Monoclonal antibodies for prevention of RSV LRTD in pediatric patients side-by-side comparison

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Executive Summary

Introduction

Respiratory syncytial virus (RSV) is a highly contagious human pathogen that is responsible for yearly epidemics during the winter season in the northern hemisphere. Typical RSV seasons in the US span October through March. Each year in the US RSV is associated with approximately 1.5 million outpatient visits, 58,000 to 80,000 hospitalizations and 100 to 300 deaths in children < 5 years of age. RSV is the most common cause of hospitalization in infants, and the highest risk of hospitalization occurs during the first months of life. Infants and children most susceptible to serious RSV illness include premature infants (with the highest risk among infants born < 29 weeks gestational age [GA]), children less than 2 years with chronic lung or heart disease, children who are immunocompromised and those with neuromuscular disorders. However, 79% of children < 2 years of age that are hospitalized due to RSV have no underlying medical conditions. Rates of severe disease are up to 10 times greater in American Indian and Alaska Native children compared with the general population.

Until recently, the only available therapy for prevention of RSV in pediatric patients was the monoclonal antibody therapy, palivizumab (Synagis), which was approved in 1998. Palivizumab is specifically indicated for use in high-risk infants and pediatric patients, which includes premature birth (≤ 35 weeks), children with bronchopulmonary disease (also referred to as chronic lung disease [CLD]), and children with hemodynamically significant congenital heart disease (CHD). Palivizumab is administered as a monthly intramuscular (IM) injection throughout the RSV season. On July 17, 2023, AstraZeneca and Sanofi's nirsevimab (Beyfortus) was approved. Nirsevimab is a new, long-acting monoclonal antibody for the prevention of RSV lower respiratory tract disease (LRTD), also referred to as lower respiratory tract infection (LRTI), in infants and children. Nirsevimab targets a unique antigenic site on the prefusion RSV F protein and is a more potent inhibitor of RSV than palivizumab *in vitro*. Nirsevimab also has a substantially longer half-life, allowing for a single IM dose for the entire RSV season. In addition to use in high-risk patients, nirsevimab is also approved for use in healthy, term infants for RSV LRTD prevention, making it the first FDA-approved drug for this indication.

Efficacy

Efficacy data reviewed here primarily focus on nirsevimab. The US Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee met on June 8, 2023, and voted unanimously (21-0) in favor of the efficacy of nirsevimab. Data from 3 pivotal trials were reviewed by the Committee and included a phase 2b study in preterm infants born at ≥ 29 to < 35 weeks GA; the phase 3 MELODY trial in predominantly healthy, normal term infants born at ≥ 35 weeks GA; and the phase 2/3 MEDLEY trial, which was a head-to-head comparison with palivizumab in premature infants and infants with CLD or CHD. Nirsevimab demonstrated a reduction in medically attended RSV LRTI (MA RSV LRTI) in preterm infants born at ≥ 29 weeks to < 35 weeks GA and in healthy term infants born at ≥ 35 weeks GA entering their first RSV season compared with placebo. A significant reduction in RSV-associated hospitalization through 150 days following nirsevimab compared with placebo was seen in preterm infants born at ≥ 29 weeks to < 35 weeks GA, but not in healthy term infants born at ≥ 35 weeks GA. Nirsevimab was compared with palivizumab in infants at higher risk for severe RSV disease, including preterm infants < 35 weeks GA and infants with CHD or CLD. Efficacy was evaluated as a descriptive endpoint across 2 RSV seasons. MA RSV LRTI through day 150 occurred in 0.6% (n = 4) of infants who received nirsevimab and 1% (n = 3) of infants who received palivizumab across the total study population. No infants in either nirsevimab or palivizumab groups experienced a MA RSV LRTI in RSV season 2. Overall, there are currently limited data on the efficacy of nirsevimab in certain high risk populations, such as extreme prematurity (born at < 29 weeks GA). These populations, among other high risk groups, have been better studied with palivizumab.

Guideline recommendations

The latest American Academy of Pediatrics (AAP) guidelines on palivizumab were published in 2014 and recently reaffirmed in 2023. The AAP 2014 guidelines outline specific, high-risk populations in whom palivizumab is recommended. On August 3, 2023, the Advisory Committee on Immunization Practices (ACIP) met to vote on recommendations for the use of nirsevimab. The complete recommendations were published in *Morbidity and Mortality Weekly Report* on August 25, 2023. ACIP recommended nirsevimab for use in all infants aged < 8 months who are born during or are entering their first RSV season and in children 8 to 19 months of age who are at increased risk of severe RSV disease and entering their second RSV season. Most recently, on August 15, 2023, AAP published a guidance statement on the use of nirsevimab. Recommendations addressed include eligible patient populations, timing of administration, choice of nirsevimab versus palivizumab, and co-administration of childhood vaccines. With regard to palivizumab versus nirsevimab, guidance from AAP seems to support a preferential

recommendation for the use of nirsevimab over palivizumab. Guideline recommendations from AAP and ACIP are presented in the side-by-side comparison table and discussed further in the summary of evidence section below.

Safety

Overall, nirsevimab appears to be safe and well tolerated across clinical studies. No cases of anaphylaxis have been reported in clinical studies. However, postmarketing surveillance for hypersensitivity reactions will be important to monitor. The rates of adverse events and event rates, including serious adverse events, were similar with nirsevimab in placebo-controlled studies and when evaluated head-to-head with palivizumab. The most common adverse reactions reported in palivizumab product labeling are fever (27%) and rash (12%). The most common adverse reactions reported in product labeling for nirsevimab are rash (0.9%) and injection-site reactions (0.3%).

Summary

Two monoclonal antibodies are approved for the prevention of RSV-associated LRTD. Palivizumab is specifically indicated for use in high-risk infants and pediatric patients. Palivizumab is administered as a monthly IM injection throughout the RSV season. Nirsevimab is a new, long-acting monoclonal antibody for the prevention of RSV LRTD in infants and children and is administered as single intramuscular dose. In addition to use in high-risk patients, nirsevimab is also approved for use in healthy, term infants for RSV LRTD prevention, making it the first FDA-approved drug for this indication. Nirsevimab has demonstrated efficacy for the prevention of MA RSV LRTI in preterm infants born at ≥ 29 to < 35 weeks GA and late-term and term infants born at ≥ 35 weeks GA. MA RSV LRTI was similar between nirsevimab and palivizumab based on a descriptive analysis of a head-to-head comparison in premature infants and infants with CLD or CHD. Overall, nirsevimab appears to be safe and well tolerated across clinical studies. When compared with palivizumab, the incidence of adverse reactions, including serious adverse reactions with nirsevimab was similar across treatment groups and cohorts. Nirsevimab will be added to the Center for Disease Control and Prevention’s childhood immunization schedule and Vaccines for Children program. It will be important for organizations to address potential administrative challenges this may present given that nirsevimab is classified as a drug and not a vaccine. Additional guidance from ACIP is expected around the use of the newly approved maternal RSV vaccination with respect to the use of monoclonal antibodies for the prevention of RSV.

Monoclonal antibodies for prevention of RSV LRTD in pediatric patients side-by-side comparison

	Generic name (brand name)	
	Palivizumab (Synagis)[1]	**Nirsevimab-alip (Beyfortus)[2]**
Manufacturer	Swedish Orphan Biovitrum	AstraZeneca / Sanofi
Approval date	June 19, 1998	July 17, 2023
FDA-approved indications		
Approved population	Infants and children ≤ 2 y	Infants and children ≤ 2 y
Indications	Prevention of serious LRTD caused by RSV in pediatric patients with: • History of premature birth (≤ 35 wks GA) and who are ≤ 6 mo of age at the beginning of RSV season • With BPD that required medical treatment within the previous 6 mo and who are ≤ 24 mo of age at the beginning of RSV season • With hemodynamically significant CHD and who are ≤ 24 mo of age at the beginning of RSV season	Prevention of LRTD caused by RSV in: • Infants and neonates born during or entering their first RSV season • Children up to 24 mo of age who remain vulnerable to severe RSV disease through their second RSV season
Limitations of use	The safety and efficacy of palivizumab have not been established for the treatment of RSV.	None listed in product labeling; however, this product is also only approved for use in the *prevention* of RSV.
Guideline recommendations		
ACIP	NA	**ACIP 2023**[3,4] Nirsevimab is recommended in: • Infants aged < 8 mo born during or entering their first RSV season. • Children aged 8 to 19 mo who are at increased risk of severe RSV disease* and entering their second RSV season. ** See AAP recommendations for children recommended to receive palivizumab when entering their second RSV season.*
AAP	**2014 guidelines (reaffirmed in 2023)**[5,6] Palivizumab may be considered in the following populations: • Preterm infants born before 29 wks, 0 d gestation who are < 12 mo old at the start of RSV season. • Preterm infants during the first year of life with CLD of prematurity, defined as gestational age < 32 wks, 0 d and a requirement for > 21% oxygen for ≥ the first 28 d after birth. During the second year of life, palivizumab is recommended only	**AAP 2023 guidance statement**[7] Recommendations for palivizumab vs nirsevimab: • If nirsevimab is administered, palivizumab should not be administered later that season. • If palivizumab was administered initially for the season and < 5 doses were administered, the infant should receive 1 dose of nirsevimab. No further palivizumab should be administered.

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	for infants who satisfy this definition of CLD of prematurity and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-mo period before the start of the second RSV season. • Infants with hemodynamically significant CHD, during the first year of life. • Children with anatomic pulmonary abnormalities or neuromuscular disorder that impairs the ability to clear airway secretions, during the first year of life. • Profoundly immunocompromised children during the RSV season who are younger than 24 mo of age. *Note: Special consideration on selection criteria for infants eligible for prophylaxis may be prudent for Alaska Native infants and American Indian populations.*	• If palivizumab was administered in season 1 and the child is eligible for RSV prophylaxis in season 2, the child should receive nirsevimab in season 2, if available. If nirsevimab is not available, palivizumab should be administered as previously recommended. Recommendations for nirsevimab: • Nirsevimab should be administered shortly before the start of the RSV season for infants younger than 8 mo. • Nirsevimab should be administered shortly before the start of the RSV season for infants and children 8 through 19 mo of age who are at increased risk of severe RSV disease (this includes children with CLD of prematurity, who are severely immunocompromised, with cystic fibrosis with severe lung disease or a weight-for-length < 10th percentile, and those who are American Indian or Alaska Natives). • Nirsevimab may be given to age-eligible infants and children who have not yet received a dose at any time during the season. • Only children who meet high-risk criteria should receive more than one dose of nirsevimab – 1 dose in their first RSV season and 1 dose in their second RSV season. Healthy newborns born at the end of RSV season who received nirsevimab around the time of delivery (first RSV season) should not receive a second dose entering their second season even if they are < 8 mo of age; conversely, healthy infants born at the end of their first RSV season who did not receive nirsevimab and are < 8 mo of age entering their second RSV season may receive 1 dose of nirsevimab.
Pharmacology		
Molecular entity	Humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology	
Mechanism of action	Monoclonal antibody directed to an epitope in the A antigenic site of the RSV F protein. Passive immunity against RSV is provided by the binding of the RSV envelope fusion protein (RSV F) on the surface of the virus, which prevents an essential step in the membrane fusion process. Cell-to-cell fusion of RSV-infected cells is also prevented.	Monoclonal antibody targeting the prefusion conformation of the RSV F protein. Nirsevimab binds to a conserved epitope in antigenic site Ø on the prefusion protein, which leads to inhibition of conformational changes in the F protein necessary for fusion of the viral and cellular membranes and viral entry. Nirsevimab is long-acting due to a triple amino acid substitution in the Fc region which increases binding to the neonatal Fc receptor leading to an increased serum half-life.

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	Palivizumab (Synagis)[1]	**Nirsevimab-alip (Beyfortus)[2]**
Half-life	20 to 24.5 d	71 d – duration of protection extends through 5 mo based on clinical data
Dosing and administration		
Dose	15 mg/kg body weight	**Neonates and infants – first RSV season:** • < 5 kg: 50 mg • ≥ 5 kg: 100 mg **Children at risk for severe RSV disease – second RSV season:** • 200 mg (2 x 100 mg)
Frequency and timing	• Administer prior to start of RSV season and give subsequent doses monthly through the RSV season. • Product labeling recommends dosing continue throughout the RSV season in children who develop an RSV infection. However, AAP recommends to discontinue monthly prophylaxis in children who experience breakthrough RSV hospitalization.[5] **AAP 2023[8]** • Historically, RSV seasons span October through March in the northern hemisphere; however, seasonality patterns were altered during the COVID-19 pandemic. AAP supports providing more than 5 consecutive doses of palivizumab in the presence of high RSV disease activity outside of the normal seasonal pattern. Data on this practice are limited, but several published studies have not demonstrated an increase in frequency or severity of adverse reactions with doses beyond 5 doses.[8]	• Given as a single dose. • For infants and neonates, administer starting from birth if born during or entering the RSV season. If born outside RSV season, administer prior to the start of RSV season considering duration of protection provided by nirsevimab. • For children at risk for severe RSV disease, administer prior to start of second RSV season (may be given during second RSV season if not initiated prior to start of the season). **AAP guidance 2023[7]** • Providers should aim for nirsevimab administration in the first week of life for infants born shortly before and during the RSV season based on geography. Administration can occur during the birth hospitalization or in the outpatient setting. Infants with prolonged birth hospitalizations because of prematurity or other causes should receive nirsevimab shortly before or promptly after discharge. • On the basis of pre-pandemic RSV infection patterns, nirsevimab may be administered in most of the continental US from October through the end of March. Because timing of the onset, peak, and decline of RSV activity may vary, providers can adjust administration schedules on the basis of local RSV activity in the community.
Need for redosing	Children undergoing cardiopulmonary bypass should receive an additional dose of palivizumab as soon as possible following the procedure. Resume monthly dosing thereafter.	An additional dose is recommended for children undergoing cardiopulmonary bypass surgery. The recommended dose depends on indications and timing of surgery.

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		Neonates and infants – first RSV season: • *Surgery ≤ 90 d since initial dose of nirsevimab:* administer additional dose based on body weight • *Surgery > 90 d since initial dose of nirsevimab*: administer 50 mg dose regardless of body weight **Children at risk for severe RSV disease – second RSV season:** • *Surgery ≤ 90 d since initial dose of nirsevimab*: administer additional dose of 200 mg (2 x 100 mg) • *Surgery > 90 d since initial dose of nirsevimab:* administer additional dose of 100 mg
Preparation	• Do not dilute. • Do not shake or vigorously agitate vial. • Use aseptic techniques to withdraw the appropriate volume of solution into the syringe using a needle. • Administer immediately after drawing the dose in to the syringe.	• Supplied in pre-filled syringes. • Do not shake. • Remove syringe cap and attach Luer lock needle to pre-filled syringe.
Administration	Intramuscular	Intramuscular – use separate injection sites for 200 mg dose (2 x 100 mg syringes)
Safety		
Contraindications	History of previous significant hypersensitivity reaction to palivizumab.	History of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the excipients.
Precautions	• **Hypersensitivity reactions:** Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to palivizumab. Ensure appropriate medical supervision and medications are available in the event of a hypersensitivity reaction. • **Coagulation disorders:** Use caution in children with thrombocytopenia or any coagulation disorder due to intramuscular administration. • **RSV diagnostic test interference:** Palivizumab may interfere with some antigen detection-based assays and viral culture assays which could lead to false-negative results. • **Treatment of RSV disease:** Safety and efficacy have not been established for the treatment of RSV disease.	• **Hypersensitivity reactions:** Cases of anaphylaxis have been observed with other IgG1 monoclonal antibodies. Ensure appropriate medical supervision and medications are available in the event of a hypersensitivity reaction. • **Coagulation disorders:** Use caution in children with thrombocytopenia or any coagulation disorder due to intramuscular administration.

	Generic name (brand name)	
	Palivizumab (Synagis)[1]	**Nirsevimab-alip (Beyfortus)[2]**
	• **Proper administration:** The SDV of palivizumab does not contain preservative; administration should occur immediately after withdrawing the dose. Do not re-enter the vial; discard any unused drug.	
Adverse reactions	The most common (incidence ≥ 10% and ≥ 1% more frequent than placebo) adverse reactions are fever (27%) and rash (12%).	The most common adverse reactions are rash (0.9%) and injection-site reactions (0.3%).
Drug-drug interactions	Formal drug-drug interaction studies have not been conducted. In clinical studies, the proportion of patients who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar between palivizumab and placebo groups; no increase in adverse reactions were observed in children receiving these agents.	• Nirsevimab may be given concomitantly with childhood vaccines; administer in separate syringes and at different injection sites. Nirsevimab is not expected to interfere with concomitantly administered vaccines. Safety and reactogenicity was similar compared with childhood vaccines administered alone in clinical trials.[7] • No information is available on the use of nirsevimab with other immunoglobulin products. Do not administer palivizumab to patients who have received nirsevimab. No data are available for substituting nirsevimab for palivizumab once prophylaxis treatment is initiated with palivizumab. *However, per 2023 guidance from AAP, nirsevimab is recommended for patients who have received < 5 doses of palivizumab during a current RSV season; when this is done, no further palivizumab should be administered.*[7]
Drug-lab interactions	Interference with immunologically-based RSV diagnostic assays has been observed following administration of palivizumab. Rapid chromatographic/enzyme immunoassays, immunofluorescence assays, and direct immunofluorescence assays using monoclonal antibodies targeting RSV F protein may be inhibited. Use caution when interpreting negative assay results from the above tests in the presence of clinical findings consistent with RSV infection. RT-PCR may be used to confirm RSV infection, as this test is not inhibited by palivizumab.	Nirsevimab does not interfere with RT-PCR or rapid antigen detection diagnostic assays that target antigenic site 1, 2, or 4 on the RSV fusion protein. Use RT-PCR to confirm negative immunological assay results in the setting of clinical observations consistent with RSV infection.
Special populations		
Pregnancy or lactation	NA	NA
Pediatric	The safety and effectiveness of palivizumab have not been established in children > 24 mo of age at the start of therapy.	The safety and effectiveness of nirsevimab have not been established in children > 24 mo of age at the start of therapy.

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	Palivizumab (Synagis)[1]	**Nirsevimab-alip (Beyfortus)[2]**
How supplied		
Supplied as	SDV, sterile liquid solution: • 50 mg / 0.5 mL • 100 mg / 1 mL	Pre-filled syringes • 50 mg / 0.5 mL • 100 mg / 1 mL
Preservatives	None	None
Storage prior to use	• Store vial refrigerated at 2˚C to 8˚C. • Do not freeze.	• Store refrigerated at 2˚C to 8˚C. May be kept at room temperature (20˚C to 25˚C) for up to 8 h. • Do not freeze or expose to heat.
Cost (WAC)[8]	• 50 mg vial: $1,821 • 100 mg vial: $3,438	• 50 mg pre-filled syringe: $495 • 100 mg pre-filled syringe: $495 *(200 mg dose will be $990 – 2 x 100 mg syringes)*
Ordering	Specialty distribution	• Direct purchasing via Sanofi's VaccineShop website • Wholesaler distribution
340B Drug Pricing	Yes	No
Insurance coverage	May be covered under pharmacy benefit, medical benefit, or both depending on the insurance plan.[9]	• Nirsevimab is expected to be covered under medical benefit.[9] • ACIP-recommend products considered preventive care are required to be covered by private insurance plans based on the Affordable Care Act. Therefore, nirsevimab is expected to be fully covered for most insured patients.
Vaccines for Children Program	Palivizumab is not covered under VFC.	Nirsevimab will be included in the VFC.[11]
Patient assistance program	Yes • Synagis Connect • Synagis Copay Assistance Program	NA

Summary of evidence

Background: RSV is a highly contagious human pathogen that is responsible for yearly epidemics during the winter season in the northern hemisphere. Typical RSV seasons in the US span October through March. However, during the COVID-19 pandemic, typical seasonality patterns of RSV were altered.[8] Additionally, areas outside of the continental US, such as Alaska, Hawaii, and overseas US territories may have variations in seasonality.[7] Infection with RSV does not confer long-term immunity. Partial protection against homologous strains of RSV following infection does occur, but reliable and durable protection is not achieved, and re-infection throughout life is common.[12]

Each year in the US RSV is associated with approximately 1.5 million outpatient visits, 58,000 to 80,000 hospitalizations and 100 to 300 deaths in children < 5 years of age.[13,14] For comparison, during the 2019-2020 influenza season, there were approximately 27,000 hospitalizations and 300 deaths related to influenza in children ≤ 4 years of age.[15] The majority (68%) of infants are infected with RSV during the first year of life, with almost all (97%) children infected by 2 years of age. RSV is the most common cause of hospitalization of infants, and the highest risk of hospitalization occurs during the first months of life. Infants and children most susceptible to serious RSV illness include premature infants (with the highest risk among infants born < 29 weeks GA), children less than 2 years with chronic lung or heart disease, children who are immunocompromised and those with neuromuscular disorders. However, 79% of children < 2 years of age that are hospitalized due to RSV have no underlying medical conditions.[4,5,13,14] Rates of severe disease are up to 10 times greater in American Indian and Alaska Native children compared with the general population.[4,16]

Until recently, the only available therapy for prevention of RSV LRTI in pediatric patients was the monoclonal antibody therapy, palivizumab (Synagis), which was approved in 1998. Palivizumab is specifically indicated for use in high-risk infants and pediatric patients, which includes premature birth (≤ 35 weeks), children with bronchopulmonary disease, and children with hemodynamically significant CHD. Palivizumab is administered as a monthly IM injection throughout the RSV season.[1] On July 17, 2023, AstraZeneca and Sanofi's nirsevimab (Beyfortus) was approved. Nirsevimab is a new, long-acting monoclonal antibody for the prevention of RSV LRTD in infants and children.[2] Nirsevimab targets a unique antigenic site on the prefusion RSV F protein and is a more potent inhibitor of RSV than palivizumab *in vitro.* Nirsevimab also has a substantially longer half-life, allowing for a single intramuscular dose for the entire RSV season.[6] In addition to use in high-risk patients, nirsevimab is also approved for use in healthy term infants for RSV LRTD prevention, making it the first FDA-approved drug for this indication.[2] Both palivizumab and nirsevimab are only approved for the prevention of RSV LRTD. Currently, there are no approved therapies approved for the treatment of RSV; treatment primarily consists of supportive care.[17]

Another possible prevention strategy for pediatric RSV disease is maternal RSV vaccination. On August 21, 2023, FDA approved Pfizer's RSV vaccine, Abrysvo, for use in pregnancy to prevent LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age.[18] Abrysvo was originally approved earlier this year in May for use in adults 60 years of age and older.[19] This is the first vaccine to be approved for maternal use to prevent RSV-associated LRTD in infants.[18] The other available RSV vaccine from GlaxoSmithKline, Arexvy, remains approved for use in adults 60 years of age and older only.[20] Maternal RSV vaccination status will be important to consider when making clinical decisions related to prevention strategies for RSV in infants and children; however, this review will be focused specifically on the monoclonal antibodies for prevention of RSV-associated LRTD in pediatrics.

Guidelines: The latest AAP guidelines on palivizumab were published in 2014 and recently reaffirmed in 2023. AAP 2014 guidelines outline specific, high-risk populations in whom palivizumab is recommended. These groups include premature infants (< 29 weeks GA), children with CLD, children with CHD, children with anatomic pulmonary abnormalities or neuromuscular disorder that impairs their ability to clear airway secretions, and children who are profoundly immunocompromised. Most of these recommendations are limited to patients within these risk groups who are < 12 months of age at the onset of RSV season. Patients with CLD who continue to require medical support and patients who are immunocompromised are also recommended to receive palivizumab up to 24 months of age. AAP also notes that special consideration may be prudent when assessing eligibility for prophylaxis in infants who are Alaska Natives or American Indian.[5,6] The AAP recommendations for palivizumab are provided in further detail in the side-by-side comparison table above. Of note, the specific populations recommended by AAP differ from the FDA-labeled indications. First, the age cut-off defined for premature births by AAP is < 29 weeks GA; AAP specifically recommends against the use of palivizumab in otherwise healthy infants born at ≥ 29 weeks GA. However, palivizumab is FDA-approved for use in premature infants who are ≤ 35 weeks GA who are ≤ 6 months of age at the start of RSV season. Additionally, palivizumab is FDA-labeled for use in children with CHD who are ≤ 24 months of age at the start of RSV season, while AAP recommends use of palivizumab in this population only within the first year of life.[1,5,6]

On August 3, 2023, ACIP met to vote on recommendations for the use of nirsevimab. The complete recommendations were published in the *Morbidity and Mortality Weekly Report* on August 25, 2023. The Committee recommended nirsevimab for use in all infants aged < 8 months who are born during or are entering their first RSV season and in children 8 to 19 months of age who are at increased risk of severe RSV disease and entering their second RSV season. Patients considered at increased risk for severe disease by ACIP include children with CLD with a need for continued medical support, children who are profoundly immunocompromised, children with cystic fibrosis who have manifestations of severe disease or a weight-for-length less than the tenth percentile, and children who are American Indian and Alaska Natives.[3,4] The FDA-labeled indications for nirsevimab also differ slightly from guideline recommendations. The first labeled indication is for infants and neonates born during or entering their first RSV season. The main difference here is the lack of specificity in age, while ACIP defines < 8 months as the cut-off for this population. The other FDA-approved indication for nirsevimab is for use in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, while ACIP recommends use in higher risk populations between the ages of 8 and 19 months of age who are entering their second RSV season.[2-4] However, given the duration of protection provided by nirsevimab, children who are given nirsevimab at 19 months of age would be expected to be protected through 24 months of age. Additionally, ACIP voted to include nirsevimab in the VFC program, which will ensure access to children without health insurance. ACIP also recommended nirsevimab be added to the childhood immunization schedule.[3,4] Palivizumab is not on the ACIP childhood immunization schedule.

On August 15, 2023, AAP published a guidance statement on the use of nirsevimab. Recommendations addressed include eligible patient populations, timing of administration, choice of nirsevimab versus palivizumab, and co-administration of childhood vaccines. The recommended patient populations provided by AAP coincide with those recommended by ACIP (ie, infants < 8 months of age at the start of RSV season and infants 8 to 19 months of age before the start of RSV season who are at increased risk of severe RSV disease). However, there are some points to note within the specific language behind the AAP recommendations. AAP clarifies that healthy infants born at the end of their first RSV season who did not receive nirsevimab and are < 8 months of age entering their second RSV season may receive 1 dose of nirsevimab. Additionally, there are some differences in the populations specifically identified as being high risk compared with the high risk populations defined in the AAP 2014 guidelines for palivizumab. Risk factors identified in the AAP 2023 guidance statement for the use of nirsevimab in patients 8 to 19 months of age match those identified by ACIP and include children with CLD of prematurity who require medical support, children who are severely immunocompromised, children with cystic fibrosis who have manifestations of severe lung disease, and American Indian and Alaska Native children. Notable differences from risk factors identified in palivizumab guidance from AAP 2014 include a lack of mention of children with CHD (risk factor for children < 12 months of age in AAP 2014), lack of mention of children with anatomic pulmonary abnormalities or neuromuscular disorder that impairs their ability to clear airway secretions (risk factor for children < 12 months of age in AAP 2014), inclusion of cystic fibrosis (previously, AAP 2014 guidelines noted there was insufficient evidence in this population), and a specific recommendation for use in Alaska Native and American Indian children (previous language in AAP 2014 guidelines was in regard to consideration for use in this population versus a recommendation).[7] In the case of children with CHD or anatomic pulmonary abnormalities or neuromuscular disorders, these children would presumably be covered during the first year of life based on the recommendations to provide nirsevimab to all infants < 8 months of age, which may be why these are not specifically mentioned in the latest AAP guidance.

With regard to palivizumab versus nirsevimab, AAP seemingly provides a preferential recommendation for the use of nirsevimab over palivizumab. Per AAP, if nirsevimab is not available or not feasible to administer, high-risk infants who are recommended to receive palivizumab in the first or second year of life should receive palivizumab, as previously recommended, until nirsevimab becomes available. If palivizumab is administered initially, but < 5 doses have been administered, the infant should receive 1 dose of nirsevimab, and no further palivizumab should be given. Additionally, if a child previously received palivizumab and is eligible for RSV prophylaxis in season 2, AAP recommends that the child receive nirsevimab instead of palivizumab.[7] The AAP 2023 recommendations for nirsevimab are provided in further detail in the side-by-side comparison table above. Timing of nirsevimab administration as well as co-administration with vaccines are also addressed in the side-by-side comparison table.

Efficacy: Palivizumab was approved over 25 years ago and experience with its use is established in clinical practice. Additionally, one of the pivotal trials that evaluated nirsevimab included a head-to-head evaluation versus palivizumab in infants at increased risk for severe RSV disease. As a result, the literature review provided here is focused primarily on nirsevimab.

FDA's VRBPAC met on June 8, 2023, and voted unanimously (21-0) in favor of the efficacy of nirsevimab.[21] Data from 3 pivotal trials were reviewed by the Committee and included a phase 2b study in preterm infants born at ≥ 29 to < 35 weeks GA; the phase 3 MELODY trial in predominantly healthy, late term and normal term infants born at ≥ 35 weeks GA; and the phase 2/3 MEDLEY trial, which was a head-to-head comparison with palivizumab in premature infants and infants with CLD or CHD.[22] Each of these studies are discussed in text below and summarized in Table 1.

Phase 2b study (Trial 03; NCT02878330)[23]
This was randomized, double-blind, multicenter, placebo-controlled trial in 1,453 preterm infants born at ≥ 29 weeks to < 35 weeks GA who were ≤ 1 year of age entering their first full RSV season. Infants were randomized 2:1 to receive a single IM injection of nirsevimab (n = 969) or placebo (n = 484) prior to the start of an RSV season. Participants were excluded from the trial if they met AAP guideline criteria for receiving prophylaxis with palivizumab. As discussed above, the cut-off for RSV prophylaxis in preterm infants for palivizumab prophylaxis defined by AAP is < 29 weeks GA.[5] Participants who were immunosuppressed, had CHD or BPD, or other significant medical conditions were also excluded. Additionally, prior receipt of palivizumab or an investigational maternal RSV vaccine were also exclusion criteria.

The primary end point was medically attended (ie, inpatient or outpatient care – this includes physician visits, urgent care, emergency room visits, and hospitalizations) RSV-associated LRTI (MA RSV LRTI) through 150 days after administration of the dose. MA RSV LRTI is considered a clinically meaningful endpoint by FDA.[22] The key secondary efficacy end point was hospitalization for RSV-associated LRTI through 150 days after administration of the dose. The definition for LRTI was met if an RSV test performed at the centralized study laboratory was positive, a physical examination indicated involvement of the lower respiratory tract (ie, presence of rhonchi, rales, crackles, or wheezing), and there was ≥ 1 indicator of clinical severity (ie, increased respiratory rate, hypoxemia in room air, or clinical signs of respiratory distress). Efficacy analyses were performed in the ITT population, and the study had > 99% power to detect a 70% relative risk reduction for the primary endpoint at a 2-sided significance level of 0.05, assuming an 8% event rate in the placebo group. Hierarchical testing was done to control for type 1 error related to multiplicity. MA RSV LRTI occurred in 2.6% (n = 25) of infants in the nirsevimab group and 9.5% (n = 46) of infants in the placebo group (RRR: 70.1%; 95% CI, 52.3-81.2%; *P* < .001). This corresponds to an ARR of 6.9% and a NNT of approximately 15. Hospitalization for RSV-associated LRTI occurred in 0.8% (n = 8) of infants in the nirsevimab group and 4.1% (n = 20) of infants in the placebo group (RRR: 78.4%; 95% CI, 51.9-90.3%; *P* < .001). The estimated ARR and NNT for hospitalization are 3.3% and 31, respectively. Efficacy for both MA RSV LRTI (HR: 0.26, 95% CI, 0.16-0.43) and hospitalization (HR: 0.19; 95% CI, 0.08-0.44) were maintained over the entire 150-day efficacy period. No deaths known to be due to RSV occurred in either study group.

Phase 3 MELODY (Trial 04; NCT03979313)[24]
This was randomized, double-blind, multicenter, international, placebo-controlled trial in 1,490 predominantly healthy, late preterm and normal term infants born at ≥ 35 weeks GA who were ≤ 1 year of age entering their first full RSV season. The majority of infants (~86%) were born at ≥ 37 weeks GA. Infants were randomized 2:1 to receive a single IM injection of nirsevimab (n = 994) or placebo (n = 496) prior to the start of an RSV season. Most infants (~58%) were administered study drug at ≤ 3 months of age. This is notable given that the risk of severe RSV infection is highest in the first few months of life. Participants were excluded from the trial if they met AAP guideline criteria for receiving prophylaxis with palivizumab (eg, immunosuppressed, CHD, BPD, or other significant medical condition). Additionally, prior receipt of palivizumab or an investigational RSV vaccine were also exclusion criteria.

The primary end point was MA RSV LRTI through 150 days after administration of the dose. The key secondary efficacy end point was hospitalization for RSV-associated LRTI through 150 days after administration of the dose. Endpoint definitions in this study were consistent with those used in the phase 2b study (Trial 03). Efficacy analyses were performed in the ITT population, and the study had > 99% power to detect a 70% relative risk reduction for the primary endpoint at a 2-sided significant level of 0.05, assuming an 8% event rate in the placebo group. Hierarchical testing was done to control for type 1 error related to multiplicity. MA RSV LRTI occurred in 1.2% (n = 12) of infants in the nirsevimab group and 5% (n = 25) of infants in the placebo group (RRR: 74.5%; 95% CI, 49.6-87.1%; *P* < .001). This corresponds to an ARR of 3.8% and a NNT of approximately 27. Efficacy for MA LRTI (HR: 0.23, 95% CI, 0.12-0.47) was maintained over the entire 150-day efficacy period. In a subgroup analysis by GA, the point estimate for prevention of RSV LRTI appeared to be higher for infants born between ≥ 35 weeks to < 37 weeks compared with ≥ 37 weeks; however, formal hypothesis testing for this analysis was not conducted. Additionally, descriptive data reported for clinical signs of RSV LRTI do not seem to demonstrate a reduction in severity of illness between nirsevimab and placebo in cases of documented RSV LRTI. For example, a larger proportion of patients with RSV LRTI who received nirsevimab (5/12; 42%) experienced hypoxemia compared with placebo (7/25; 28%). However, the number of events are low and no formal testing was conducted for these data; therefore, no conclusions can be made with regard to attenuation of illness in those infants who developed RSV LRTI. The secondary efficacy endpoint of hospitalization for RSV-associated LRTI was not significantly different between groups. Hospitalization occurred in 0.6% (n = 6) of infants in the nirsevimab group and 1.6% (n = 8) of infants in the placebo group (RRR: 62.1%; 95% CI, -8.6-86.8%; *P* = NS). While hospitalization events were low, the mean (SD) number of hospitalized days was numerically higher with nirsevimab (7.2 [4.6]) compared with placebo (4 [2.2]) in infants hospitalized due to RSV LRTI. These data are descriptive in nature and no formal conclusions may be drawn. No deaths known to be due to RSV occurred in either study group.

Phase 2/3 MEDLEY (Trial 05; NCT03959488)[2,22,25,26]
This was a randomized, double-blind, multicenter, active-controlled trial in 925 infants at increased risk for severe RSV disease. This study is currently not published. Information discussed here comes from product labeling, ClincalTrials.gov, a letter to the editor, including a supplementary appendix, discussing high level results of Trial 05, and manufacturer data presented at the June 2023 VRBPAC meeting. Trial 05 was separated into 2 cohorts: infants with CHD or CLD (n = 310) and preterm infants ≤ 35 weeks GA (n = 615). Infants were randomized 2:1 to receive nirsevimab or palivizumab prior to RSV season 1. Infants in the CHD-CLD cohort received additional RSV prophylaxis for a second RSV season. Infants who were initially randomized to nirsevimab continued nirsevimab for RSV season 2. Infants who were initially randomized to palivizumab in season 1 received either nirsevimab or continued with palivizumab in RSV season 2. The primary endpoint of this trial was focused on safety. Efficacy analysis was descriptive and included an evaluation of MA RSV LRTI for RSV season 1 and RSV season 2.

In RSV season 1, MA RSV LRTI through day 150 occurred in 0.6% (n = 4) of infants who received nirsevimab and 1% (n = 3) of infants who received palivizumab across the total study population. Results for the individual cohort groups were not reported. No infants in either nirsevimab or palivizumab groups for the total study population experienced a MA RSV LRTI in RSV season 2. RSV-associated hospitalizations is listed as another secondary efficacy outcome on ClincalTrials.gov; however, data for this outcome are not currently available. Data from Trial 03 and Trial 04 (MELODY) were used to extrapolate nirsevimab efficacy in Trial 05. Based on an exposure-response analysis in Trial 03 and Trial 04, a target AUC baseline clearance of 12.8 mg*day/mL was identified. In Trial 05, 93.6% of infants in the preterm cohort who received nirsevimab met this threshold. In the CHD-CLD cohort, 94.1% of infants with CLD and 80.3% of infants with CHD met this threshold. No deaths known to be due to RSV occurred in either study group.

Table 1. Summary of efficacy endpoints for pivotal nirsevimab trials[2,22-26]

	Phase 2b (Trial 03)	Phase 3 MELODY (Trial 04)	Phase 2/3 MEDLEY (Trial 05)
N	1,453	1,490	925
Population	Preterm infants born at ≥ 29 weeks to < 35 weeks GA	Predominantly healthy, late preterm and normal term infants born at ≥ 35 weeks GA	Premature infants ≤ 35 weeks GA and infants with CHD or CLD
Comparator	Placebo	Placebo	Palivizumab
Primary endpoint	**MA RSV LRTI**	**MA RSV LRTI**	**Safety**
RRR	70.1%; 95% CI, 52.3-81.2%; *P* < .001	74.5%; 95% CI, 49.6-87.1%; *P* < .001	--
ARR (estimated)	6.9%	3.8%	--
NNT (estimated)	15	27	--
Secondary endpoint	**RSV-associated hospitalization through day 150**	**RSV-associated hospitalization through day 150**	**MA RSV LRTI (descriptive)**
RRR	78.4%; 95% CI, 51.9-90.3%; *P* < .001	62.1%; 95% CI, -8.6-86.8%; *P* = NS	RSV season 1: MA RSV LRTI occurred in 0.6% (n = 4) of infants who received nirsevimab and 1% (n = 3) palivizumab RSV season 2: No cases of MA RSV LRTI occurred in patients who received nirsevimab or palivizumab
ARR (estimated)	3.3%	NA[a]	NA[a]
NNT (estimated)	31	NA[a]	NA[a]

[a] ARR and NNT not calculated for results that are not statistically significant or descriptive.

Clinical considerations
There are currently limited data on the efficacy of nirsevimab in certain high risk populations, such as extreme prematurity (born at < 29 weeks GA) and infants with CHD or CLD. These populations, among other high risk groups, have been better studied with palivizumab.[6] Premature infants and infants with CHD or CLD were included in Trial 05, but the total number of patients studied is relatively low, and the study was not powered to evaluate efficacy.[2,22,25,26] Consequently, the only currently available

studies designed with power to evaluate nirsevimab efficacy were conducted in predominantly healthy infants ≥ 29 weeks GA.[23,24] Across both cohorts in Trial 05, approximately 21% (n =130) infants who received nirsevimab were born at < 29 weeks GA. The total number of infants with CHD or CLD in Trial 05 was 310.[2,22,25,26] For other high risk conditions such as children who are severely immunocompromised, data on the use of nirsevimab are not available. Alaska Natives and American Indians are another group identified by ACIP and AAP as being at increased risk of severe RSV disease.[4,7] Alaska Natives and American Indians were not well represented across clinical studies. No patients in this demographic group were included in the nirsevimab group in Trial 03.[23] In Trial 04 and Trial 05, 5.8% (n = 57) and 1.8% (n = 11) of infants, respectively, in the nirsevimab groups were Alaska Natives or American Indian.[24,25]

Safety: Overall, nirsevimab appears to be safe and well tolerated across clinical studies. No cases of anaphylaxis have occurred in the clinical studies presented above.[22] The rates of adverse events and event rates, including serious adverse events, between nirsevimab and placebo were similar in the phase 2b study (Trial 03) and MELODY (Trial 04). No serious adverse event in either study was considered related to study drug.[23.24] Safety was the primary endpoint in the MELEDY study (Trial 05), which compared nirsevimab with palivizumab. The incidence of adverse reactions, including serious adverse reactions was similar across treatment groups and cohorts. Treatment-related adverse events were reported in 1.5% (n = 6) infants who received nirsevimab and 1.9% (n = 1) infants who received palivizumab. No cases of serious adverse reactions were attributed to study drug.[25] The most common adverse reactions reported in palivizumab product labeling are fever (27%) and rash (12%).[1] The most common adverse reactions reported in product labeling for nirsevimab are rash (0.9%) and injection-site reactions (0.3%).[2]

FDA's VRBPAC voted 19-2 in support of nirsevimab's safety.[21] The Committee raised hypersensitivity reactions and an imbalance of deaths in trials with nirsevimab as key safety considerations. While no cases of anaphylaxis occurred in trials with nirsevimab, these reactions have been reported with palivizumab and other monoclonal antibodies. Therefore, postmarketing reports will be needed to further evaluate this potential with nirsevimab. Across clinical studies reviewed by the Committee, there were 12 deaths (0.32%) in infants who received nirsevimab compared with 4 deaths (0.22%) in infants who received control (placebo or palivizumab). While the absolute number of deaths with nirsevimab was higher than control arms, the percentage of deaths was low and similar between groups. Additionally, none of the deaths were attributed to study drug in either group.[22]

Other considerations around the use of nirsevimab: Given the recent approval of a maternal RSV vaccine, it is currently unclear how this might impact recommendations around the use of monoclonal antibodies for prevention of RSV-associated LRTD. Per ACIP discussions at the June 2023 meeting, the combined use of a maternal RSV vaccine and nirsevimab hasn't been studied. Additionally, based on modeling studies, it seems unlikely that both options will be routinely used together, due to lack of cost effectiveness.[4,27] Now that both a maternal RSV vaccine and nirsevimab are approved, it will be important that ACIP provide guidance on how to navigate the availability of both a vaccine and monoclonal antibodies for RSV prevention. Use of the maternal RSV vaccine may also present challenges in terms of documentation and ensuring provider visibility across care settings when deciding on a specific RSV prevention strategy.

Nirsevimab, though it will be added to the CDC's childhood immunization schedule, is not technically a vaccine. Nirsevimab is classified as a drug or therapeutic per its CPT code classification which could present administrative challenges. It is possible that there may be issues with documentation in electronic health record systems and reporting to state immunization information systems. Billing issues may also be possible. Differences in scope of practice regulations related to who is allowed to administer nirsevimab should also be considered since it is not a traditional vaccine. Most states allow medical assistants to also deliver injection drugs; however, this will be important to verify before implementing this into practice. Organizations may also have different policies in place around medication administration that may need to be considered.[11,16] Additionally, since nirsevimab will be added to the VFC, ambulatory practices will need to carry both VFC and private stock of nirsevimab, which may be challenging from an inventory management standpoint.[11]

Health systems will need to determine how they will decide between inpatient and outpatient administration of nirsevimab. It is likely that administration in both settings will need to be available depending on timing, patient characteristics, and other factors. From a financial standpoint, outpatient administration offers the potential for separate reimbursement versus bundled payment when administered in the inpatient setting. Per AAP 2023 guidance, nirsevimab should be administered within the first week of life to infants born shortly before or during the RSV season. AAP states that this may occur during the birth hospitalization or in the outpatient setting.[7] If deferred to the outpatient setting, coordination of care and confidence in patient follow-up will be essential. Children who require nirsevimab for their second RSV season will likely receive this in the outpatient setting.

Reporting of suspected adverse effects with nirsevimab will also be more complicated compared with other immunizations. Suspected adverse effects should be reported through MedWatch when nirsevimab is administered alone. However, if nirsevimab is given concomitantly with any vaccine, suspected adverse effects should be reported to VAERS; an additional report to MedWatch is not needed.[11]

Conclusion: Two monoclonal antibodies are approved for the prevention of RSV-associated LRTD (aka LRTI). Palivizumab is specifically indicated for use in high-risk infants and pediatric patients. Palivizumab is administered as a monthly IM injection throughout the RSV season. Nirsevimab is a new, long-acting monoclonal antibody for the prevention of RSV LRTD in infants and children and is administered as single intramuscular dose. In addition to use in high-risk patients, nirsevimab is also approved for use in healthy, term infants for RSV LRTD prevention, making it the first FDA-approved drug for this indication. Nirsevimab demonstrated a reduction in MA RSV LRTI in preterm infants born at ≥ 29 weeks to < 35 weeks GA and in healthy term infants born at ≥ 35 weeks GA entering their first RSV season compared with placebo. A significant reduction in RSV-associated hospitalization through 150 days following nirsevimab compared with placebo was seen in preterm infants born at ≥ 29 weeks to < 35 weeks GA, but not in healthy, term infants born at ≥ 35 weeks GA. Nirsevimab was compared with palivizumab in infants at higher risk for severe RSV disease, including preterm infants ≤ 35 weeks GA and infants with CHD or CLD. Efficacy was evaluated as a descriptive endpoint across 2 RSV seasons. MA RSV LRTI through day 150 occurred in 0.6% (n = 4) of infants who received nirsevimab and 1% (n = 3) of infants who received palivizumab across the total study population. No infants in either nirsevimab or palivizumab groups for the total study population experienced a MA RSV LRTI in RSV season 2. Overall, nirsevimab appears to be safe and well tolerated across clinical studies. When compared with palivizumab, the incidence of adverse reactions, including serious adverse reactions with nirsevimab was similar across treatment groups and cohorts. Nirsevimab will be added to the CDC's childhood immunization schedule and VFC program. It will be important for organizations to address potential administrative challenges this may present given that nirsevimab is classified as a drug and not a vaccine. Additional guidance from ACIP is expected around the use of the newly approved maternal RSV vaccination with respect to the use of monoclonal antibodies for the prevention of RSV.

Abbreviations: AAP = American Academy of Pediatrics; ACIP = Advisory Committee on Immunization Practices; aka = also known as; ARR = absolute risk reduction; BPD = bronchopulmonary disease; CHD = congenital heart disease; CI = confidence interval; CLD = chronic lung disease; COVID-19 = coronavirus disease of 2019; DNA = deoxyribonucleic acid; FDA = US Food and Drug Administration; GA = gestational age; IgG1κ = human immunoglobulin G1 kappa; HR = hazard ratio; IM = intramuscular; ITT = intention-to-treat; LRTD = lower respiratory tract disease; LRTI = lower respiratory tract infection; MA LRTI = medically attended LRTI; MMWR = Morbidity and Mortality Weekly Report; NA = not applicable; NNT = number-needed-to-treat; NS = not statistically significant; RRR = relative risk reduction; RSV = respiratory syncytial virus; RSVpreF = RSV glycoprotein F stabilized in pre-fusion conformation; RT-PCR = reverse transcriptase polymerase chain reaction; SD = standard deviation; SDV = single-dose vial; VAERS = Vaccine Adverse Event Reporting System; VFC = Vaccines for Children Program; VRBPAC = Vaccines and Related Biological Products Advisory Committee

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