Asian	36 (5.8)	14 (4.5)	26 (6.4)	9 (4.3)	10 (4.8)	5 (5.0)
American Indian or Alaska Native	11 (1.8)	5 (1.6)	11 (2.7)	5 (2.4)	0	0
Native Hawaiian or Pacific Islander	4 (0.6)	1 (0.3)	3 (0.7)	1 (0.5)	1 (0.5)	0
Other	17 (2.8)	6 (1.9)	10 (2.5)	6 (2.9)	7 (3.3)	0
Multiple categories checked	6 (1.0)	4 (1.3)	3 (0.7)	2 (1.0)	3 (1.4)	2 (2.0)
Weight, mean (SD), kg	4.7 (1.86)	4.6 (1.79)	4.6 (1.83)	4.5 (1.89)	5.1 (1.88)	4.9 (1.52)
Weight group, n (%)						
> 5 kg	344 (56.1)	174 (57.2)	243 (60.0)	123 (59.7)	101 (48.6)	51 (52.0)
≥ 5 kg	269 (43.9)	130 (42.8)	162 (40.0)	83 (40.3)	107 (51.4)	47 (48.0)
GA, mean (SD), weeks	31.7 (3.74)	31.4 (3.68)	31.9 (2.47)	31.5 (2.27)	31.3 (5.41)	31.2 (5.58)
GA group, n (%)						
< 29 weeks	130 (21.1)	70 (22.7)	49 (12.0)	28 (13.5)	81 (38.8)	42 (41.6)
≥ 29 to < 32 weeks	128 (20.8)	71 (23.0)	91 (22.4)	59 (28.4)	37 (17.7)	12 (11.9)

Patient characteristic	Overall		Cohort 1 — Preterm		Cohort 2 — CLD or CHD	
	Nirsevimab N = 616	Palivizumab N = 309	Nirsevimab N = 407	Palivizumab N = 208	Nirsevimab N = 209	Palivizumab N = 101
≥ 32 to < 35 weeks	262 (42.5)	126 (40.8)	235 (57.7)	114 (54.8)	27 (12.9)	12 (11.9)
≥ 35 weeks	96 (15.6)	42 (13.6)	32 (7.9)	7 (3.4)	64 (30.6)	35 (34.7)
Birth weight group, n (%)						
≤ 2.5 kg	534 (86.7)	274 (88.7)	375 (92.1)	203 (97.6)	159 (76.1)	71 (70.3)
> 2.5 kg	82 (13.3)	35 (11.3)	32 (7.9)	5 (2.4)	50 (23.9)	30 (29.7)
Multiple birth, n (%)						
Yes	189 (30.7)	107 (34.6)	149 (36.6)	90 (43.3)	40 (19.1)	17 (16.8)
No	427 (69.3)	202 (65.4)	258 (63.4)	118 (56.7)	169 (80.9)	84 (83.2)
Underlying lung disease, n (%)						
Yes	148 (24.0)	70 (22.7)	0	0	148 (70.8)	70 (69.3)
No	468 (76.0)	239 (77.3)	407 (100.0)	208 (100.0)	61 (29.2)	31 (30.7)
CHD, n (%)						
Yes	70 (11.4)	34 (11.0)	0	0	70 (33.5)	34 (33.7)
No	546 (88.6)	275 (89.0)	407 (100.0)	208 (100.0)	139 (66.5)	67 (66.3)
CLD, n (%)						
Yes	148 (24.0)	70 (22.7)	0	0	148 (70.8)	70 (69.3)
No	468 (76.0)	239 (77.3)	407 (100.0)	208 (100.0)	61 (29.2)	31 (30.7)
Down syndrome, n (%)	9 (1.5)	3 (1.0)	2 (0.5)	0	7 (3.3)	3 (3.0)
Cystic fibrosis, n (%)	2 (0.3)	0	2 (0.5)	0	0	0

CHD = congenital heart disease; CLD = chronic lung disease; GA = gestational age; SD = standard deviation.
Source: Interim Clinical Study Report for the MEDLEY trial.[18]

Table 7: Baseline Characteristics — MELODY Trial and Study 3 (ITT Population)

Patient characteristic	MELODY		Study 3	
	Nirsevimab N = 994	Placebo N = 496	Nirsevimab N = 969	Placebo N = 484
Age, mean (SD), months	2.9 (2.21)	3.0 (2.25)	3.3 (2.22)	3.3 (2.31)
Age group, n (%)				
≤ 3 months	577 (58.0)	285 (57.5)	516 (53.3)	257 (53.1)
> 3 to ≤ 6 months	317 (31.9)	162 (32.7)	320 (33.0)	153 (31.6)
> 6 months	100 (10.0)	49 (9.9)	133 (13.7)	74 (15.3)
Sex, n (%)				
Female	464 (46.7)	257 (51.8)	468 (48.3)	224 (46.3)

Patient characteristic	MELODY		Study 3	
	Nirsevimab N = 994	Placebo N = 496	Nirsevimab N = 969	Placebo N = 484
Male	530 (53.3)	239 (48.2)	501 (51.7)	260 (53.7)
Race, n (%)				
White	524 (52.9)	272 (54.8)	693 (71.6)	355 (73.3)
Black or African American	286 (28.9)	136 (27.4)	189 (19.5)	67 (13.8)
American Indian or Alaska Native	57 (5.8)	26 (5.2)	0	1 (0.2)
Asian	36 (3.6)	18 (3.6)	5 (0.5)	10 (2.1)
Native Hawaiian or Pacific Islander	6 (0.6)	5 (1.0)	8 (0.8)	3 (0.6)
Other	70 (7.1)	38 (7.7)	61 (6.3)	43 (8.9)
Multiple categories checked	12 (1.2)	1 (0.2)	12 (1.2)	5 (1.0)
Weight, mean (SD), kg	5.5 (1.84)	5.6 (1.82)	4.6 (1.92)	4.5 (1.96)
Weight group, n (%)				
> 5 kg	403 (40.6)	192 (38.7)	NR	
≥ 5 kg	589 (59.4)	304 (61.3)		
GA, mean (SD), weeks	NR		32.7 (1.40)	32.7 (1.50)
GA group, n (%)				
≥ 35 to < 37 weeks	132 (13.3)	76 (15.4)	NR	
≥ 37 weeks	861 (86.7)	419 (84.6)		
Birth weight group, n (%)				
≤ 2.5 kg	145 (14.6)	88 (17.7)	NR	
> 2.5 kg	848 (85.4)	408 (82.3)		
Multiple births, n (%)				
Yes	96 (9.7)	45 (9.1)	NR	
No	897 (90.3)	451 (90.9)		
Down syndrome, n (%)	3 (0.3)	0	NR	
Cystic fibrosis, n (%)	0	1 (0.2)	NR	
Siblings enrolled in the study, n (%)				
Yes	NR		336 (34.7)	172 (35.5)
No			633 (65.3)	312 (64.5)

GA = gestational age; ITT = intent to treat; NR = not reported; SD = standard deviation.

Note: The number of patients with nonmissing data for the corresponding characteristics was used as the denominator for calculating percentages for each category.

Sources: Interim Clinical Study Report for the MELODY trial.[19] Final Clinical Study Report for Study 3.[20]

Key Efficacy Results

Key efficacy results for the MEDLEY trial are presented in Table 8. The primary outcome of medically attended RSV LRTI in season 1 was observed in 4 patients (0.6%) in the nirsevimab group and 3 patients (1.0%) in the palivizumab group. No statistical comparison between treatment arms was reported for the efficacy outcomes assessed in the trial. The secondary outcome of medically attended RSV LRTI with hospitalization in season 1 was reported in 2 patients (0.3%) in the nirsevimab group and 2 patients (0.6%) in the palivizumab group. No results were available at the time of the review pertaining to the second RSV season. Additional exploratory efficacy analyses included caregiver burden and antidrug antibody response.

The key efficacy results for the MELODY primary efficacy cohort and for Study 3 are presented in Table 9.

The reduction in the risk of experiencing medically attended RSV LRTI associated with the use of nirsevimab was 74.5% (95% CI, 49.6 to 87.1; P < 0.0001) in the MELODY trial and 70.1% (95% CI, 52.3 to 81.2; P < 0.0001) in Study 3 compared with placebo in healthy term and preterm infants entering their first RSV season. Results of the supporting models for analysis of the primary outcome confirmed the magnitude of the risk reduction associated with nirsevimab when compared with placebo in both studies.

As for the secondary outcome in the studies, the reduction in the risk of experiencing medically attended RSV LRTI with hospitalization was 62.1% (95% CI, −8.6 to 86.8; P = 0.07) in the MELODY trial and 78.4% (95% CI, 51.9 to 90.3; P = 0.0002) in Study 3. When results from the MELODY trial (primary efficacy cohort) and Study 3 are pooled together, the use of nirsevimab was associated with a reduction of 73.5% (95% CI, 50.2 to 85.9; P < 0.0001) in the risk of RSV hospitalization compared with placebo. The RRR was 77.3% (95% CI, 50.3 to 89.7; P = 0.0002) when only patients who received the recommended dose according to their body weight (patients < 5 kg) in Study 3 were included.

Additional exploratory outcomes included very severe medically attended RSV LRTI; in the pooled analysis of the MELODY trial (primary efficacy cohort) and Study 3 (patients < 5 kg), the use of nirsevimab was associated with a reduction in the risk of experiencing very severe medically attended RSV LRTI of 86.0% (95% CI, 62.5 to 94.8; P < 0.0001) compared with placebo.

Study 3 reported health care resource utilization in patients who had a primary outcome event. In addition, both studies reported on the caregiver burden and antidrug antibody response. However, no statistical analyses were reported comparing the effect of nirsevimab versus placebo on any of these exploratory outcomes.

Table 8: Key Efficacy Results — Descriptive Analysis of Nirsevimab vs. Palivizumab in the MEDLEY Trial for First RSV Season, Through Day 150 (ITT Population)

Outcomes	Overall		Cohort 1 — Preterm		Cohort 2 — CLD or CHD	
	Nirsevimab N = 616	Palivizumab N = 309	Nirsevimab N = 407	Palivizumab N = 208	Nirsevimab N = 209	Palivizumab N = 101
Primary outcome in the trial: Medically attended RSV LRTI in season 1						
Primary analysis DCO through day 150						
ITT population, n (%)	4 (0.6)	3 (1.0)	2 (0.5)	1 (0.5)	2 (1.0)	2 (2.0)
RSV subtype, n (%)						
RSV A	4 (0.6)	1 (0.3)	2 (0.5)	1 (0.5)	2 (1.0)	0
RSV B	0	2 (0.6)	0	0	0	2 (2.0)
Secondary outcome in the trial: Medically attended RSV LRTI with hospitalization in season 1						
Inpatient, n (%)	2 (0.3)	2 (0.6)	0	0	2 (1.0)	2 (2.0)
Outpatient, n (%)	2 (0.3)	1 (0.3)	2 (0.5)	1 (0.5)	0	0
Emergency department	1 (0.2)	0	1 (0.2)	0	0	0
Urgent care	0	1 (0.3)	0	1 (0.5)	0	0
Outpatient clinic	1 (0.2)	0	1 (0.2)	0	0	0
Exploratory outcomes in the trial						
Caregiver burden for families of patients with medically attended RSV LRTI in season 1						
Number of days of work missed for caregiver, mean (range)	2.0 (2 to 2)	1.5 (1 to 2)	2.0 (2 to 2)	1.0 (1 to 1)	0	2.0 (2 to 2)
ADA response						
Number of responders	581	286	384	193	197	93
ADA positive, n (%)	12 (2.1)	15 (5.2)	11 (2.9)	11 (5.7)	1 (0.5)	4 (4.3)

ADA = antidrug antibody; CHD = congenital heart disease; CLD = chronic lung disease; DCO = data cut-off; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus; vs. = versus.

Source: Interim Clinical Study Report for the MEDLEY trial.[18]

Table 9: Key Efficacy Results — Nirsevimab vs. Placebo in the MELODY Trial (Primary Efficacy Cohort) and Study 3 (All Patients) for First RSV Season, Through Day 150 (ITT Population)

Outcomes	MELODY		Study 3	
	Nirsevimab N = 994	Placebo N = 496	Nirsevimab N = 969	Placebo N = 484
Primary outcome in the trial: Medically attended RSV LRTI in season 1				
Primary analysis: Poisson regression with robust variance				
Patients with observed events, n (%)	12 (1.2)	25 (5.0)	25 (2.6)	46 (9.5)
RRR (95% CI); P value[a,b]	74.5% (49.6 to 87.1); P < 0.0001		70.1% (52.3 to 81.2); P < 0.0001	
Supporting analysis model: Poisson regression with robust variance with adjustment of follow-up time				
Patients with observed events, n (%)	12 (1.2)	25 (5.0)	25 (2.6)	46 (9.5)
RRR (95% CI); P value[c]	76.5% (53.2 to 88.2); P < 0.0001		73.9% (57.5 to 84.0); P < 0.0001	
Supporting analysis model: Stratified Cochran-Mantel-Haenszel test				
Patients with observed events, n (%)	12 (1.2)	25 (5.0)	25 (2.6)	46 (9.5)
RRR (95% CI); P value[d]	76.1% (52.7 to 87.9); P < 0.0001		72.9% (56.5 to 83.1); P < 0.0001	
RSV subtype, n (%)				
RSV A	12 (1.2)	21 (4.2)	11 (1.1)	24 (5.0)
RSV B	0	4 (0.8)	14 (1.4)	22 (4.5)
Secondary outcome in the trial: Medically attended RSV LRTI with hospitalization in season 1				
Patients with observed events, n (%)	6 (0.6)	8 (1.6)	8 (0.8)	20 (4.1)
RRR (95% CI); P value[e]	62.1% (−8.6 to 86.8); P = 0.07		78.4% (51.9 to 90.3); P = 0.0002	
Pooled MELODY primary efficacy cohort and Study 3 all patients	N = 1,963 (Nirsevimab)		N = 980 (Placebo)	
Patients with observed events, n (%)	14 (0.7) (Nirsevimab)		28 (2.9) (Placebo)	
RRR (95% CI); P value[e]	73.5% (50.2 to 85.9); P < 0.0001			
Pooled MELODY primary efficacy cohort and Study 3 patients < 5 kg	N = 1,564 (Nirsevimab)		N = 786 (Placebo)	
Patients with observed events, n (%)	9 (0.6) (Nirsevimab)		21 (2.7) (Placebo)	
RRR (95% CI); P value[e]	77.3% (50.3 to 89.7); P = 0.0002			
Exploratory outcomes in the trial				
Pooled MELODY primary efficacy cohort and Study 3 patients < 5 kg	N = 1,564 (Nirsevimab)		N = 786 (Placebo)	

Outcomes	MELODY		Study 3	
	Nirsevimab N = 994	Placebo N = 496	Nirsevimab N = 969	Placebo N = 484
Very severe medically attended RSV LRTI, n (%)	5 (0.3) (Nirsevimab)		18 (2.3) (Placebo)	
RRR (95% CI); P value[e]	86.0% (62.5 to 94.8); P < 0.0001			
Health care resource utilization and caregiver burden for patients with medically attended RSV LRTI (primary outcome)				
Hospital admission, n (%)	NR		8 (32.0)	20 (43.5)
Duration in days, mean (range)			7.5 (3 to 14)	8.3 (2 to 20)
ICU admission, n (%)			0	5 (10.9)
Duration in days, mean (range)			NA	7.4 (3 to 14)
Respiratory support (CPAP), n (%)			0	4 (8.7)
Duration in days, mean (range)			NA	3.8 (2 to 6)
Supplemental oxygen use, n (%)			4 (16.0)	15 (32.6)
Duration in days, mean (range)			9.0 (6 to 13)	5.5 (1 to 13)
Prescription medications, n (%)			21 (84.0)	42 (91.0)
Average number of drugs per event			2.8	2.9
Duration in days, mean (SD)			33 (48.8)	27 (44.5)
OTC medications, n (%)[f]			6 (24.0)	11 (24)
Duration in days, mean (SD)			4.8 (5.2)	34.4 (86.2)
Caregiver work missed, mean (SD), days	6.2 (6.3)	2.0 (1.0)	8.8 (16.7)	7.5 (4.5)
Outpatient RSV LRTI, n (%)	6 (0.6)	17 (3.4)	17 (1.8)	26 (5.4)
Emergency department	1 (0.1)	1 (0.2)	2 (0.2)	5 (1.0)
Urgent care	0	1 (0.2)	2 (0.2)	2 (0.4)
Outpatient clinic	5 (0.5)	15 (3.0)	13 (1.3)	19 (3.9)
ADA Response	N = 951	N = 473	N = 929	N = 469
ADA positive, n (%)	58 (6.1)	5 (1.1)	52 (5.6)	18 (3.8)

ADA = antidrug antibody; CI = confidence interval; CPAP = continuous positive airway pressure; ICU = intensive care unit; LRTI = lower respiratory tract infection; NA = not applicable; NR = not reported; OTC = over the counter; RRR = relative risk reduction; RSV = respiratory syncytial virus; SD = standard deviation.

[a]In the MELODY trial, 15 patients (1.5%) receiving nirsevimab and 6 patients (1.2%) receiving placebo required imputation (i.e., they had no events and were not followed through 150 days postdose). In Study 3, this was the case for 24 patients (2.5%) receiving nirsevimab and 11 patients (2.3%) receiving placebo.

[b]For RRR nirsevimab versus placebo, the 95% CI and P value estimated were based on a Poisson regression with robust variance (with age group as a covariate) after missing data imputation.

[c]For RRR nirsevimab versus placebo, the 95% CI and P value estimated were based on a Poisson regression with robust variance (with age group as a covariate) with log (follow-up time) as an offset.

[d]RRR nirsevimab versus placebo, the 95% CI and P value were estimated based on the stratified Cochran-Mantel-Haenszel test (adjusted for the stratification factor of age group at randomization).

[e]Based on a Poisson regression with robust variance.

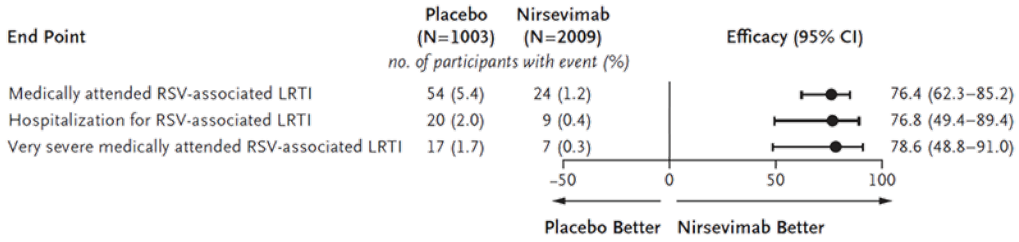
Sources: Interim Clinical Study Report for the MELODY trial.[19] Final Clinical Study Report for Study 3.[20]

Results for the key efficacy outcomes in the MELODY full complementary safety cohort are presented in Figure 1.[24] Point estimates and associated CIs were consistent with those obtained in the primary efficacy

cohort. In the full complementary safety cohort, the use of nirsevimab compared with placebo was associated with a reduction in the risk of medically attended RSV LRTI of 76.4% (95% CI, 62.3 to 85.2), a reduction in the risk of medically attended RSV LRTI with hospitalization of 76.8% (95% CI, 49.4 to 89.4), and a reduction in the risk of very severe medically attended RSV LRTI of 78.6% (95% CI, 48.8 to 91.0).

Results of supplementary time-to-event analyses for the primary outcome, that is, Kaplan-Meier estimates for time-to-first medically attended RSV LRTI, are shown in Figure 2 for MELODY and Figure 3 for Study 3.

Figure 1: Medically Attended RSV LRTI — MELODY Full-Cohort Population for First RSV Season, Through Day 150

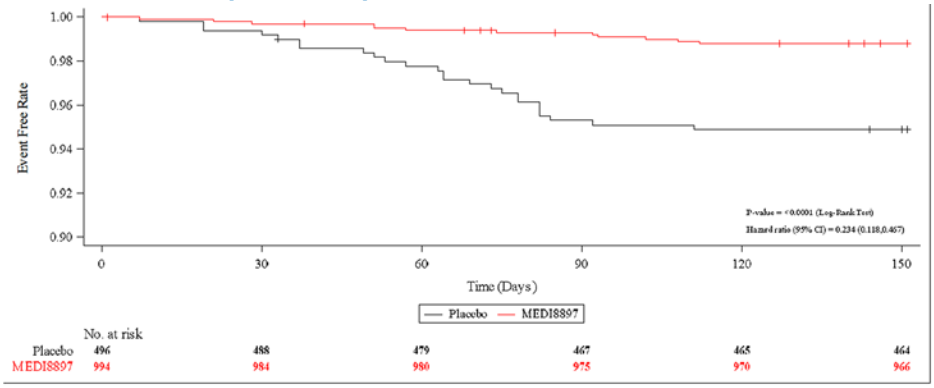


CI = confidence interval; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus.

Note: Very severe medically attended RSV-associated LRTI was defined as infection for which hospitalization and supplemental oxygen or IV fluids were warranted. Data are from the intent-to-treat population, which consisted of all infants who had undergone randomization.

Source: Muller et al. 2023. From *The New England Journal of Medicine*, Muller MJ, Madhi SA, Seoane Nuñez B et al. Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants. Volume No. 388, p.1553-1534. Copyright © 2023 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[24]

Figure 2: Kaplan-Meier Estimate for Time-to-First Medically Attended RSV LRTI — MELODY Primary Efficacy Cohort for First RSV Season, Through Day 150 (ITT Population)

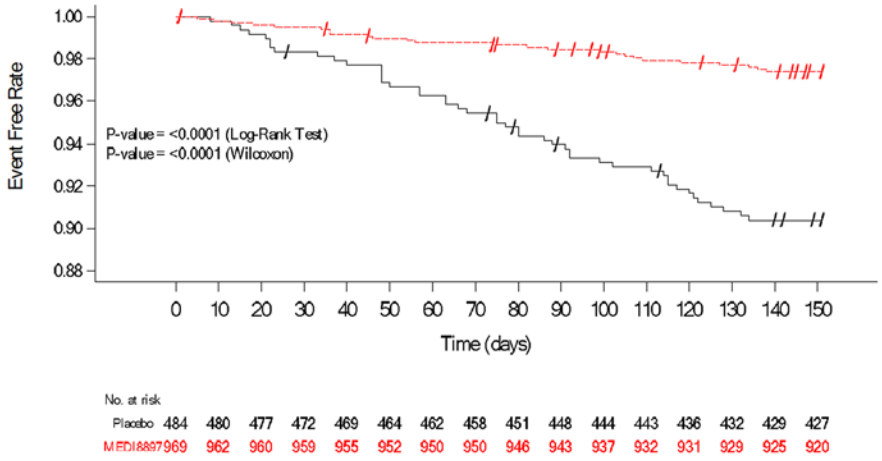


CI = confidence interval; ITT1 = intent-to-treat population 1; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; RSV = respiratory syncytial virus.

Notes: P values were obtained from stratified log-rank test with stratification factor (age at randomization) as the strata. Hazard ratio and the corresponding 95% CI were from a stratified Cox proportional hazard model with stratification factor (age at randomization). Tick marks indicate censored data.

Source: Interim Clinical Study Report for the MELODY trial.[19]

Figure 3: Kaplan-Meier Estimate for Time-to-First Medically Attended RSV LRTI — Study 3 for First RSV Season, Through Day 150 (ITT Population)



ITT = intent-to-treat; LRTI = lower respiratory tract infection; No = numbers; RSV = respiratory syncytial virus.
Note: P values were obtained from stratified log-rank test and Wilcoxon test with 2 stratification factors (age at randomization and hemisphere) as the strata.
Source: Final Clinical Study Report for Study 3.[20]

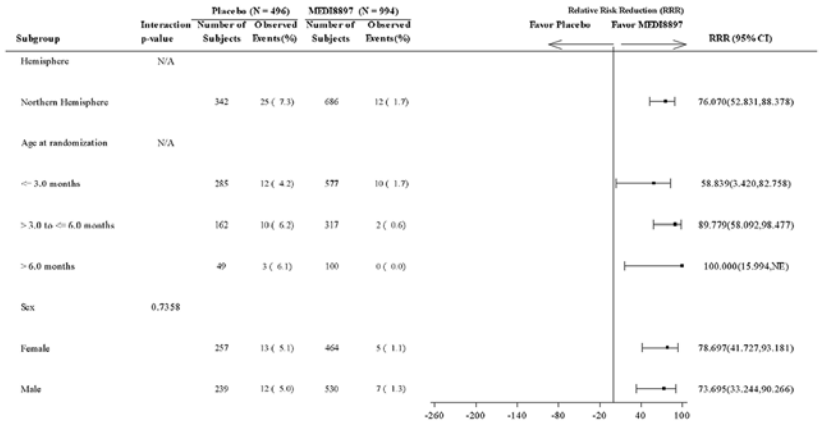
Subgroup Analyses

Selected subgroup analyses were reported for the primary outcome for the MELODY primary efficacy cohort and for Study 3; these are presented in Figure 4, Figure 5, Figure 6, Figure 7, and Figure 8. Subgroup results for the full complementary safety cohort in the MELODY trial were published by Muller et al. and were overall consistent with those from the primary analysis.[24]

Limited conclusions can be drawn from these analyses because the study was not designed to show a treatment difference between subgroups. As a result, the number of events occurring within in each individual subgroup is often too low to allow for conclusive statistical analysis between treatment arms.

In the subgroup analyses, the point estimates for most subpopulations were consistent with that of the overall population; however, they were associated with a wide CIs in some subgroups of patients that could overlap the null hypothesis, which was likely due to small sample sizes and low event rates within these subgroups. Therefore, in light of the previoulsy mentioned limitations, the subgroup results should be interpreted carefully.

Figure 4: Subgroup Analysis — Forest Plot for Medically Attended RSV LRTI in MELODY (Primary Efficacy Cohort) for First RSV Season, Through Day 150 (ITT Population)

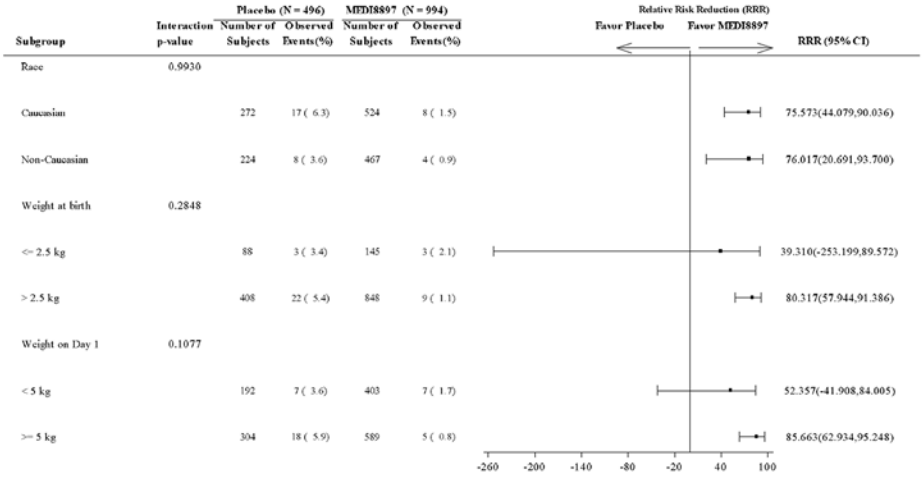


CI = confidence interval; ITT1 = intent-to-treat population 1; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; N = number of patients; RRR = relative risk reduction; RSV = respiratory syncytial virus.

Note: The interaction P value was obtained from Poisson regression with robust variance, including the terms of treatment group, age group, subgroup being tested, and treatment-by-subgroup interaction. The relative risk reduction and its 95% CI (mid-P adjusted) were estimated based on exact conditional method using PROC GENMOD with no strata. If RRR – 100% or – infinity, 1-sided 97.5% CI was reported.

Source: Interim Clinical Study Report for the MELODY trial.[19]

Figure 5: Subgroup Analysis — Forest Plot for Medically Attended RSV LRTI in MELODY (Primary Efficacy Cohort) for First RSV Season, Through Day 150 (ITT Population); Continued From Figure 4

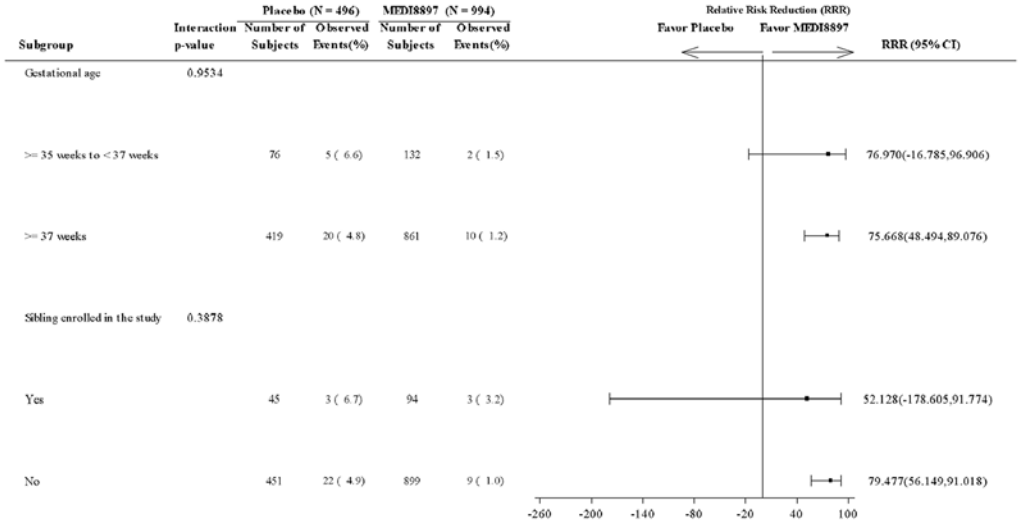


CI = confidence interval; ITT1 = intent-to-treat population 1; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; N = number of patients; RRR = relative risk reduction; RSV = respiratory syncytial virus.

Note: The interaction P value was obtained from Poisson regression with robust variance, including the terms of treatment group, age group, subgroup being tested, and treatment-by-subgroup interaction. The relative risk reduction and its 95% CI (mid-P adjusted) were estimated based on exact conditional method using PROC GENMOD with no strata. If RRR – 100% or – infinity, 1-sided 97.5% CI was reported.

Source: Interim Clinical Study Report for the MELODY trial.[19]

Figure 6: Subgroup Analysis — Forest Plot for Medically Attended RSV LRTI in MELODY (Primary Efficacy Cohort) for First RSV Season, Through Day 150 (ITT Population); Continued From Figure 4 and Figure 5

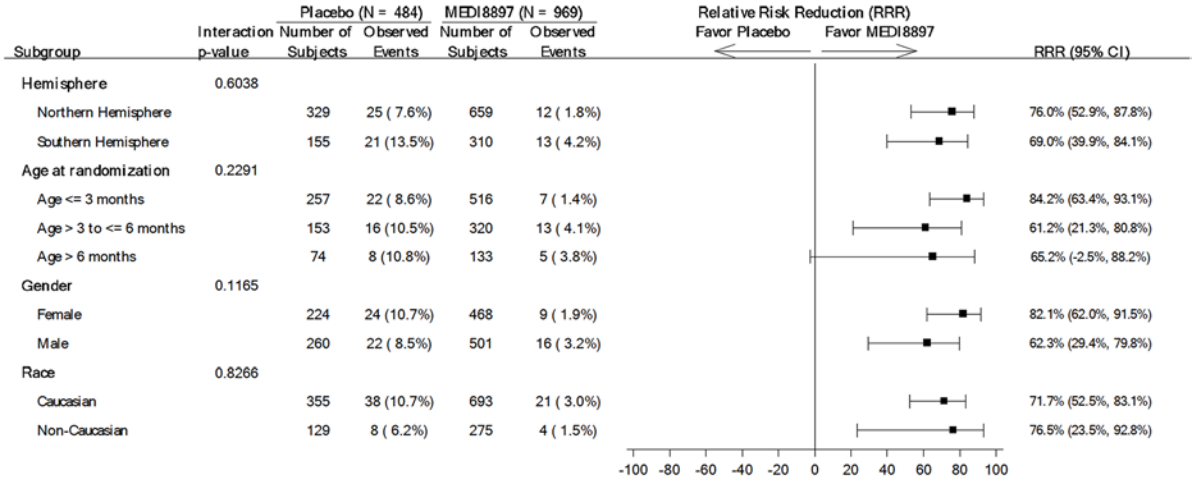


CI = confidence interval; ITT1 = intent-to-treat population 1; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; N = number of patients; RRR = relative risk reduction; RSV = respiratory syncytial virus.

Note: The interaction P value was obtained from Poisson regression with robust variance, including the terms of treatment group, age group, subgroup being tested, and treatment-by-subgroup interaction. The relative risk reduction and its 95% CI (mid-P adjusted) were estimated based on exact conditional method using PROC GENMOD with no strata. If RRR – 100% or – infinity, 1-sided 97.5% CI was reported.

Source: Interim Clinical Study Report for the MELODY trial.[19]

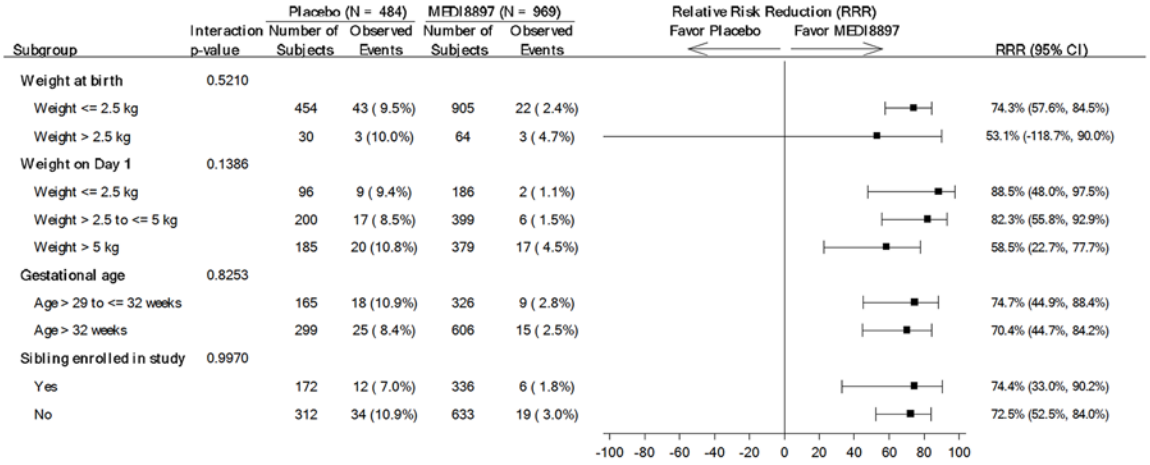
Figure 7: Subgroup Analysis — Forest Plot for Medically Attended RSV LRTI for Nirsevimab vs. Placebo in Study 3 for First RSV Season, Through Day 150 (ITT Population)



CI = confidence interval; ITT = intention-to-treat; LRTI = lower respiratory tract infection; RRR = relative risk reduction; RSV = respiratory syncytial virus; vs. = versus.

Source: Final Clinical Study Report for Study 3.[20]

Figure 8: Subgroup Analysis — Forest Plot for Medically Attended RSV LRTI for Nirsevimab vs. Placebo in Study 3 for First RSV Season, Through Day 150 (ITT Population); Continued From Figure 7



CI = confidence interval; ITT = intent-to-treat; LRTI = lower respiratory tract infection; RRR = relative risk reduction; RSV = respiratory syncytial virus; vs. = versus.
Source: Final Clinical Study Report for Study 3.[20]

Harms Results

For all trials, the safety analyses provide a 360-day follow-up duration (as treated population). Detailed harms results are presented in Table 10 and Table 11.

Throughout the first RSV season, 68% of patients who received nirsevimab or palivizumab experienced AEs in the MEDLEY trial. The most common AEs reported were consistent with acute respiratory illnesses and the proportions of patients experiencing the events were similar between treatment groups. These included upper respiratory tract infection, pyrexia, rhinitis, nasopharyngitis, and nasal congestion. The proportions of patients experiencing serious adverse events (SAEs) in the MEDLEY trial were 11.1% with nirsevimab and 10.2% with palivizumab. One patient in the nirsevimab treatment group discontinued the study due to maculopapular rash.

A total of 5 patients (0.8%) who received nirsevimab died during the available study follow-up; the causes of death were COVID-19, bronchiolitis, pneumonia, cardiogenic shock, and cardiac congestive failure. In the palivizumab group, 1 patient (0.3%) died of bronchiolitis. No deaths were considered to be related to the study treatment and all events occurred in patients with serious, complex underlying medical conditions. However, the proportions of patients who died in the nirsevimab group were numerically higher than the corresponding proportions in the palivizumab group.

Throughout the first RSV season, 87% of patients who received nirsevimab or placebo experienced AEs in the MELODY trial (primary efficacy cohort), and 86% of patients who received nirsevimab and 87% of patients who received placebo experienced AEs in Study 3. As was previously described for the MEDLEY trial, the most common AEs reported were consistent with acute respiratory illnesses and the proportions of patients

experiencing the events were similar between treatment groups. The proportions of patients experiencing SAEs in the MELODY trial were 6.8% with nirsevimab and 7.3% with placebo; in Study 3, these proportions were 11.2% with nirsevimab and 16.9% with placebo. Withdrawals due to AEs were not evaluated in the MELODY trial or in Study 3.

In the MELODY trial, 3 patients (0.3%) who received nirsevimab died during the available study follow-up; the causes of death, gastroenteritis for 2 patients and unknown for the third patient, were considered to be unrelated to the study treatment. No deaths were reported in the placebo group. In Study 3, there were 2 patients (0.2%) in the nirsevimab group and 3 patients (0.6%) in the placebo group who died throughout the study. The causes of death were pulmonary vein stenosis and unknown in the active treatment group and pneumonia and pericardial effusion in the placebo group.

Further information on harms results in the full MELODY complementary safety cohort have been published by Muller et al. and are being described in this paragraph.[24] In the full MELODY complementary safety cohort, the proportions of patients who experienced AEs throughout the trial were 84% in patients who received nirsevimab (n = 1,673 and N = 1,998) and 82% in patients who received placebo (n = 815 and N = 996).[24] The proportions of patients reporting SAEs were 6.3% in patients who received nirsevimab (n = 125 and N = 1,998) and 7.4% in patients who received placebo (n = 74 and N = 996).[24] One additional death was reported in the nirsevimab group due to a road traffic accident.

Table 10: Key Harms Results — MEDLEY Trial for First RSV Season, Through Day 360

Harms	Overall		Cohort 1 — Preterm		Cohort 2 — CLD or CHD	
	Nirsevimab N = 614	Palivizumab N = 304	Nirsevimab N = 406	Palivizumab N = 206	Nirsevimab N = 208	Palivizumab N = 98
AEs, n (%)	**416 (67.8)**	**206 (67.8)**	**268 (66.0)**	**134 (65.0)**	**148 (71.2)**	**72 (73.5)**
Most common events (reported in ≥ 5% of patients in any cohort treatment arm), n (%)						
URTI	125 (20.4)	65 (21.4)	95 (23.4)	47 (22.8)	30 (14.4)	18 (18.4)
Pyrexia	71 (11.6)	30 (9.9)	47 (11.6)	23 (11.2)	24 (11.5)	7 (7.1)
Rhinitis	69 (11.2)	32 (10.5)	45 (11.1)	25 (12.1)	24 (11.5)	7 (7.1)
Nasopharyngitis	42 (6.8)	31 (10.2)	26 (6.4)	14 (6.8)	16 (7.7)	17 (17.3)
Nasal congestion	38 (6.2)	13 (4.3)	30 (7.4)	11 (5.3)	8 (3.8)	2 (2.0)
Constipation	35 (5.7)	19 (6.3)	16 (3.9)	10 (4.9)	19 (9.1)	9 (9.2)
Teething	30 (4.9)	14 (4.6)	17 (14.2)	11 (5.3)	13 (6.3)	3 (3.1)
Viral URTI	29 (4.7)	10 (3.3)	14 (3.4)	4 (1.9)	15 (7.2)	6 (6.1)
Gastroenteritis	20 (3.3)	12 (3.9)	14 (3.4)	11 (5.3)	6 (2.9)	1 (1.0)
Vaccination complication	25 (4.1)	16 (5.3)	18 (4.4)	9 (4.4)	7 (3.4)	7 (7.1)
LRTI	10 (1.6)	6 (2.0)	5 (1.2)	1 (0.5)	5 (2.4)	5 (5.1)

Harms	Overall		Cohort 1 — Preterm		Cohort 2 — CLD or CHD	
	Nirsevimab N = 614	Palivizumab N = 304	Nirsevimab N = 406	Palivizumab N = 206	Nirsevimab N = 208	Palivizumab N = 98
SAEs, n (%)	**68 (11.1)**	**31 (10.2)**	**28 (6.9)**	**11 (5.3)**	**40 (19.2)**	**20 (20.4)**
Most common events (reported in ≥ 2 patients in any cohort treatment arm), n (%)						
Bronchiolitis	11 (1.8)	3 (1.0)	5 (1.2)	0	6 (2.9)	3 (3.1)
Gastroenteritis	5 (0.8)	1 (0.3)	0	1 (0.5)	5 (2.4)	0
Bronchitis	4 (0.7)	2 (0.7)	2 (0.5)	1 (0.5)	2 (1.0)	1 (1.0)
Pneumonia	4 (0.7)	1 (0.3)	1 (0.2)	0	3 (1.4)	1 (1.0)
COVID-19	3 (0.5)	1 (0.3)	3 (0.7)	1 (0.5)	0	0
Viral URTI	3 (0.5)	1 (0.3)	0	0	3 (1.4)	1 (1.0)
Sepsis	2 (0.3)	1 (0.3)	1 (0.2)	0	1 (0.5)	1 (1.0)
Urinary tract infection	2 (0.3)	1 (0.3)	1 (0.2)	0	1 (0.5)	1 (1.0)
Feeding intolerance	2 (0.3)	0	0	0	2 (1.0)	0
Pyrexia	2 (0.3)	0	1 (0.2)	0	1 (0.5)	0
Viral LRTI	2 (0.3)	0	1 (0.2)	0	1 (0.5)	0
Bradycardia	1 (0.2)	2 (0.7)	1 (0.2)	2 (1.0)	0	0
LRTI	1 (0.2)	2 (0.7)	0	0	1 (0.5)	2 (2.0)
WDAEs, n (%)	**1 (0.2)**	**0**	**1 (0.2)**	**0**	**0**	**0**
Maculopapular rash	1 (0.2)	0	1 (0.2)	0	0	0
Deaths, n (%)	**5 (0.8)**	**1 (0.3)**	**2 (0.5)**	**0**	**3 (1.4)**	**1 (1.0)**
COVID-19	1 (0.2)	0	1 (0.2)	0	0	0
Bronchiolitis	1 (0.2)	1 (0.3)	1 (0.2)	0	0	1 (1.0)
Pneumonia	1 (0.2)	0	0	0	1 (0.5)	0
Cardiogenic shock	1 (0.2)	0	0	0	1 (0.5)	0
Cardiac failure congestive	1 (0.2)	0	0	0	1 (0.5)	0

AE = adverse event; CHD = congenital heart disease; CLD = chronic lung disease; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus; SAE = serious adverse event; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

Source: Interim Clinical Study Report for the MEDLEY trial.[18]

Critical Appraisal and Interpretation of the Findings

The MEDLEY and MELODY trials and Study 3 were overall methodologically rigorous. However, some issues have been identified, mainly regarding how the study findings may be interpreted and applied to the Canadian clinical setting.

Table 11: Key Harms Results — MELODY Trial Primary Efficacy Cohort, Study 3, Through Day 360

Harms	MELODY		Study 3	
	Nirsevimab N = 987	Placebo N = 491	Nirsevimab N = 968	Placebo N = 479
AEs, n (%)	**863 (87.4)**	**426 (86.8)**	**834 (86.2)**	**416 (86.8)**
Most common events (reported in ≥ 5% of patients in any treatment arm), n (%)				
URTI	421 (42.7)	215 (43.8)	395 (40.8)	170 (35.5)
Pyrexia	141 (14.3)	63 (12.8)	111 (11.5)	64 (13.4)
Nasal congestion	120 (12.2)	68 (13.8)	71 (7.3)	24 (5.0)
Teething	111 (11.2)	53 (10.8)	62 (6.4)	32 (6.7)
Dermatitis diaper	110 (11.1)	47 (9.6)	76 (7.9)	36 (7.5)
Otitis media	97 (9.8)	52 (10.6)	64 (6.6)	42 (8.8)
Viral URTI	96 (9.7)	43 (8.8)	49 (5.1)	34 (7.1)
Gastroenteritis	89 (9.0)	42 (8.6)	122 (12.6)	46 (9.6)
Rhinorrhea	87 (8.8)	40 (8.1)	63 (6.5)	29 (6.1)
Rhinitis	80 (8.1)	41 (8.4)	111 (11.5)	50 (10.4)
Diarrhea	78 (7.9)	44 (9.0)	100 (10.3)	50 (10.4)
Conjunctivitis	71 (7.2)	31 (6.3)	86 (8.9)	39 (8.1)
Nasopharyngitis	65 (6.6)	51 (10.4)	164 (16.9)	94 (19.6)
Cough	64 (6.5)	31 (6.3)	37 (3.8)	15 (3.1)
Bronchiolitis	59 (6.0)	55 (11.2)	96 (9.9)	55 (11.5)
Rash	58 (5.9)	30 (6.1)	43 (4.4)	17 (3.5)
Constipation	56 (5.7)	26 (5.3)	34 (3.5)	21 (4.4)
Eczema	54 (5.5)	32 (6.5)	34 (3.5)	15 (3.1)
Otitis media acute	51 (5.2)	23 (4.7)	51 (5.3)	24 (5.0)
Bronchitis	34 (3.4)	21 (4.3)	96 (9.9)	55 (11.5)
LRTI	19 (1.9)	14 (2.9)	86 (8.9)	53 (11.1)
Pharyngitis	29 (2.9)	13 (2.6)	58 (6.0)	27 (5.6)
Oral candidiasis	39 (4.0)	18 (3.7)	36 (3.7)	26 (5.4)
SAEs, n (%)	**67 (6.8)**	**36 (7.3)**	**108 (11.2)**	**81 (16.9)**
Most common events (reported in > 2 patients in any group), n (%)				
Bronchiolitis	12 (1.2)	12 (2.4)	20 (2.1)	21 (4.4)
Gastroenteritis	7 (0.7)	0	9 (0.9)	4 (0.8)

Harms	MELODY		Study 3	
	Nirsevimab N = 987	Placebo N = 491	Nirsevimab N = 968	Placebo N = 479
Pneumonia	5 (0.5)	3 (0.6)	13 (1.3)	10 (2.1)
Pyrexia	5 (5.0)	0	3 (0.3)	1 (0.2)
LRTI	4 (0.4)	0	14 (1.4)	13 (2.7)
Urinary tract infection	3 (0.3)	2 (0.4)	0	4 (0.8)
Viral URTI	3 (0.3)	0	12 (1.2)	11 (2.3)
Bronchitis	NR		14 (1.4)	11 (2.3)
Pneumonia viral	NR		7 (0.7)	2 (0.4)
Viral LRTI	2 (0.2)	1 (0.2)	5 (0.5)	3 (0.6)
URTI	2 (0.2)	1 (0.2)	3 (0.3)	3 (0.6)
Inguinal hernia	NR		1 (0.1)	6 (1.3)
WDAEs, n (%)	**NE**		**NE**	
Deaths, n (%)	**3 (0.3)**	**0**	**2 (0.2)**	**3 (0.6)**
Gastroenteritis	2 (0.2)	0	0	0
Unknown	1 (0.1)	0	1 (0.1)	0
Pulmonary vein stenosis	0	0	1 (0.1)	0
Pneumonia	0	0	0	2 (0.4)
Pericardial effusion	0	0	0	1 (0.2)

AE = adverse event; LRTI = lower respiratory tract infection; NE = no evaluated; NR = not reported; SAE = serious adverse event; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

Sources: Interim Clinical Study Report for the MELODY trial.[19] Final Clinical Study Report for Study 3.[20]

The MEDLEY Trial

The MEDLEY study compared nirsevimab to palivizumab in a population of patients eligible to receive palivizumab, through descriptive analyses; therefore, the ability to use the results of this trial to inform the comparative effectiveness between the 2 prophylactic treatment options is limited. The number of primary outcome events reported throughout the first RSV season was particularly low in both treatment groups. Considering MEDLEY included a population at high risk for RSV disease (because of prematurity and/or CLD or CHD), a relatively high event rate without any prophylaxis would be expected. Therefore, these study results may suggest that both nirsevimab and palivizumab are effective in preventing LRTI associated with RSV throughout the first season, but any conclusion derived from the study remains unsubstantiated by formal statistical analysis.

At the time of the CADTH review, the MEDLEY trial was still ongoing. Results for the second RSV season in the MEDLEY trial were not available to the review team; according to the Health Canada product monograph for nirsevimab, no primary outcome event of medically attended RSV LRTI was reported through 150 days in

the second RSV season.[21] Considering the lack of evidence, no conclusions can be drawn on the efficacy and safety of nirsevimab in children entering their second RSV season.

The most common AEs reported in the MEDLEY trial were consistent with acute respiratory illnesses and were overall similar between treatment groups. The proportions of patients who died throughout the first RSV season were small, but numerically higher in patients receiving nirsevimab than in patients receiving palivizumab. Findings from the trial are based on a sample size of 925 patients; in reality, uncertainty around the safety profile of nirsevimab cannot be excluded, especially considering the possible widespread use of the drug.

The MELODY Trial and Study 3

Nirsevimab was compared to placebo in 2 trials, which, overall, included a population of healthy term and preterm infants (≥ 35 weeks in the MELODY trial and between 29 and 34 weeks in Study 3) entering their first RSV season and who were not eligible to receive palivizumab. At the time of this review, Study 3 is completed, but the MELODY trial is still ongoing. In terms of follow-up, efficacy results are available after 1 RSV season (150 days or 5 months) and safety results cover a period of 360 days, which is considered appropriate in a clinical trial setting and is representative of how nirsevimab will be used in clinical practice in infants entering their first RSV season.

The main efficacy findings from the MELODY trial and Study 3 appeared credible and were consistent with supporting analyses for the primary outcome and additional exploratory analyses for key secondary outcomes. These show that nirsevimab was consistently superior to placebo in reducing the risk of experiencing medically attended RSV LRTI in healthy term and preterm infants. The overall body of evidence collected from the MELODY full complementary safety cohort, from Study 3, and from an exploratory pooled analysis of the 2 trials, suggests that nirsevimab was also superior to placebo in reducing the risk of experiencing medically attended RSV LRTI with hospitalization in these patients. The lack of statistical significance in the MELODY primary efficacy cohort for this secondary outcome might be a result of the study's lack of power due to disruption by the COVID-19 pandemic that forced analysis based on a smaller cohort. Finally, the superiority of nirsevimab over placebo was demonstrated for the exploratory outcome of very severe medically attended RSV LRTI by a pooled analysis of the MELODY primary efficacy cohort and Study 3, as well as confirmed by results from the MELODY full complementary safety cohort.

In terms of magnitude and clinical meaningfulness, the relative results reported by the sponsor in their analysis of the data may be interpreted in light of the absolute risk reduction, as well, given that a relatively low number of events were observed in the trials. For example, consider the key secondary outcome of medically attended RSV LRTI with hospitalization in the pooled population of the MELODY trial (primary efficacy cohort) and Study 3 (patients who received the recommended dose of nirsevimab for their body weight). The event rates of 0.6% (n = 9 and N = 1,564) in the nirsevimab group and 2.7% (n = 21 and N = 786) in the placebo group result in a relative reduction of 77% in the risk of experiencing hospitalization from RSV disease (95% CI, 50 to 90; P = 0.0002), and also with an absolute risk reduction of 2.1% (i.e., 21 fewer hospitalizations from RSV disease per 1,000 patients treated with nirsevimab in clinical practice or 1 fewer hospitalization due to RSV disease for every 48 patients receiving nirsevimab, a number needed to

treat of 48). This suggests that, with a RRR of 77%, nirsevimab is effective in preventing the clinically serious outcome of hospitalization from RSV disease; however, this outcome is relatively infrequent in the overall population. Therefore, unless relevant subgroups of patients are identified, a large number of patients would need to receive nirsevimab in clinical practice to observe the benefits demonstrated in the clinical trials, with related costs and safety considerations.

Results of the subgroup analyses were mostly aligned with those of the total population; however, the MELODY trial and Study 3 were not designed for drawing conclusions for any subgroup. As such, the number of events occurring within in each individual subgroup is often too low to allow for conclusive statistical superiority of nirsevimab over placebo, with CIs overlapping the null hypothesis in some cases. Thus, these results cannot support firm conclusions regarding effects within subgroups of patients.

Similar proportions of patients reported AEs and SAEs in the active treatment and placebo groups in both studies. The most common AEs reported were consistent with acute respiratory illnesses. In the MELODY trial and Study 3, the proportions of patients who died throughout the studies were small; however, in the MELODY trial, all deaths occurring throughout the study follow-up, including in the full complementary safety cohort, were in patients receiving nirsevimab. All deaths were considered to be unrelated to the study treatment; however, paired with similar findings from the MEDLEY trial, this raises uncertainty regarding the safety profile of nirsevimab.

In terms of generalizability, findings from the MELODY trial and Study 3 are based on a sample size of approximately 3,000 patients for the main analyses, which is considered appropriate to show efficacy in the setting of clinical trials. In a Canadian clinical context, the effectiveness of nirsevimab may differ from what was observed in clinical trials, especially considering the selection criteria targeting very specific populations and consistently excluding some categories of patients. In addition, it should be noted that 40% of patients in each treatment group in Study 3 weighed 5 kg or more, so their recommended nirsevimab dose would be 100 mg. However, all patients in Study 3 who were in the nirsevimab group received a dose of 50 mg no matter their weight, which may result in an underestimation of the efficacy of nirsevimab, but also in an underestimation of harms events in the trial. Considering the overall evidence available, including unbalanced harms events between nirsevimab and comparators, uncertainty around the safety profile of the drug is of concern, especially considering its possible widespread use.

Evidence Gaps

The efficacy of nirsevimab as prophylactic treatment has been established over placebo in healthy term and preterm infants entering their first RSV season who were not eligible to receive palivizumab. Important gaps in the available evidence were noted by the CADTH clinical review team and include the following:

- No clinical trial formally assessed via statistical comparisons the efficacy of nirsevimab versus any other RSV prophylaxis option such as palivizumab; therefore, it is unknown whether these drugs are similar in preventing severe RSV disease in clinical practice.
- As an ongoing, descriptive safety study, MEDLEY had no hypothesis testing; therefore, the study provided no statistically informed efficacy assessment of nirsevimab in infants who are eligible to

receive palivizumab (i.e., who are at high risk of severe RSV disease, including term or preterm infants with clinically significant CLD or CHD).

- There is currently a lack of evidence regarding the clinical efficacy and safety of nirsevimab in children 24 months of age or younger who remain vulnerable to severe disease and who are entering their second RSV season. In this patient population, the efficacy of nirsevimab was established by extrapolation from the MELODY trial and Study 3 based on pharmacokinetic exposure.[21]
- There is a lack of efficacy and safety data in the following categories of patients, as these were systematically excluded from the nirsevimab clinical trials:
  - patients who had any prior RSV infection
  - patients with recent fever or acute illness, which would include patients with current symptoms of RSV infection, or in whom an RSV infection is suspected
  - patients who received any prior monoclonal antibody (including incomplete doses of palivizumab prophylactic treatment) for RSV specifically or for any other indication
  - patients with exposure to any prior RSV vaccination, including maternal RSV vaccination during pregnancy.
- Nirsevimab is approved for RSV prophylaxis; the efficacy and safety of the drug has not been evaluated in the treatment of RSV disease.
- There is a lack of data on nirsevimab pertaining specifically to rural or remote communities.
- The proportions of patients who died throughout the first RSV season, assessed as harms outcomes in the studies reviewed by CADTH, were small and considered to be unrelated to the study treatment; however, they were numerically higher in patients receiving nirsevimab compared to patients receiving palivizumab or placebo in the comparator group (i.e., in the 2 ongoing studies with results from interim analyses). Follow-up data in larger patient populations are needed to fully characterize the safety profile.

References

1. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet.* 2022;399(10340):2047-2064. PubMed
2. Health Canada. Respiratory syncytial virus (RSV): For health professionals. 2023; https://www.canada.ca/en/public-health/services/diseases/respiratory-syncytial-virus-rsv/health-professionals.html. Accessed 10 April 2023.
3. Public Health Agency of Canada. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI). Recommended use of palivizumab to reduce complications of respiratory syncytial virus infection in infants. 2022: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/vaccines-immunization/palivizumab-respiratory-syncitial-virus-infection-infants/palivizumab-resp-infection-infants-eng.pdf. Accessed 10 April 2023.
4. Duong D. What RSV interventions are in the research pipeline? *CMAJ.* 2023;195(1):E19-E20. PubMed
5. AstraZeneca Canada Inc, Sanofi Pasteur Ltd. Beyfortus (nirsevimab injection): solution for injection, 100 mg/mL, intramuscular use, 50 mg single-use, pre-filled syringe, 100 mg single-use, pre-filled syringe [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2022 Nov 1.
6. Health Canada. Respiratory syncytial virus: Canadian Immunization Guide. 2023; https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/respiratory-syncytial-virus.html. Accessed 10 April 2023.
7. CADTH. Procedures for CADTH Review of Nationally Procured Drug Products. June 2022: https://www.cadth.ca/sites/default/files/Drug_Review_Process/CADTH_Nationally_Procured_Drugs_Procedures.pdf. Accessed 10 April 2023.
8. Lorcy A, Gilca R, Dube E, Rochette M, De Serres G. Feasibility and ethical issues: experiences and concerns of healthcare workers regarding a new RSV prophylaxis programme in Nunavik, Quebec. *Int J Circumpolar Health.* 2020;79(1):1742564. PubMed
9. Pisesky A, Benchimol EI, Wong CA, et al. Incidence of Hospitalization for Respiratory Syncytial Virus Infection amongst Children in Ontario, Canada: A Population-Based Study Using Validated Health Administrative Data. *PLoS One.* 2016;11(3):e0150416. PubMed
10. Schanzer DL, Langley JM, Tam TW. Hospitalization attributable to influenza and other viral respiratory illnesses in Canadian children. *Pediatr Infect Dis J.* 2006;25(9):795-800. PubMed
11. Robinson JL, Le Saux N, Canadian Paediatric Society ID, Immunization C. Preventing hospitalizations for respiratory syncytial virus infection. *Paediatr Child Health.* 2015;20(6):321-333. PubMed
12. Bont L, Checchia PA, Fauroux B, et al. Defining the Epidemiology and Burden of Severe Respiratory Syncytial Virus Infection Among Infants and Children in Western Countries. *Infect Dis Ther.* 2016;5(3):271-298. PubMed
13. Paes B, Fauroux B, Figueras-Aloy J, et al. Defining the Risk and Associated Morbidity and Mortality of Severe Respiratory Syncytial Virus Infection Among Infants with Chronic Lung Disease. *Infect Dis Ther.* 2016;5(4):453-471. PubMed
14. Tam J, Papenburg J, Fanella S, et al. Pediatric Investigators Collaborative Network on Infections in Canada Study of Respiratory Syncytial Virus-associated Deaths in Pediatric Patients in Canada, 2003-2013. *Clin Infect Dis.* 2019;68(1):113-119. PubMed
15. Health Canada. Respiratory Virus Detections in Canada. 2023; https://www.canada.ca/en/public-health/services/surveillance/respiratory-virus-detections-canada.html. Accessed 10 April 2023.
16. European Medicines Agency. Beyfortus. 2023; https://www.ema.europa.eu/en/medicines/human/EPAR/beyfortus#authorisation-details-section. Accessed 10 April 2023.
17. Medical Professionals Reference. FDA Panel Votes in Favor of Nirsevimab for RSV Disease Prevention in Infants. 2023 Jun 9; https://www.empr.com/home/news/drugs-in-the-pipeline/fda-panel-votes-in-favor-of-nirsevimab-for-rsv-disease-prevention-in-infants/. Accessed 17 Jul 2023.
18. AstraZeneca. Clinical Study Report: D5290C00005. A phase 2/3 randomised, double-blind, palivizumab-controlled study to evaluate the safety of medi8897, a monoclonal antibody with an extended half-life against respiratory syncytial virus, in high-risk children (MEDLEY) Gaithersburg (MD): AstraZeneca; 2021 Oct 1.

19. AstraZeneca. Clinical Study Report: D5290C00004. A phase III randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of nirsevimab (MEDI8897), a monoclonal antibody with an extended half-life against respiratory syncytial virus, in healthy late preterm and term infants (MELODY). Gaithersburg (MD): AstraZeneca; 2021 Sep 27.
20. AstraZeneca. MedImmune LLC. A Study to Evaluate the Safety and Efficacy of MEDI8897 for the Prevention of Medically Attended RSV LRTI in Healthy Preterm Infants. (MEDI8897 Ph2b). ClinicalTrials.gov Identifier: NCT02878330. Rockville (MD): National Library of Medicine (U.S.); 2019 Oct 14. .
21. Health Canada. Beyfortus (nirsevimab injection). Solution for injection, 100 mg/mL, intramuscular use, 50 mg single-use, pre-filled syringe, 100 mg single-use, pre-filled syringe [product monograph]. Mississauga: AstraZeneca Canada Inc; 2023 Apr 19.
22. Domachowske J, Madhi SA, Simoes EAF, et al. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. *N Engl J Med.* 2022;386(9):892-894. PubMed
23. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *N Engl J Med.* 2022;386(9):837-846. PubMed
24. Muller WJ, Madhi SA, Seoane Nunez B, et al. Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants. *N Engl J Med.* 2023;388(16):1533-1534. PubMed
25. Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *N Engl J Med.* 2020;383(5):415-425. PubMed

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Questions or requests for information about this report can be directed to **Requests@CADTH.ca**.