

RAPID RESPONSE REPORT

**EVALUATION OF NIRSEVIMAB
AGAINST RSV INFECTION IN INFANTS**

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FABIAN DESIMPEL, DOMINIQUE ROBERFROID

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■ LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ARI	Acute Respiratory Illness
CHD	Congenital Heart Disease
CI	Confidence Interval
CLD	Chronic Lung Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
KCE	Belgian Health Care Knowledge Center
ICU	Intensive Care Unit
LOS	Length of Stay
LRTI	Lower Respiratory Tract Infection
NNT	Number Needed to Treat
RCT	Randomised Controlled Trial
RoB	Risk of Bias
RR	Risk Ratio
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
SHC	Superior Health Council
SR	Systematic Review

ABSTRACT



BACKGROUND

We performed a rapid review of the evidence on nirsevimab, a monoclonal antibody against respiratory syncytial virus (RSV) infections in infants. Either in infants who had been born premature or in late-preterm and term infants, there is good quality evidence from two trials that a single dose of nirsevimab resulted in a lower incidence of medically attended RSV-associated lower respiratory tract infection (LRTI) and of hospitalization than placebo through 150 days — the length of a typical RSV season — after administration of the dose. In the meta-analysis of the 2 trials (N=4465), the vaccine efficacy against medically attended RSV-confirmed LRTI is 75% (95% confidence interval (CI): 66; 82), and vaccine efficacy against RSV-related hospitalisations is 79% (95% CI: 63; 88). The unpublished preliminary results of the HARMONIE trial seem to confirm these results. There was no data on RSV-related mortality or admission in intensive care unit (ICU). The evidence available so far indicates that nirsevimab has a favorable safety profile, although safety follow-up data beyond 360 days are limited. Studies on the duration of immunity and efficacy of nirsevimab injections across several RSV seasons are needed.

■ REPORT

1 BACKGROUND

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections (LRTI) in children under one year of age, especially those related to bronchiolitis and pneumonia, as well as an important agent of respiratory infections in the adult population over 65 years of age and in people at risk.

To feed into the advisory report of the Superior Health Council (SHC) on preventive strategies against RSV disease in infants, the Belgian Health Care Knowledge Center (KCE) reviewed the evidence on the efficacy and safety of nirsevimab (Beyfortus®, Sanofi) and a maternal vaccine (Abrysvo®, Pfizer). Nirsevimab is an extended half live monoclonal antibody indicated for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season. Abrysvo® is indicated for passive protection against LRTI caused by RSV in infants from birth through 6 months of age through maternal immunisation during pregnancy. Both products were granted a marketing authorization from EMA. The final SHC advice can be found on the SHC website (<https://www.health.belgium.be/en/superior-health-council>).

The current report evaluates the efficacy and safety of nirsevimab.

2 METHODS

We performed a rapid review of the evidence based on retrieval and critical appraisal of the pivotal randomised controlled trials (RCTs). We aimed to summarize the evidence coming from RCTs investigating the clinical effectiveness and safety of nirsevimab compared to placebo or standard of care in infants. We searched evidence on outcomes described in Table 1, based on the PICO (Participants–Interventions–Comparator–Outcomes) framework. First of all, we performed a Medline search (October 2023) using the search term 'nirsevimab', which allowed us to identify two systematic reviews (SRs)^{1, 2} with meta-analysis and a total of three RCTs (the Nirsevimab NCT02878330 trial,³ the MELODY trial,⁴ and the MEDLEY trial⁵). For the MELODY trial, we retrieved updated results that were published after the publication date of the SRs.⁶ Therefore, we decided to redo the meta-analysis with these updated trial results. Meta-analysis of data was conducted using RevMan 5.4.1. Log-transformed risk ratios (RR) and their standard errors were either extracted directly from the publications or were calculated using the data provided by the papers. Finally, we assessed publicly available advisory reports of regulatory agencies and Health Technology Assessment (HTA) agencies abroad,⁷⁻⁹ as well as reports shared within the National Immunization Technical Advisory Groups (NITAGs), which allowed us to identify preliminary data of the HARMONIE trial.¹⁰

Table 1 – Review inclusion & exclusion criteria

PICO	Inclusion	Exclusion
Patients	Infants aged one year old and below entering their first RSV season	
Intervention	Nirsevimab	
Comparators	Placebo, or standard of care (palivizumab)	
Outcomes	a. Critical outcomes: - RSV-related mortality rate - RSV-related ICU admission - RSV-related hospitalisation rate - Hospitalisation length of stay (LOS) - Rate of severe RSV-related lower respiratory tract illness (LRTI) - Rate of serious adverse events b. Important outcomes: - Rate of RSV-related LTRI - Rates of acute respiratory illness (ARI) - Reactogenicity	
Duration	At least 5 months follow-up including 1 RSV high-transmission season	< 5 months
Setting	High-income countries	
Type of studies	Phase 3 RCT	Phase 1-2 trials

For each relevant outcome, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to grade the quality of the supporting evidence, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.¹¹ GRADE assessments of quality are determined through consideration of five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Retrieved evidence was assessed for quality using Risk of Bias 2 (RoB 2)¹² tool, in order to assess various aspects of the trial design, conduct, and reporting to determine the level of bias in the study. Following the GRADE methodology (Table 2), the quality of evidence was classified into four categories: high, moderate, low, and very low (Table 3).

Table 2 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕) Low (⊕⊕⊕) Very low (⊕⊕⊕)
Observational studies	Low			

Source: Guyatt et al. (2011)¹³

Table 3 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem et al. (2011)¹⁴

3 CLINICAL EVIDENCE

3.1 Nirsevimab in preterm infants

The Nirsevimab trial (NCT02878330) is a 2:1 randomised double-blind placebo-controlled trial including healthy infants who had been born preterm with a gestational age from week 29 to week 35 and who were 1 year of age or younger and entering their first RSV season.³ Participants received one intramuscular injection of 50 mg of nirsevimab or normal saline placebo during a 2-month period immediately before the RSV season. Main characteristics of the trial are presented in Table 4.

Table 4 – PICO of Nirsevimab NCT02878330 trial

Patients	a. Inclusion: preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age; age: ≤1 y (≤8 mo for infants born in Europe); entering their first full RSV season b. Exclusion: infants who are recommended to receive palivizumab per local or national guidelines; other exclusion criteria are listed in footnote^a The mean gestational age of the participants was 33 weeks; the mean age was 3.3 months; 72% were White; 48% were of female sex; the majority (61%) had a weight ≤5 kg. The demographic characteristics were broadly similar across the trial groups. Randomization was stratified by subject age at randomization (i.e. < 3 months, > 3 to <6 months, > 6 months).
Intervention	Participants (n=1 453) were randomly assigned in a 2:1 ratio to receive one intramuscular injection of nirsevimab at a dose of 50 mg
Comparators	Placebo
Outcomes	a. Primary end point: incidence of medically attended RSV-confirmed LRTI (inpatient and outpatient) through 150 days post dose. A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by reverse transcription polymerase chain reaction (RT-PCR) performed at a central laboratory AND a physical examination finding indicating involvement of the lower respiratory tract (rhonchi, rales, crackles, or wheeze) AND at least one indicator of clinical severity^b b. Secondary end point: hospitalization for RSV-confirmed LRTI through 150 days post dose. A RSV hospitalization is defined as either - A respiratory hospitalization with a positive RSV test within 2 days of hospitalization (primary), OR

^a Participants were excluded in case of any of the following: any fever ($\geq 38.0^{\circ}\text{C}$, regardless of route) or lower respiratory illness within 7 days prior to randomization; acute illness (defined as the presence of moderate or severe signs and symptoms) at the time of randomization; active RSV infection (a child with signs/symptoms of respiratory infection must have negative RSV testing) or known prior history of RSV infection; Any drug therapy (chronic or other) within 7 days prior to randomization (with some exceptions); any current or expected receipt of immunosuppressive agents including steroids; receipt of any investigational drug; known renal impairment; known hepatic dysfunction including known or suspected active or chronic hepatitis infection; history of CLD/bronchopulmonary dysplasia; clinically significant congenital anomaly of the respiratory tract; chronic seizure or evolving or unstable neurologic disorder; congenital heart disease, except for children with uncomplicated CHD (eg, patent ductus arteriosus, small septal defect); prior history of a suspected or actual acute life-threatening event; known immunodeficiency; mother with HIV infection; any known allergy; receipt of palivizumab or other RSV monoclonal antibody or any RSV vaccine; receipt of any monoclonal or polyclonal antibody (for example, Hepatitis B immune globulin, intravenous immunoglobulin), including maternal RSV vaccination.

^b

- Increased respiratory rate at rest (age: < 2 months, ≥ 60 breaths/min; 2–6 months, ≥ 50 breaths/min; > 6 months – 2 years, ≥ 40 breaths/min), OR
- Hypoxemia (in room air - oxygen saturation < 95% at altitudes ≤ 1800 meters or < 92% at altitudes > 1800 meters), OR
- Clinical signs of severe respiratory disease (e.g. acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

	- A new onset of respiratory symptoms in an already hospitalized child, with an objective measure of worsening respiratory status and positive RSV test (nosocomial) c. Exploratory end point: incidence of hospitalizations with supplementary oxygen (severe RSV); number of admissions to hospitals and intensive care units (ICUs) and duration of stay d. Safety was measured in 913 participants through 360 days post dose e. Determination of pharmacokinetics of nirsevimab and the incidence of antidrug antibodies
Setting	164 sites in 23 countries in both hemispheres: 68% of participants in the Northern Hemisphere (Bulgaria, Canada, Czech Republic, France, Hungary, Italy, Poland, Russian Federation, Spain, United Kingdom, and USA), and 32% in the Southern Hemisphere (Argentina, Australia, Brazil, Chile, New Zealand, and South Africa). The sample size was aiming at 99% power to detect a 70% relative risk reduction. The incidence rate in the placebo group was assumed to be 8%.
Duration	Between November 2016 and December 2017, a total of 1 453 participants underwent randomization
Analysis	Efficacy analyses were performed in the intention-to-treat population, safety analyses were based on the as-treated population. A hierarchical approach was used; the secondary end point would be tested only if statistical significance for the primary end point was shown. For subjects who do not have an event (RSV LRTI) prior to discontinuation from participation, their event status was imputed assuming the observed placebo RSV LRTI rate.

Table 5 – Quality appraisal of Nirsevimab NCT02878330 trial (RoB2)

Domain	RoB	Explanation
1: Randomization process	Low	Participants were randomly assigned in a 2:1 ratio, with the use of a central system (i.e. an interactive web response system). Stratification by hemisphere and age at the time of randomization (i.e. ≤ 3 months, > 3 to ≤ 6 months, > 6 months).
2: Deviations from the intended interventions	Low	Double-blind trial. Nirsevimab and placebo are visually indistinguishable once in syringes. Neither the participant nor any of the investigator or site staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. Intention-to-treat analysis performed.
3: Missing outcome data (outcomes: LRTI and hospitalization)	Low	98% of participants completed day 151 efficacy follow-up.
4: Measurement of the outcome (outcomes: LRTI and hospitalization)	Low	Investigator or site staff who are involved in the clinical evaluation of the subjects are not aware of the treatment received.
5. Selection of the reported result	Low	Outcomes were prespecified in the protocol (primary and secondary efficacy hypotheses by a hierarchical order). Only unadjusted/unimputed data will be considered.
Overall RoB	Low	

RoB: Risk of Bias

Table 6 – Results of Nirsevimab NCT02878330 trial

Outcome	Intervention group (N=969)	Control group (N=484)	Vaccine efficacy* (95% CI)	Absolute risk difference** (95% CI)	NNT (95%CI)
Incidence of medically attended RSV-confirmed LRTI through 150 days***	2.6% (25)	9.5% (46)	70.1% (52.3; 81.2)	6.7% (5.0; 7.7)	15 (13; 20)
Incidence of hospitalization for RSV-confirmed LRTI through 150 days	0.8% (8)	4.1% (20)	78.4% (51.9; 90.3)	3.2% (2.1; 3.7)	31 (27; 48)
Incidence of severe RSV (supplementary oxygen)****	0.4% (4)	3.3% (15)	87.5% (62.9; 95.8)	2.9% (2.1; 3.2)	34 (31; 48)
Adverse events of grade 3 or higher	8.0% (77)	12.5% (60)	-	-	-

*: Vaccine efficacy measured by Poisson regression with robust variance, as reported in the paper; **: Absolute risk difference computed by us on the basis of the vaccine efficacy reported in the paper; ***: A case was defined as positive result for RSV in a real-time, reverse-transcriptase–polymerase-chain reaction assay performed at a central laboratory, a physical examination finding indicating involvement of the lower respiratory tract, and at least one indicator of clinical severity, ****: exploratory end point (Healthcare Resource Utilisation). CI: Confidence Interval; LRTI: Lower respiratory tract infection; NNT: Number Needed to treat; RSV: Respiratory syncytial virus

The trial was at low risk of bias (see Table 5). Vaccine efficacy was 70.1% (95% CI: 52.3; 81.2) against medically attended RSV-confirmed LRTI and 78.4% (95% CI: 51.9; 90.3) against hospitalization for RSV-confirmed LRTI in the 150 days following hospitalization. The corresponding NNT were 15 (95% CI: 13; 20) and 31 (95% CI: 27; 48), respectively. Vaccine efficacy against severe RSV infection was 87.5% (95% CI: 62.9; 95.8).

Adverse events of grade 3 or higher were similar in the two groups, the investigator considered none to be related to the investigational product. Serious adverse events were reported in 11.2% (108 of 968) of the participants who received nirsevimab and in 16.9% (81 of 479) of those who received placebo. Five deaths occurred through day 361 (two deaths in the nirsevimab group and three in the placebo group), no deaths were known to be due to RSV or were considered by the investigator to be related to nirsevimab or placebo. In the nirsevimab group, 1 death on day 97 was caused by previously undiagnosed pulmonary vein stenosis, and 1 death of unknown cause occurred on day 123. In the placebo group, 1 death on day 343 was caused by pericardial effusion, and 2 deaths (on days 26 and 109) were caused by pneumonia. Five participants required an ICU admission, all in the placebo group.

3.2 Nirsevimab in late-preterm and term infants

The MELODY trial is a phase 3 trial evaluating Nirsevimab for the prevention of RSV in healthy infants who had been born late-preterm and term infants $\geq$ week 35 gestational age.⁴ Based on results from the nirsevimab trials NCT02878330 showing suboptimal exposure to nirsevimab and lower efficacy in children > 5 kg, participants received one intramuscular injection of nirsevimab (at a dose of 50 mg if they weighed < 5 kg or at a dose of 100 mg if they weighed ≥ 5 kg) or placebo.

The authors explained the trial was paused during several months because of no RSV circulation due to COVID-19 lockdown. Given that the target enrollment was initially not reached, the trial had less power than originally planned to evaluate the efficacy of nirsevimab with respect to preventing hospitalizations or the difference in efficacy in subgroups. When trial enrolment was paused, efficacy against medically attended RSV-associated lower respiratory tract infection among 1 490 participants who had undergone randomization at that point was 74.5% (95% CI:

49.6; 87.1; $p < 0.001$. Vaccine efficacy against hospitalization for RSV-confirmed LRTI was 62.1% (95% CI: -8.6; 86.8; $p = 0.07$) but did not reach statistical significance.⁴ A prespecified pooled evaluation of data from the Nirsevimab NCT02878330 trial and the (paused) MELODY trial was also performed by the study authors, excluding participants from the Nirsevimab NCT02878330 trial with a birth weight of > 5 kg (who received only 50 mg of nirsevimab). The pooled vaccine efficacy against medically attended RSV-confirmed LRTI was 79% (95% CI: 66; 88), and vaccine efficacy against RSV-related hospitalisations was 77% (95% CI: 50; 90).¹⁵

In the meanwhile, complete results of the MELODY trial including the post-pause cohort were published and will be presented here.⁶

Table 7 – PICO of MELODY trial

Patients	a. Inclusion: infants born at term or late preterm $\geq$ week 35 gestational age; entering their first full RSV season b. Exclusion: infants who are recommended to receive palivizumab per local or national guidelines; other exclusion criteria are listed in footnote^c and are nearly the same as those in the Nirsevimab trial 88% of the participants had a gestational age of ≥ 37 weeks; 53% were White; 48% were of female sex; 40% had a weight of < 5 kg. The demographic characteristics were broadly similar across the trial groups. Randomization was stratified by subject age at randomization (i.e. < 3 months, > 3 to < 6 months, > 6 months).
Intervention	Participants (n=3 012) were randomly assigned in a 2:1 ratio to receive one intramuscular injection of nirsevimab at a dose of 50 mg if they weighed < 5 kg or at a dose of 100 mg if they weighed ≥ 5 kg
Comparators	Placebo
Outcomes	a. Primary end point: incidence of medically attended RSV-confirmed LRTI (inpatient and outpatient) through 150 days post dose. A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by RT-PCR performed at a central laboratory AND a physical examination finding indicating involvement of the lower respiratory tract (rhonchi, rales, crackles, or wheeze) AND at least one indicator of clinical severity^d b. Secondary end point: hospitalization for RSV-confirmed LRTI through 150 days post dose. A RSV hospitalization is defined as either - A respiratory hospitalization with a positive RSV test within 2 days of hospitalization (primary), OR

^c Participants were excluded in case of any of the following: any fever ($\geq 38.0^{\circ}\text{C}$, regardless of route) or lower respiratory illness within 7 days prior to randomization; any history of LRTI or active LRTI prior to, or at the time of, randomization; known history of RSV infection or active RSV infection prior to, or at the time of randomization; any drug therapy (chronic or other) within 7 days prior to randomization (with some exceptions); any current or expected receipt of immunosuppressive agents including steroids; history of receipt of blood, blood products, or immunoglobulin products, or expected receipt through the duration of the study; receipt of any investigational drug; known renal impairment; known hepatic dysfunction including known or suspected active or chronic hepatitis infection; history of CLD/bronchopulmonary dysplasia; clinically significant congenital anomaly of the respiratory tract; chronic seizure or evolving or unstable neurologic disorder; congenital heart disease, except for children with uncomplicated CHD (eg, patent ductus arteriosus, small septal defect); prior history of a suspected or actual acute life-threatening event; known immunodeficiency; mother with HIV infection; any known allergy; receipt of palivizumab or other RSV monoclonal antibody or any RSV vaccine; receipt of any monoclonal or polyclonal antibody (for example, Hepatitis B immune globulin, intravenous immunoglobulin), including maternal RSV vaccination

^d

- Increased respiratory rate at rest (age: < 2 months, ≥ 60 breaths/min; 2–6 months, ≥ 50 breaths/min; > 6 months – 2 years, ≥ 40 breaths/min), OR
- Hypoxemia (in room air - oxygen saturation $< 95\%$ at altitudes ≤ 1800 meters or $< 92\%$ at altitudes > 1800 meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

	- A new onset of respiratory symptoms in an already hospitalized child, with an objective measure of worsening respiratory status and positive RSV test (nosocomial) c. Exploratory end point: RSV infection after 150 days; incidence of hospitalizations with supplementary oxygen (severe RSV); number of admissions to hospitals and intensive care units (ICUs) and duration of stay d. Safety: participants in the primary cohort were followed for 360 days post-dose, those enrolled after the pause were followed for a minimum of 150 days post-dose e. Determination of pharmacokinetics of nirsevimab and the incidence of antidrug antibodies
Setting	Northern Hemisphere (Austria, Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Poland, Republic of Korea, Russia, Spain, Sweden, Turkey, Ukraine, United Kingdom, and United States of America [USA]) and Southern Hemisphere (Argentina, Australia, Brazil, Chile, Colombia, New Zealand, Panama, and South Africa). The sample size was aiming at 99% power to detect a 70% relative risk reduction. The incidence rate in the placebo group was assumed to be 8%. A pooled analysis of efficacy against hospitalization for RSV-LRTI in the nirsevimab trial involving was prespecified.
Duration	1 490 participants were included in the primary cohort, 1 522 were included in the post-pause cohort. Enrollment was paused during the peak of the coronavirus disease 2019 (COVID-19) pandemic (between March 15, 2020 and April 9, 2021).
Analysis	Efficacy analyses were performed in the intention-to-treat population, safety analyses were based on the as-treated population. A hierarchical approach was used; the secondary end point would be tested only if statistical significance for the primary end point was shown. For subjects who do not have an event (RSV LRTI) prior to discontinuation from participation, their event status was imputed assuming the observed placebo RSV LRTI rate.

Table 8 – Quality appraisal of MELODY trial (RoB2)

Domain	RoB	Explanation
1: Randomization process	Low	Participants were randomly assigned in a 2:1 ratio, with the use of a central system (ie, an interactive web response system).
2: Deviations from the intended interventions	Low	Double-blind trial. Nirsevimab and placebo are visually indistinguishable once in syringes. Neither the participant nor any of the investigator or site staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. Intention-to-treat analysis performed.
3: Missing outcome data (outcomes: LRTI and hospitalization)	Low	94% of participants completed day 151 efficacy follow-up.
4: Measurement of the outcome (outcomes: LRTI and hospitalization)	Low	Investigator or site staff who are involved in the clinical evaluation of the subjects are not aware of the treatment received.
5: Selection of the reported result	Low	Outcomes were prespecified in the protocol (primary and secondary efficacy hypotheses by a hierarchical order).
Overall RoB	Low	

Table 9 – Results of MELODY trial

Outcome	Intervention group (N=2009)	Control group (N=1003)	Vaccine efficacy* (95% CI)	Absolute risk difference** (95% CI)	NNT (95% CI)
Incidence of medically attended RSV-confirmed LRTI through 150 days***	1.2% (24)	5.4% (54)	76.4% (62.3; 85.2)	4.1% (3.4; 4.6)	24 (22; 30)
Incidence of hospitalization for RSV-confirmed LRTI through 150 days	0.4% (9)	2.0% (20)	76.8% (49.4; 89.4)	1.5% (1.0; 1.8)	67 (56; 100)
Incidence of severe RSV (supplementary oxygen)****	0.3% (7)	1.7% (17)	78.6% (48.8; 91.0)	1.3% (0.8; 1.5)	77 (67; 125)
Adverse events of grade 3 or higher	3.1% (61)	3.8% (38)	-	-	-

*: Vaccine efficacy measured by Poisson regression with robust variance, as reported in the paper; **: Absolute risk difference computed by us on the basis of the vaccine efficacy reported in the paper; ***: A case was defined as positive result for RSV in a real-time, reverse-transcriptase–polymerase-chain reaction assay performed at a central laboratory, a physical examination finding indicating involvement of the lower respiratory tract, and at least one indicator of clinical severity, ****: exploratory end point (Healthcare Resource Utilisation). CI: Confidence Interval; LRTI: Lower respiratory tract infection; NNT: Number Needed to treat; RSV: Respiratory syncytial virus

The trial was at low risk of bias (see Table 8). Vaccine efficacy against medically attended RSV-confirmed LRTI was 76.4% (95% CI: 62.3; 85.2), with a NNT of 24 (95% CI: 22; 30). Vaccine efficacy against hospitalization for RSV-confirmed LRTI was 76.8% (95% CI: 49.4; 89.4).

When results of the Nirsevimab NCT02878330 trial and the final results of the MELODY trial are pooled (see Figure 1 and Figure 2), the vaccine efficacy against medically attended RSV-confirmed LRTI is 75% (95% CI: 66; 82), and vaccine efficacy against RSV-related hospitalisations is 79% (95% CI: 63; 88).

Figure 1 – Meta-analysis of nirsevimab efficacy against medically attended RSV-confirmed LRTI through 150 days

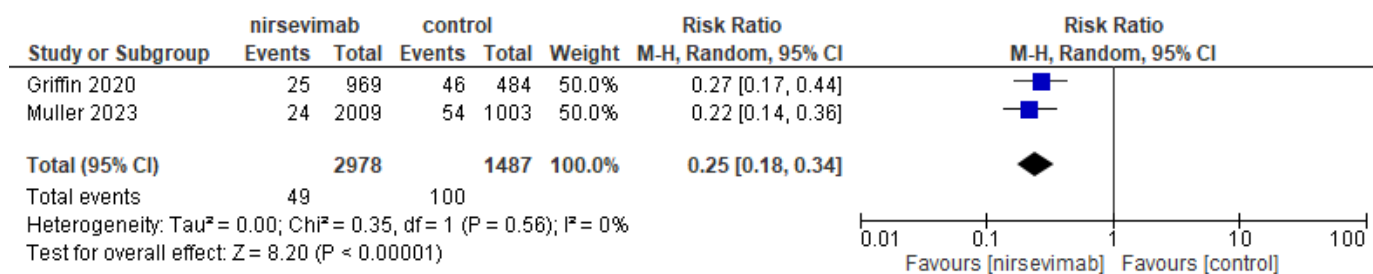
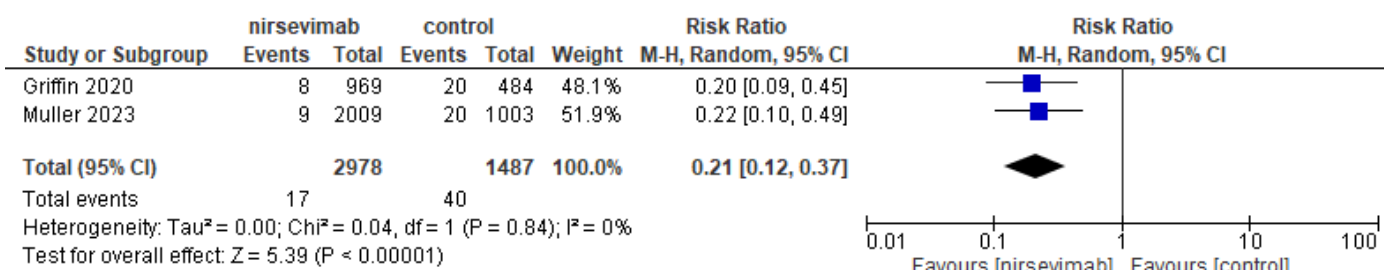


Figure 2 – Meta-analysis of nirsevimab efficacy against hospitalization for RSV-confirmed LRTI through 150 days



Adverse events related to nirsevimab or placebo were reported in 1.3% of the nirsevimab recipients and 1.5% of the placebo recipients through 360 days after injection. Adverse events of grade 3 or higher were similar in the two groups. Four adverse events of special interest were reported in the nirsevimab group: a grade 1 maculopapular rash reported in 2 participants (Study Day 1), a grade 1 papular rash in 1 participant (Study Day 1), and a grade 3 erythematous macular rash (Study Day 7, 6 days post-dose). No anaphylaxis or other serious hypersensitivity was reported. Four deaths occurred through day 361, all among nirsevimab recipients. One death of unknown cause occurred on day 140, two deaths (on days 143 and 338) were attributed to gastroenteritis in infants who did not have a health care visit for the illness, one death occurred after skull base fracture following road traffic accident.

3.3 MEDLEY trial

This phase 2/3 trial evaluated safety of nirsevimab in comparison to palivizumab in preterm infants born < 35 weeks gestational age without chronic lung disease (CLD) or congenital heart disease (CHD) and term and preterm infants with CLD or CHD. The primary endpoint in the MEDLEY trial was safety, secondary efficacy endpoints are extrapolated as palivizumab was the comparator. In total, 925 children under 12 months were randomised in a 2:1 ratio, 615 in the cohort of preterm infants and 310 in the cohort of patients with CLD or CHD. The latter cohort were followed through a consecutive RSV season: nirsevimab recipients received a second dose of nirsevimab in the consecutive season, whereas palivizumab recipients were re-randomised to receive a nirsevimab or second palivizumab dose.

The incidence of adverse events was similar across treatment groups and cohorts. Five deaths occurred in the nirsevimab group: two in the preterm cohort and three in the CHD–CLD cohort. One death occurred in the palivizumab group (CHD–CLD cohort), all deaths were thought to be unrelated to the treatment by the investigator.⁵

3.4 HARMONIE trial (preliminary data)

This pragmatic trial (phase 3b) is conducted in the UK, France, and Germany, evaluating nirsevimab for the prevention of hospitalization due to RSV-associated LRTI in infants. Infants (≥29 weeks gestational age) were randomised in an open label 1:1 ratio to receive a single intramuscular injection of nirsevimab (<5 kg 50 mg; ≥5 kg 100 mg), or no intervention (standard of care) before or during the RSV season.

At the time of the primary analysis, 8 058 infants were randomized, 4 037 in nirsevimab group and 4 021 in the no intervention group. Of these, 3 916 (48.6%), 1912 (23.7%) and 2 230 (27.7%) were ≤3.0, >3.0 and ≤6.0, and >6.0 months of age. Efficacy against RSV LRTI hospitalization was 83.21% (95% CI: 67.77%, 92.04%) and 75.71% (32.75%, 92.91%) against severe RSV LRTI.¹⁰

4 EVIDENCE QUALITY

The quality of evidence was judged high. Both the Nirsevimab NCT02878330 trial and the MELODY trial were at low risk of bias, and their results (together with the unpublished preliminary results of the HARMONIE trial) were consistent. There was some degree of indirectness. First, infants with any history of LRTI were excluded whereas they may have represented a group of more fragile individuals. Second, there were no results on mortality reduction. But we considered that these two elements did not justify downgrading the evidence. Finally, the results had sufficient precision to decide on their minimum clinical benefits, and no publication bias was apparent.

Table 10 – Summary of findings and GRADE quality of evidence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirsevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
RSV-related mortality in infants												
2	randomised trials					a			not estimable		-	CRITICAL
RSV-related ICU admission in infants												
2	randomised trials					b			not estimable		-	CRITICAL
RSV-related hospitalisation in infants (follow-up: 150 days)												
2	randomised trials	not serious	not serious	not serious	not serious	none	17/2978 (0.6%)	40/1487 (2.7%)	RR 0.21 (0.12 to 0.37)	21 fewer per 1,000 (from 24 fewer to 13 fewer)	⊕⊕⊕⊕ High	CRITICAL
Severe Medically Attended RSV-related Lower Respiratory Tract Infection (follow-up: 150 days)												
2	randomised trials					c			not estimable		-	CRITICAL
Medically Attended RSV-related Lower Respiratory Tract Infection (follow-up: 150 days)												
2	randomised trials	not serious	not serious	not serious	not serious	none	49/2978 (1.6%)	100/1487 (6.7%)	RR 0.25 (0.18 to 0.34)	51 fewer per 1,000 (from 57 fewer to 42 fewer)	⊕⊕⊕⊕ High	IMPORTANT

CI: confidence interval; RR: risk ratio

Explanations

a. No deaths were known to be due to RSV

b. Unclear whether reported ICU admissions are due to RSV, small number of events observed (7 events in both trials). Reported as exploratory end point (Healthcare Resource Utilisation)

c. Reported as exploratory end point (Healthcare Resource Utilisation)

5 CONCLUSION

Either in infants who had been born premature or in late-preterm and term infants, there is good quality evidence from two trials that a single dose of nirsevimab resulted in a lower incidence of medically attended RSV-associated LRTI and of hospitalization than placebo through 150 days — the length of a typical RSV season — after administration of the dose. In the meta-analysis of the two trials (N=4465), the vaccine efficacy against medically attended RSV-confirmed LRTI is 75% (95% CI: 66; 82), and vaccine efficacy against RSV-related hospitalisations is 79% (95% CI: 63; 88). The unpublished preliminary results of the HARMONIE trial seem to confirm these results. There was no data on RSV-related mortality or admission in ICU. The evidence available so far indicates that nirsevimab has a favorable safety profile, although safety follow-up data beyond 360 days are limited. Studies on the duration of immunity and efficacy of nirsevimab injections across several RSV seasons are needed.

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Colophon



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Authors: Desimpel Fabian (KCE)

Reviewers: Roberfroid Dominique (KCE)

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