Drugs & Therapy Perspectives (2023) 39:413–420
https://doi.org/10.1007/s40267-023-01039-4

ADIS DRUG Q&A

Nirsevimab in the prevention of respiratory syncytial virus lower respiratory tract disease: a profile of its use

Matt Shirley[1]

Accepted: 4 December 2023 / Published online: 22 December 2023

Abstract

Nirsevimab (Beyfortus™), a long-acting monoclonal antibody targeting the respiratory syncytial virus (RSV) fusion (F) protein, is the first prophylactic monoclonal antibody against RSV to be licensed for use in all infants in their first RSV season, and thus presents a highly valuable tool in the fight against RSV disease in children. Additionally, in the USA and Canada, nirsevimab is licensed for use in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Data from randomized, double-blind, placebo-controlled clinical trials show that a single intramuscular dose of nirsevimab is efficacious in reducing the incidence of medically attended RSV lower respiratory tract (LRT) disease in healthy term and preterm infants through at least 150 days in their first RSV season. Pharmacokinetic data also support the efficacy of nirsevimab in infants at higher risk of severe RSV disease, including in the second RSV season with a second nirsevimab dose. Nirsevimab has an extended serum half-life, resulting in a duration of protection from a single dose which can cover a full typical RSV season. Nirsevimab is well tolerated, with low rates of reactogenicity, and can be administered concomitantly with childhood vaccines.

Plain Language Summary

Respiratory syncytial virus (RSV) is a significant cause of infant morbidity and mortality worldwide, and prevention strategies involving vaccines or monoclonal antibodies against RSV have been global health priorities. The monoclonal antibody palivizumab has been licensed for 25 years; however, its use in children is restricted to a small subset of infants at increased risk of severe RSV disease, and five monthly doses are necessary to cover the RSV season. Nirsevimab (Beyfortus™) is a long-acting monoclonal antibody designed to provide protection against RSV through the RSV season from a single dose. Based on clinical trial data, nirsevimab, administered as a single intramuscular injection, reduces the incidence of medically attended RSV lower respiratory tract disease in infants through the RSV season. Nirsevimab is well tolerated, with low rates of adverse reactions. As the first monoclonal antibody for the prevention of RSV disease to be licensed for use in all infants in their first RSV season, nirsevimab represents an important advance in the fight against RSV.

Digital Features for this Adis Drug Q&A can be found at https://doi.org/10.6084/m9.figshare.24732294.

What is the rationale for developing nirsevimab for the prevention of RSV lower respiratory tract disease?

Respiratory syncytial virus (RSV) is a significant cause of infant morbidity and mortality worldwide. Associated with an estimated 33.0 million episodes globally in children ≤ 5 years of age annually, RSV is the leading cause of lower respiratory tract (LRT) infection in infants [1]. In 2019, RSV was responsible for an estimated 3.6 million hospital admissions and 101,400 deaths in children ≤ 5 years of age, with 45,700 (45%) of these deaths occurring in infants ≤ 6 months of age [1]. Although there is more variability in tropical regions, in temperate regions such as Europe and North America, RSV activity is highly seasonal, peaking in the winter months [2]. Thus, by coinciding with other winter illnesses, the burden of RSV in infants on healthcare systems is further heightened.

Treatment of RSV in infants remains generally supportive, with the focus of easing the burden of RSV targeted towards prevention strategies, involving active immunisation using vaccines (including maternal immunisation) or passive immunisation using monoclonal antibodies [3–6]. Palivizumab, a

✉ Matt Shirley
dtp@adis.com

[1] Springer Nature, Mairangi Bay, Private Bag 65901, Auckland 0754, New Zealand

Adis evaluation of nirsevimab (Beyfortus™) in the prevention of RSV LRT disease

Licensed for use in all infants in their first RSV season; in the USA and Canada, additionally licensed for use in high-risk individuals aged up to 24 months in their second RSV season
A single weight-banded intramuscular dose offers protection through the RSV season
Reduces the incidence of medically attended RSV LRT disease in infants in their first RSV season
Low rates of reactogenicity; can be administered concomitantly with childhood vaccines

monoclonal antibody targeted against an epitope in the A antigenic site (antigenic site II) of the RSV fusion (F) protein, has been available for 25 years [7, 8]. However, its approval in children has been restricted to select infants at high risk of serious RSV LRT disease which, together with the need for five monthly intramuscular (IM) doses to cover the RSV season and restrictive costs, has limited its widespread use [3, 5, 6]. Thus, there has continued to be a large unmet clinical need towards reducing the impact of RSV.

Many vaccine candidates have been in clinical development for the prevention of RSV in infants [3–6]. With its recent approval, RSVpreF (Abrysvo™), a maternal vaccine targeted against the RSV F protein for immunisation of pregnant individuals for the prevention of RSV LRT disease in infants from birth through 6 months of age, has recently become the first to be granted licensure [9–11].

Alongside the development of vaccines against RSV, interest in passive immunisation against RSV infection has focused on the development of long-acting monoclonal antibodies [3–6]. Nirsevimab (Beyfortus™), a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody targeted against the site Ø epitope on the pre-fusion conformation of the RSV F protein [12, 13], was engineered through modifications in the antibody Fc region to have an extended serum half-life, designed to enable a single dose to provide protection against RSV through a full RSV season [14]. Based on findings from a well-designed clinical trial programme, nirsevimab has now been approved in the EU [12], the USA [13] and other countries.

For whom is nirsevimab indicated?

Nirsevimab is indicated in the USA [13], the EU [12] and other countries for the prevention of RSV LRT disease in neonates and infants during their first RSV season. In the USA [13] and Canada [15], nirsevimab is additionally approved for the prevention of RSV LRT disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

How should nirsevimab be used?

Nirsevimab should be administered by a trained healthcare professional and should be given as a single dose prior to the start of the RSV season (or from birth for infants born during the RSV season) [12, 13]. Nirsevimab can be administered concomitantly with childhood vaccines; when giving concomitantly with injectable vaccines, separate syringes and different injection sites should be used [12, 13].

A summary of the US [13] and EU [12] prescribing information for nirsevimab is provided in Table 1. Local prescribing information should be consulted for full details relating to the use of nirsevimab.

How does nirsevimab work?

During the process of RSV infection, the viral surface glycoprotein F protein undergoes conformational changes to mediate the fusion of the viral and cellular membranes and facilitate cell entry [16]. Nirsevimab works by binding the highly conserved site Ø epitope on the pre-fusion conformation of F protein, thereby inhibiting the conformational changes in the F protein which are required for fusion of the membranes [12–14]. Through this action, by blocking viral entry into host cells, nirsevimab protects against RSV infection.

Nirsevimab binds the pre-fusion conformation of F protein with dissociation constants for RSV subtype A and B laboratory strains of 0.12 nM and 1.22 nM, respectively [12, 13, 17]. In an in vitro study using a diverse panel of 102 RSV clinical isolates collected between 2003 and 2013 from a range of countries, nirsevimab neutralised all viruses tested, with median half-maximal inhibitory concentration (IC_{50}) values of 3.1 ng/mL (range, 0.48–15 ng/mL) against RSV A isolates ($n = 59$) and 3.0 ng/mL (range, 0.8–59.7 ng/mL) against RSV B isolates ($n = 43$) [14].

The pharmacokinetics of nirsevimab after a single IM injection in paediatric subjects are dose-proportional over the dose range of 25 mg to 200 mg [12, 13]. Maximum serum concentrations are observed at a median of 6 days. Through a triple amino acid substitution (YTE) in the Fc region, nirsevimab has been engineered to have an extended serum half-life, with a terminal half-life of approximately 70 days [12, 13, 18]. The drug is long-acting. An analysis of RSV neutralising antibody (NAb) levels in nirsevimab recipients in clinical trials found NAb levels were > 140-fold, >50-fold and > 7-fold higher than baseline levels at

Table 1 Summary of the prescribing information of nirsevimab (Beyfortus™) in the prevention of RSV lower respiratory tract disease in the USA [13] and EU [12]. Unless otherwise indicated, information applies to both the USA and the EU

What is the approved indication for nirsevimab?	
USA: the prevention of RSV lower respiratory tract disease in: • neonates and infants born during or entering their first RSV season • children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season	
EU: the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season	
How is nirsevimab available?	
As a single-dose pre-filled syringe containing: • nirsevimab 50 mg in 0.5 mL (syringe with a purple plunger rod), or • nirsevimab 100 mg in 1 mL (syringe with a light blue plunger rod)	
How should nirsevimab be administered?	
By intramuscular injection, preferably in the anterolateral aspect of the thigh; the gluteal muscle should not be used as an injection site	
What is the recommended dosage of nirsevimab?	
First RSV season	For infants with a body weight of < 5 kg: a single dose of nirsevimab 50 mg
	For infants with a body weight of ≥ 5 kg: a single dose of nirsevimab 100 mg
Second RSV season (in children who remain vulnerable to severe disease; USA only)	A single dose of nirsevimab 200 mg (given as two injections of nirsevimab 100 mg)
How should nirsevimab be used in special populations?	
Individuals with clinically significant bleeding disorders	Use with caution in individuals with thrombocytopenia or any coagulation disorder (USA and EU), or those on anticoagulation therapy (EU)
Children undergoing cardiac surgery with cardiopulmonary bypass	An additional dose is recommended as soon as the child is stable after surgery; see local prescribing information for dose recommendations
Infants with a body weight of < 1 kg (EU)	Carefully consider the benefits and risks of nirsevimab due to higher anticipated nirsevimab exposure
Infants with a postmenstrual age of < 32 weeks (EU)	No clinical data available
What are the contraindications to the use of nirsevimab?	
Hypersensitivity to the active substance or to any of the excipients	
What other special warnings/precautions pertain to the use of the nirsevimab?	
Hypersensitivity including anaphylaxis	If signs/symptoms of clinically significant hypersensitivity or anaphylaxis occur, initiate appropriate medications and/or supportive care

RSV respiratory syncytial virus

day 31, day 151 and day 361, respectively [19]. Based on clinical trial data, the duration of protection of nirsevimab against RSV infection following a single dose extends through 5 months or longer [12, 13].

What is the efficacy of nirsevimab in the prevention of RSV lower respiratory tract disease?

In healthy term and preterm infants

A single IM injection of nirsevimab administered prior to the RSV season is efficacious in preventing medically attended RSV LRT infection throughout the RSV season in healthy term and preterm infants, based on the findings of two randomized, double-blind, placebo-controlled, multinational clinical trials (a phase 2b trial [20] and the phase 3 MELODY trial [21]), with a pooled analysis of the two trials supporting the use of a weight-banded nirsevimab dosing regimen [22]. In addition, preliminary data from the ongoing phase 3b HARMONIE trial provide further support for the efficacy of nirsevimab against hospitalisation for RSV LRT infection in real-world settings [23].

The phase 2b trial enrolled otherwise healthy infants who had been born preterm (gestational age of ≥ 29 weeks to < 35 weeks) [20] whereas the MELODY trial enrolled healthy late-preterm and term infants (gestational age of ≥ 35 weeks) [21]. Aside from the distinct populations by gestational age, the two trials were of similar design [20, 21]. Eligible participants were 1 year of age or younger (or ≤ 8 months of age for EU participants in the phase 2b trial), and were entering their first RSV season. Infants who met local or national criteria to receive commercial palivizumab, had any fever or an acute illness, or had a history of prior RSV infection were among those excluded. In both trials, participants were randomized 2 : 1 to receive a single IM injection of nirsevimab or placebo before the RSV season. In the phase 2b trial, all infants randomized to the nirsevimab group received nirsevimab 50 mg [20]; in the MELODY trial, infants randomized to the nirsevimab group received nirsevimab 50 mg if they weighed < 5 kg or nirsevimab 100 mg if they weighed ≥ 5 kg [21]. In both trials, the primary endpoint was the incidence of medically attended RSV LRT infection through 150 days after study drug administration [20, 21].

In total, 1453 infants were enrolled in the phase 2b trial (969 randomized to nirsevimab, 484 randomized to placebo) [20]. In the MELODY trial, enrolment was paused in 2020 after the end of the first RSV season of observation due to disruption caused by the global coronavirus pandemic [21]. In consultation with regulatory authorities, it was decided that efficacy analyses in MELODY would be performed in the primary cohort ($n = 1490$; 994 randomized to nirsevimab, 496 randomized to placebo), which consisted of 1028 infants enrolled in the northern hemisphere and 462 infants enrolled in South Africa [21]. In both trials, baseline characteristics were well balanced between groups [20, 21]. At baseline in the phase 2b and MELODY trials respectively, 53.2% and 57.9% of participants were aged ≤ 3 months, 32.6% and 32.1% were aged > 3 to ≤ 6 months and 14.2% and 10.0% were aged > 6 months [20, 21].

Based on relative risk reduction, nirsevimab had an efficacy of 70.1% in the phase 2b trial (in otherwise healthy preterm infants) and an efficacy of 74.5% in the MELODY trial (in term and late-preterm infants) against medically attended RSV LRT infection (Table 2) [20, 21]. In both trials, results from prespecified subgroup analyses of the primary endpoint were consistent with those from the overall population, including those based on hemisphere (northern or southern), age (≤ 3 months, > 3 to ≤ 6 months or > 6 months), sex (male or female), race (Caucasian or non-Caucasian) and gestational age (≥ 29 to ≤ 32 weeks or > 32 weeks in the phase 2b trial; ≥ 35 to < 37 or ≥ 37 weeks in MELODY) [20, 21].

In terms of preventing hospitalisation due to RSV LRT infection (secondary endpoint in both trials), nirsevimab had an efficacy of 78.4% ($p < 0.001$) in the phase 2b trial and 62.1% ($p = 0.07$) in MELODY (Table 2) [20, 21]. Again, findings from prespecified subgroup analyses based on hemisphere, age, sex, race and gestational age were consistent with those from the overall trial populations [20, 21]. While the secondary endpoint in the MELODY trial did not reach statistical significance in the primary cohort [21], of note, an analysis based on the full trial population ($n = 3012$; 2009 in the nirsevimab group and 1003 in the placebo group), after study enrolment was resumed in 2021, found nirsevimab efficacy against hospitalisation for RSV LRT infection was 76.8% (95% CI 49.4–89.4) [24].

The efficacy of nirsevimab used with a weight-banded dosing regimen [corresponding to the EMA- and FDA-approved dose regimen for infants in their first RSV season (Table 1)] was further assessed in a prespecified pooled analysis of data from the phase 2b and MELODY trials [22]. Since all participants in the phase 2b trial received nirsevimab 50 mg (or equivalent placebo) regardless of weight, only infants weighing < 5 kg from the phase 2b trial (along with all infants from MELODY) were included in the pooled analysis; infants from the phase 2b trial weighing ≥ 5 kg at enrolment were excluded since they did not receive study drug treatment in alignment with the (subsequently approved) weight-banded dosing regimen [22].

In the pooled analysis, a single weight-banded dose of nirsevimab was found to have an efficacy of 79.5% ($p < 0.0001$) against medically attended RSV LRT infection (primary endpoint), an efficacy of 77.3% ($p = 0.0002$) against hospitalisation for RSV LRT infection (secondary endpoint), and an efficacy of 86.0% ($p < 0.0001$) against very severe RSV LRT infection (defined as hospitalisation for medically attended RSV LRT infection that required supplemental oxygen or intravenous fluids; prespecified exploratory endpoint) over the 150 days post-dose (Table 2) [22]. In further prespecified exploratory analyses, nirsevimab was also found to reduce the risk of medically attended LRT infection (in the investigator's judgement) of any cause (efficacy 35.4%; $p < 0.0001$), and the risk of hospitalisation for respiratory illness of any cause (efficacy 43.8%; $p = 0.0022$).

The efficacy of nirsevimab in the real-world setting is being evaluated in HARMONIE, an ongoing open-label phase 3b trial being conducted in the UK, France and Germany [23]. At the time of the primary analysis, 8058 infants with a gestational age of ≥ 29 weeks had been enrolled and randomized (1 : 1) to nirsevimab ($n = 4037$) or no intervention ($n = 4021$). Infants randomized to nirsevimab received a single IM dose of nirsevimab 50 mg (for infants with a body weight < 5 kg) or nirsevimab 100 mg (for infants with a body weight ≥ 5 kg) before or during the RSV season. Following an initial physical visit, participants were monitored remotely through the RSV season. At study entry, 48.6%, 23.7% and 27.7% of participants were aged ≤ 3.0 months, > 3.0 to ≤ 6.0 months and > 6.0 months, respectively [23].

At the time of the primary analysis in HARMONIE, nirsevimab efficacy against hospitalisation for RSV LRT infection (primary endpoint) was 83.21% (95% CI 67.77–92.04) and efficacy against very severe RSV LRT infection (defined as hospitalisation for RSV LRT infection with an oxygen saturation < 90% at any time and a requirement for oxygen supplementation; secondary endpoint) was 75.71% (95% CI 67.77–92.04) [23]. Additionally, nirsevimab showed an efficacy against all-cause hospitalisation for LRT infection of 58.04% (95% CI 39.69–71.19).

In infants at higher risk of severe disease

The efficacy of nirsevimab in preventing medically assisted RSV LRT infection in infants at higher risk of severe RSV disease was established by extrapolation of the efficacy demonstrated in the phase 2b and MELODY trials to the population enrolled in the randomized, double-blind, palivizumab-controlled phase 2/3 MEDLEY trial based on pharmacokinetic exposure data [12, 13, 22].

Table 2 Efficacy of nirsevimab in RSV lower respiratory tract disease through 150 days post-administration

Endpoint	Phase 2b trial [20]		MELODY [21]		Pooled analysis[a] [22]	
	Nirsevimab ($n = 969$)	Placebo ($n = 484$)	Nirsevimab ($n = 994$)	Placebo ($n = 496$)	Nirsevimab ($n = 1564$)	Placebo ($n = 786$)
MA RSV LRTI (%)[b]	2.6	9.5	1.2	5.0	1.2	6.5
Nirsevimab efficacy [% (95% CI)][c]	70.1 (52.3–81.2)*		74.5 (49.6–87.1)*		79.5 (65.9–87.7)*	
Hospitalisation due to RSV LRTI (%)[d]	0.8	4.1	0.6	1.6	0.6	2.7
Nirsevimab efficacy [% (95% CI)][c]	78.4 (51.9–90.3)*		62.1 (−8.6 to 86.8)		77.3 (50.3–89.7)*	
Very severe RSV LRTI (%)[e]					0.3	2.3
Nirsevimab efficacy [% (95% CI)][c]					86.0 (62.5–94.8)*	

LRTI lower respiratory tract infection, *MA* medically attended, *RSV* respiratory syncytial virus

*$p < 0.001$ by Poisson regression

[a]Included all participants from the phase 2b trial and MELODY who received the (EMA- and FDA-approved) weight-banded dosing regimen

[b]Primary endpoint

[c]Relative risk reduction (i.e. 1 minus the relative risk) in the nirsevimab group versus the placebo group, expressed as a percentage

[d]Secondary endpoint

[e]Prespecified exploratory endpoint; defined as hospitalisation for MA RSV LRTI requiring supplemental oxygen or intravenous fluids

In MEDLEY, participants were enrolled into one of two cohorts: the preterm cohort included infants ($n = 615$) born with a gestational age of ≤ 35 weeks without chronic lung disease (CLD) or congenital heart disease (CHD) who were eligible to receive commercial palivizumab in accordance with local or national guidelines; the CLD/CHD cohort included infants ($n = 310$) with CLD of prematurity or haemodynamically significant CHD [25]. In the trial, participants were randomized 2 : 1 to nirsevimab or palivizumab. Infants in the nirsevimab group ($n = 616$) received a single IM dose of nirsevimab 50 mg (for infants with a body weight < 5 kg) or nirsevimab 100 mg (for infants with a body weight ≥ 5 kg) followed by four once-monthly doses of IM placebo (to maintain blinding); infants in the palivizumab group ($n = 309$) received five once-monthly IM doses of palivizumab 15 mg/kg of body weight. In the preterm cohort, 13% of infants had a gestational age of < 29 weeks, 81% had a gestational age of ≥ 29 weeks to < 35 weeks and 6% had a gestational age of ≥ 35 weeks. In the CLD/CHD cohort, 70% of infants had CLD of prematurity and 34% had haemodynamically significant CHD; 40%, 28% and 32% of infants, respectively, had a gestational age of < 29 weeks, ≥ 29 weeks to < 35 weeks and ≥ 35 weeks [25]. While the MEDLEY trial was primarily designed to evaluate the safety and pharmacokinetics of nirsevimab in infants at higher risk of severe RSV disease, the efficacy of nirsevimab in this population was investigated as a secondary endpoint [12, 13, 22, 25]. Exposure-response analyses in the phase 2b and MELODY (primary cohort) trial populations identified a nirsevimab pharmacokinetic target as a surrogate for efficacy, expressed as area under the concentration–time curve, of 12.8 days × mg/mL [22]. To successfully demonstrate extrapolation in the MEDLEY trial population, serum nirsevimab exposures needed to be at or above the exposure target for efficacy in > 80% of infants [22].

Based on pharmacokinetic data, the efficacy of nirsevimab could be extrapolated to infants at higher risk of severe RSV disease [12, 13, 22], with nirsevimab exposure being above the pharmacokinetic target in 94.3% of infants in the overall MEDLEY population [22]. Furthermore, exposures were above the pharmacokinetic target in > 80% of infants for all subgroups of special interest, including infants with CLD (94.1%), infants with haemodynamically significant CHD (80.3%), and infants with a gestational age of < 29 weeks (93.6%) [22]. In a descriptive analysis, 0.6% (4/616) of infants in the nirsevimab group and 1.0% (3/309) of infants in the palivizumab group had medically attended RSV LRT infection through 150 days after the first dose of study drug [25].

MEDLEY was continued for a second RSV season, with 262 participants (up to 24 months of age) with CLD of prematurity or haemodynamically significant CHD continuing in the trial [26]. Among these participants, those who received nirsevimab during their first RSV season ($n = 180$) were given a single IM dose of nirsevimab 200 mg prior to their second RSV season followed by four once-monthly doses of IM placebo. Participants who received palivizumab during their first RSV season were re-randomized (1 : 1) to receive nirsevimab or palivizumab entering their second RSV season. Participants re-randomized to nirsevimab ($n = 40$) received a single IM dose of nirsevimab followed by four once-monthly doses of IM placebo in their second RSV season; participants re-randomized to palivizumab ($n = 42$) received a further five once-monthly IM doses of palivizumab 15 mg/kg going into and during their second RSV season [26].

Pharmacokinetic data support the efficacy of nirsevimab in the second RSV season in children who remain vulnerable to severe RSV disease, with 98% of participants who received nirsevimab prior to the second RSV season in MEDLEY achieving the nirsevimab exposure target for efficacy [26]. No cases of medically attended RSV LRT infection were reported through 150 days after the first dose of study drug in the second RSV season in participants who received either nirsevimab or palivizumab [26].

What is the tolerability profile of nirsevimab?

IM nirsevimab, used according to the recommended weight-banded dosing regimen (Table 1), is well tolerated in infants based on clinical trial data, with low levels of reactogenicity observed [20–22, 25–27].

Across the phase 2b and MELODY trials (including both the primary and safety cohorts of MELODY), the pooled safety population included 2570 nirsevimab recipients who received the recommended weight-banded dose and 1284 placebo recipients [27]. In the pooled safety population, adverse reactions were reported in 1.2% of nirsevimab recipients and were mild to moderate in intensity in the vast majority (97%) of cases [13]. The most commonly reported adverse reactions were rash occurring ≤ 14 days post-dose (in 0.9% of nirsevimab recipients vs 0.6% of placebo recipients), pyrexia occurring ≤ 7 days post-dose (0.5% vs 0.6%) and injection-site reaction occurring ≤ 7 days post-dose (0.3% vs 0%) [13, 27]. All injection-site reactions were non-serious [12].

Infants in the pooled safety population were followed for 360 days (five nirsevimab half-lives) post-dose to evaluate nirsevimab safety [27]. Treatment-related adverse events occurred in few participants in both the nirsevimab (1.3%) and placebo (1.4%) groups. Serious adverse events (SAEs) were reported in 8.5% of nirsevimab recipients and 11.2% of placebo recipients. No SAEs in the nirsevimab group and one in the placebo group were considered to be related to study treatment. Adverse events of special interest (which included immediate hypersensitivity, immune complex disease and thrombocytopenia) occurred in six (0.2%) nirsevimab recipients and no placebo recipients. All reported adverse events of special interest were characterised as cutaneous hypersensitivity events, were grade ≤ 3 in severity, and resolved in 1–20 days. No cases of anaphylaxis or other serious allergic reactions were reported. Deaths occurred in 0.2% of participants in both groups; no deaths in either group were considered to be related to study treatment [27].

The tolerability and safety profile of nirsevimab in infants at higher risk of severe RSV disease in the phase 2/3 MEDLEY trial was similar to that observed in the pooled phase 2b and MELODY safety population [12, 13, 25]. Additionally, the safety profile of nirsevimab in infants from MEDLEY with CLD of prematurity or haemodynamically significant CHD who continued in the trial for their second RSV season was consistent with that observed during their first RSV season [13]. No treatment-related adverse events or adverse events of special interest were observed in any of the three treatment groups in the second season of the trial [26].

Post-baseline antidrug antibodies were detected in 5.6% of nirsevimab recipients and 3.8% of placebo recipients up to day 361 in the phase 2b trial [20], in 6.1% of nirsevimab recipients and 1.1% of placebo recipients up to day 361 in the MELODY trial (primary cohort) [21], and in 0.4% of nirsevimab recipients and 3.6% of palivizumab recipients up to day 151 in the MEDLEY trial [25].

What is the current clinical position of nirsevimab in the prevention of RSV lower respiratory tract disease?

As the first prophylactic monoclonal antibody against RSV to be licensed for use in all infants in their first RSV season, nirsevimab presents a highly valuable tool in the fight against RSV infection in children. Data from a well-designed programme of clinical trials show that a single weight-banded dose of nirsevimab is efficacious in providing protection against RSV LRT disease, with low rates of reactogenicity, in infants in their first RSV season [20–25]. The clinical trial programme included infants born at term, preterm (including extremely preterm), and with CLD or CHD, with evidence supporting the efficacy and low reactogenicity of nirsevimab in all groups. With its approval in the EU [12], the USA [13] and several other countries, nirsevimab presents an important advance in the fight against RSV. In addition to the data in infants in their first RSV season, further data (albeit more limited) suggest that infants at an increased risk of severe RSV disease can benefit from a second dose of nirsevimab entering their second RSV season, with nirsevimab additionally indicated in this population in the USA [13] and Canada [15], although not in the EU (Table 1).

Recently published advice from the Spanish Society of Paediatric Infectious Disease recommends routine administration of nirsevimab for all neonates born during the RSV season and infants aged < 6 months at the season onset [28]. In August 2023, the US Advisory Committee on Immunization Practices (ACIP) issued a recommendation for the use of nirsevimab for all infants aged < 8 months who are born during or entering their first RSV season and for infants aged

8–19 months who are at increased risk for severe RSV disease and are entering their second RSV season [29]. While its use is supported in national recommendations, the widespread use of nirsevimab globally is likely to depend on cost-effectiveness determinations, particularly in lower- to middle-income countries with more limited resources. Modelling (based on settings in high- to upper middle-income countries) has suggested that nirsevimab used as a seasonal passive immunisation in all infants is likely to be a cost-effective strategy; however, the findings are limited by a number of variables and uncertainties, including the nirsevimab cost per dose, the duration of nirsevimab efficacy, and accurate hospitalisation rates [30–35]. Furthermore, the advances in vaccine development, including the recent approval of the RSVpreF maternal vaccine for the prevention of RSV LRT disease in infants up to 6 months of age [9–11], are likely to substantially alter the landscape. Indeed, in September 2023, ACIP issued a recommendation for RSVpreF using seasonal administration (i.e. in September to January in most areas of continental USA) for pregnant persons at 32–36 weeks' gestation for the prevention of RSV-associated LRT infection in infants aged < 6 months [36]. ACIP recommends that all infants should be protected against RSV-associated LRT infection through the use of either RSVpreF or nirsevimab (although most infants do not need both products) [36].

While prophylactic monoclonal antibodies (such as nirsevimab) and maternal vaccines both have great potential for reducing the burden of RSV in infants, there are notable advantages and disadvantages for the two strategies [4]. The most apparent advantage of nirsevimab over RSV maternal vaccination is the flexibility in terms of the timing of immunisation. By timing nirsevimab administration to align with the start of the RSV season (or at birth for infants born during the RSV season), and with a duration of protection of 5 months or more, nirsevimab has the ability to cover a full RSV season in all infants. In contrast, with maternal vaccines requiring administration in the third trimester of pregnancy, together with a limited duration of protection (likely ≤ 4 months), there is a concern that, for some infants, the window of protection may not coincide with (or cover the duration of) the RSV season, depending on timing of vaccination [4]. Another potential advantage of nirsevimab over RSV maternal vaccination is the delivery of consistent levels of antibody, in contrast to antibody levels delivered through maternal vaccination, which may be more susceptible to variability [4, 37]. In particular, given that maternal antibody transfer peaks in the last 4 weeks of pregnancy, babies born preterm may be at higher risk of having levels of antibody below the level required for protection from maternal vaccination [37]. On the other hand, a likely advantage of maternal vaccines over prophylactic monoclonal antibodies is a potentially lower susceptibility to antigenic evolution [4]. Nirsevimab is targeted against a highly conserved epitope in the pre-fusion F protein [14], and the prevalence of RSV variants with reduced susceptibility to nirsevimab neutralisation appears to be low (< 1%) [17, 38]. Nonetheless, the potential for the emergence of escape mutants remains a concern regarding prophylactic monoclonal antibodies, highlighting the importance of continual RSV genomic surveillance [4, 17].

Given the differences in the two strategies, it seems likely that prophylactic monoclonal antibodies and maternal vaccines will play complementary roles in the global fight to reduce the burden of RSV in infants. The recent advances in this clinical area mark important progress.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40267-023-01039-4.

Acknowledgements The manuscript was reviewed by: *S. Hegde*, Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India; *F. Rustemi*, Department of Pharmacy, Albanian University, Tirana, Albania. During the peer review process, AstraZeneca and Sanofi, the marketing authorisation holders of nirsevimab, were also offered an opportunity to provide a scientific accuracy review of their data. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and conflict of interest M. Shirley is a salaried employee of Adis International Ltd/Springer Nature and declares no relevant conflicts of interest. All authors contributed to this article and are responsible for its content.

Ethics approval, Consent to participate, Consent for publication, Availability of data and material, Code availability Not applicable.

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):2047–64.
2. Obando-Pacheco P, Justicia-Grande AJ, Rivero-Calle I, et al. Respiratory syncytial virus seasonality: a global overview. J Infect Dis. 2018;217(9):1356–64.
3. Eichinger KM, Kosanovich JL, Lipp M, et al. Strategies for active and passive pediatric RSV immunization. Ther Adv Vaccines Immunother. 2021;9:1–21.
4. Esposito S, Abu Raya B, Baraldi E, et al. RSV prevention in all infants: which is the most preferable strategy? Front Immunol. 2022;13(880368):1–13.
5. Principi N, Autore G, Perrone S, et al. Current and emerging pharmacotherapy for respiratory syncytial virus (RSV) infection in infants. Expert Opin Pharmacother. 2023;24(6):747–62.
6. Scotta MC, Stein RT. Current strategies and perspectives for active and passive immunization against respiratory syncytial virus in childhood. J Pediatr (Rio J). 2023;99(Suppl 1):S4-11.
7. US FDA. Synagis® (palivizumab) injection, for intramuscular use: US prescribing information. 2017. https://www.accessdata.fda.

gov/drugsatfda_docs/label/2017/103770s5200lbl.pdf. Accessed 20 Oct 2023.
8. European Medicines Agency. Synagis (palivizumab): summary of product characteristics. 2009. https://www.ema.europa.eu/en/documents/product-information/synagis-epar-product-information_en.pdf. Accessed 20 Oct 2023.
9. US FDA. Abrysvo™ (respiratory syncytial virus vaccine) solution for intramuscular injection: US prescribing information. 2023. https://www.fda.gov/media/168889/download?attachment. Accessed 20 Oct 2023.
10. European Medicines Agency. Abrysvo: summary of product characteristics. 2023. https://www.ema.europa.eu/en/documents/product-information/abrysvo-epar-product-information_en.pdf. Accessed 20 Oct 2023.
11. Syed YY. Respiratory syncytial virus prefusion F subunit vaccine: first approval of a maternal vaccine to protect infants. Paediatr Drugs. 2023;25(6):729–34.
12. European Medicines Agency. Beyfortus: summary of product characteristics. 2023. https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf. Accessed 20 Oct 2023.
13. US FDA. Beyfortus (nirsevimab-alip) injection, for intramuscular use: US prescribing information. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761328s000lbl.pdf. Accessed 20 Oct 2023.
14. Zhu Q, McLellan JS, Kallewaard NL, et al. A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants. Sci Transl Med. 2017;9(388):1–11.
15. Health Canada. Beyfortus™ nirsevimab injection: Canadian prescribing information. 2023. https://pdf.hres.ca/dpd_pm/00070439.PDF. Accessed 20 Oct 2023.
16. McLellan JS, Ray WC, Peeples ME. Structure and function of respiratory syncytial virus surface glycoproteins. Curr Top Microbiol Immunol. 2013;372:83–104.
17. Zhu Q, Lu B, McTamney P, et al. Prevalence and significance of substitutions in the fusion protein of respiratory syncytial virus resulting in neutralization escape from antibody MEDI8897. J Infect Dis. 2018;218(4):572–80.
18. Domachowske JB, Khan AA, Esser MT, et al. Safety, tolerability and pharmacokinetics of MEDI8897, an extended half-life single-dose respiratory syncytial virus prefusion F-targeting monoclonal antibody administered as a single dose to healthy preterm infants. Pediatr Infect Dis J. 2018;37(9):886–92.
19. Wilkins D, Yuan Y, Chang Y, et al. Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants. Nat Med. 2023;29(5):1172–9.
20. 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):415–25.
21. 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):837–46.
22. Simões EAF, Madhi SA, Muller WJ, et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. Lancet Child Adolesc Health. 2023;7(3):180–9.
23. Drysdale SB, Cathie K, Flamein F, et al. Efficacy of nirsevimab against RSV lower respiratory tract infection hospitalization in infants: preliminary data from the HARMONIE phase 3b trial [abstract no. O0082/#1178]. In: 41st Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID). 2023.
24. Muller WJ, Madhi SA, Seoane Nuñez B, et al. Nirsevimab for prevention of RSV in term and late-preterm infants. N Engl J Med. 2023;388(16):1533–4.
25. Domachowske J, Madhi SA, Simões EAF, et al. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity. N Engl J Med. 2022;386(9):892–4.
26. Domachowske JB, Chang Y, Atanasova V, et al. Safety of redosing nirsevimab prior to RSV season 2 in children with heart or lung disease. J Pediatric Infect Dis Soc. 2023;12(8):477–80.
27. Mankad VS, Leach A, Chang Y, et al. Comprehensive summary of all safety data of nirsevimab in healthy infants: experience to date from pivotal trials [abstract no. PD0122 / #2651]. In: 41st Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID). 2023.
28. Francisco L, Cruz-Cañete M, Pérez C, et al. Nirsevimab for the prevention of respiratory syncytial virus disease in children—statement of the Spanish Society of Paediatric Infectious Disease (SEIP). An Pediatr (Engl Ed). 2023;99(4):257–63.
29. Jones JM, Fleming-Dutra KE, Prill MM, et al. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices - United States, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(34):920–5.
30. Hodgson D, Koltai M, Krauer F, et al. Optimal respiratory syncytial virus intervention programmes using nirsevimab in England and Wales. Vaccine. 2022;40(49):7151–7.
31. Kieffer A, Beuvelet M, Sardesai A, et al. Expected impact of universal immunization with nirsevimab against rsv-related outcomes and costs among all US infants in their first RSV season: a static model. J Infect Dis. 2022;226(Suppl 2):S282–92.
32. Beuvelet M, Hoestlandt C, Lemaitre M, et al. Modeled impact of nirsevimab against respiratory syncytial virus (RSV) among French infants experiencing their first RSV season [abstract no. POSB191 and poster]. In: Value Health. 2022.
33. Beuvelet M, Davidson C, Hudson R, et al. Modeled impact of nirsevimab against respiratory syncytial virus (RSV) among UK infants experiencing their first RSV season [abstract no. POSA197 and poster]. In: Value Health. 2022.
34. Beuvelet M, Chung-Delgado K, Kieffer A. Cost-effectiveness of nirsevimab against respiratory syncytial virus (RSV) among US infants experiencing their first RSV season [abstract no. PIN29]. In: Value Health. 2021.
35. Hutton DW. Economic analysis of nirsevimab in pediatric populations. In: Presentation to the ACIP, February 23, 2023.
36. Fleming-Dutra KE, Jones JM, Roper LE, et al. Use of the Pfizer respiratory syncytial virus vaccine during pregnancy for the prevention of respiratory syncytial virus-associated lower respiratory tract disease in infants: recommendations of the Advisory Committee on Immunization Practices—United States, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(41):1115–22.
37. Saso A, Kampmann B. Maternal immunization: nature meets nurture. Front Microbiol. 2020;11(1499):1–21.
38. Wilkins D, Langedijk AC, Lebbink RJ, et al. Nirsevimab binding-site conservation in respiratory syncytial virus fusion glycoprotein worldwide between 1956 and 2021: an analysis of observational study sequencing data. Lancet Infect Dis. 1956;2023:1–11.