Nirsevimab (prevention of RSV lower respiratory tract disease)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Medical and scientific advice

- Thomas O.F. Wagner

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Sebastian Kahnt.

IQWiG thanks the respondent and the patient organization “Bundesverband Herzkranke Kinder e. V.” for participating in the written exchange and for their support. The respondent and the “Bundesverband Herzkranke Kinder e. V.” were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of tables[2]

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nirsevimab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 18 February 2025.

Research question

The aim of this report is to assess the added benefit of nirsevimab compared with the appropriate comparator therapy (ACT) for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in children during their first RSV season who are not addressed in the therapeutic information on RSV antibodies.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of nirsevimab

Therapeutic indication	**ACT**[a]
Prevention of RSV lower respiratory tract disease in children during their first RSV season who are not addressed in the therapeutic information on RSV antibodies[b]	Watchful waiting

a. Presented is the ACT specified by the G-BA.
b. The present benefit assessment of nirsevimab only covers children without an indication for secondary prophylaxis of lower respiratory tract infections according to AM-RL Appendix IV – Therapeutic information according to §92 para. 2 sentence 7 SGB V. Thus, the following children are not covered by this benefit assessment:
- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically relevant congenital heart defects (e.g. relevant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21
- Children ≤ 6 months of age at the onset of the RSV season who were born prematurely before the completed 35th week of gestation (34 weeks [+ 6 days])

AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee; RSV: respiratory syncytial virus

The company followed the specification of the ACT.

The present benefit assessment only covers children who are not addressed in the therapeutic information on the economical prescription of RSV antibodies (Pharmaceutical Directive

Appendix IV – Therapeutic information according to §92 para. 2 sentence 7 SGB V) and thus have no indication for secondary prophylaxis.

Thus, the following children are not covered by this benefit assessment:

- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically relevant congenital heart defects (e.g. relevant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21
- Children ≤ 6 months of age at the onset of the RSV season who were born prematurely before the completed 35th week of gestation (34 weeks [+ 6 days])

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit.

Study pool and study design

The studies HARMONIE and MELODY were used for the benefit assessment.

HARMONIE study

The HARMONIE study is an ongoing randomized, open-label, multicentre study investigating treatment with nirsevimab versus no intervention for the prevention of RSV lower respiratory tract disease in children during their first RSV season. The study enrolled mainly healthy infants ≤ 12 months of age and born at a gestational age of at least 29 weeks. The children were enrolled both before and during their first RSV season and, according to the inclusion criteria of the study, should not be eligible for palivizumab as per local guidelines.

A total of 8057 children were enrolled in the HARMONIE study and randomized at a 1:1 ratio either to treatment with nirsevimab (N = 4038) or to no intervention (N = 4019). Treatment with nirsevimab was in compliance with the recommendations of the SPC.

The primary outcome of the study was RSV hospitalization. Patient-relevant secondary outcomes included outcomes in the categories morbidity and side effects (including mortality). Outcomes on health-related quality of life were not recorded.

MELODY study

The MELODY study is a completed, double-blind RCT, comparing nirsevimab versus placebo for the prevention of RSV lower respiratory tract infections in children. The study enrolled mainly healthy infants ≤ 12 months of age and born at a gestational age of at least 35 weeks. Most children were enrolled before their first RSV season and, according to the eligibility criteria of the study, were not to be eligible for palivizumab as per local guidelines.

A total of 3012 children were enrolled in the study and randomized at a 2:1 ratio either to treatment with nirsevimab (N = 2009) or to placebo (N = 1003). Treatment with nirsevimab was in compliance with the recommendations of the SPC. Randomization took place in 2 cohorts, at different times. The primary cohort included 1490 children who were included in the study for the 2019/2020 RSV season in the northern hemisphere and for the 2020 RSV season in the southern hemisphere. No further children were included between 15 March 2020 and 9 April 2021 due to the COVID-19 pandemic. The second cohort (called "safety cohort" by the company) included 1522 children who were included in the study for the 2021/2022 RSV season in the northern hemisphere and for the 2021 RSV season in the southern hemisphere. In this benefit assessment, the results of the overall population of the MELODY study were considered.

The primary outcome of the MELODY study was the occurrence of RSV lower respiratory tract infection. Patient-relevant secondary outcomes included outcomes in the categories morbidity and side effects (including mortality). Outcomes on health-related quality of life were not recorded.

Analysis dates considered

The company delimited the RSV season for the morbidity outcomes using a specific date (date of the primary analysis: 28 February 2023 [referred to by the company as the end of the RSV season], HARMONIE study) or a defined period (Day 151, MELODY study). Even though it can be assumed that a large proportion of RSV infections occur up to this date or within this period, seasonal and regional differences mean it is not possible to delimit the duration or end of an RSV season with certainty on the basis of specific dates or a 5-month period. In order to obtain a complete picture of the RSV infections that have occurred, an observation period beyond a fixed cut-off date or 5-month period is therefore generally useful (Day 366 in the HARMONIE study, Day 361 in the MELODY study).

In the HARMONIE study, almost all children were enrolled during their first RSV season. In the MELODY study, it can be assumed that a large proportion of the children were enrolled before the start of their first RSV season. Correspondingly, treatment with the study medication was administered mainly during (HARMONIE) or before (MELODY) the RSV season defined by the company.

The analysis for the HARMONIE study at the data cut-off date 28 February 2023 only covered a mean observation period of approximately 2 months because the majority of the children were included during the RSV season and were therefore only under observation for a relatively short period of time until the data cut-off. This analysis date was therefore not used for the benefit assessment. The analysis date Day 151 represented a uniform and longer observation period for all included children, and thus contained more information. However, even the analyses at this date did not cover all periods in which RSV infections can occur during the first RSV season. For the analysis date that provided the most information (Day 366), however, it can be assumed that this covers part of the second RSV season for the children included, which is not part of the given research question.

For the MELODY study, results were available for Day 151 and Day 361. Since the majority of the included children were enrolled before the start of the RSV season defined by the company, the analysis date of Day 151 largely represented the period defined by the company as the RSV season. RSV infections that occurred outside this defined period were not included in the analysis. The analysis date Day 361 therefore contained notably more information. Due to substantial study inclusion prior to the start of the RSV season, it was assumed that, in contrast to the HARMONIE study, part of the second RSV season was covered for no more than a small proportion of the children included.

In the given data situation, the analysis dates Day 151 and Day 361/366 for the morbidity outcomes in the studies HARMONIE and MELODY were pooled into one meta-analysis each, considered together and used for the benefit assessment. For the side effect outcomes, the results at the analysis date Day 361/366 were considered.

The total populations of the studies HARMONIE and MELODY included children who are not included in the research question

The total populations of HARMONIE and MELODY included children with an indication for secondary prophylaxis. In Module 4 C, the company therefore presented analyses excluding those children which it considered to have an indication for secondary prophylaxis. These were children with trisomy 21 or children with a gestational age of less than 36 weeks. The exclusion of children with trisomy 21 was appropriate. The blanket exclusion of children with a gestational age of less than 36 weeks was not appropriate, as children born at 35 weeks gestational age or earlier who were older than 6 months at the start of the RSV season are included in the given research question and should therefore be included in the analysis. The number of children affected was unclear; the company potentially excluded children from these analyses who were included in the given research question. The proportion of 7.8% of children in the total population of both studies who did not correspond to the research question was therefore potentially an overestimate. Analogous to the company's approach, the total populations of the studies were used for the benefit assessment in the present

situation. However, the consideration of children outside the given research question led to a limitation of the certainty of conclusions.

Meta-analysis of the study results

Due to the sufficiently similar designs and patient characteristics of the studies HARMONIE and MELODY, a meta-analytical summary is in principle feasible and useful.

Risk of bias and certainty of conclusions

The risk of bias of the results of all patient-relevant outcomes except the outcome study discontinuation due to AEs in the HARMONIE study was assessed as low. The reason for the high risk of bias of the results for the outcome discontinuation due to AEs in the HARMONIE study was the lack of blinding in subjective recording of outcomes. However, there were uncertainties in both studies, HARMONIE and MELODY, regarding the proportion of children included who are not covered by the research question for this benefit assessment. These uncertainties led to a limitation of the certainty of conclusions. The results from the individual studies can therefore at most be used to derive hints, for example of an added benefit. A meta-analytical summary of the results of the studies HARMONIE and MELODY allows for at most the derivation of indications, for example of an added benefit.

Results

Mortality

Overall survival

For the outcome all-cause mortality, 4 events occurred in the intervention arm only in the MELODY study. No statistically significant difference between treatment groups was found. There was no hint of an added benefit of nirsevimab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

RSV lower respiratory tract infection

For the composite outcome of RSV lower respiratory tract infection, which was only recorded in the MELODY study, the analysis both at Day 361 and at Day 151 showed a statistically significant difference in favour of nirsevimab compared with watchful waiting. There is a hint of an added benefit of nirsevimab in comparison with watchful waiting for this outcome.

Severe RSV lower respiratory tract infection

For the outcome of severe RSV lower respiratory tract infection, operationalized as hospitalization due to RSV lower respiratory tract infection, the meta-analysis showed a statistically significant difference in favour of nirsevimab compared with watchful waiting in the analyses both at Day 361/366 and at Day 151. There was an indication of an added benefit of nirsevimab in comparison with watchful waiting for this outcome.

Health-related quality of life

Outcomes in the category of health-related quality of life were not recorded in the studies HARMONIE and MELODY. There was no hint of an added benefit of nirsevimab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of SAEs and severe AEs. In each case, there was no hint of greater or lesser harm from nirsevimab in comparison with watchful waiting; an added benefit is therefore not proven.

Study discontinuations due to AEs

Only in the HARMONIE study did one child in each treatment arm discontinue the study. No statistically significant difference between treatment groups was found. There was no hint of greater or lesser harm from nirsevimab in comparison with watchful waiting; greater or lesser harm is therefore not proven for this outcome.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Overall, only positive effects were shown for nirsevimab in comparison with watchful waiting. In the category of serious/severe symptoms/late complications, there was an indication of considerable added benefit for the outcome of severe RSV lower respiratory tract infection. There was also a hint of a considerable added benefit for the outcome of RSV lower respiratory tract infections in the category of non-serious/non-severe symptoms/late complications. However, it should be noted that this outcome includes events that were already included in the outcome of severe RSV lower respiratory tract infection, so these are not completely independent outcomes.

In summary, there is an indication of a considerable added benefit of nirsevimab versus the ACT for the prevention of RSV lower respiratory tract disease in children during their first RSV season who are not addressed in the therapeutic information on RSV antibodies.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3 shows a summary of probability and extent of the added benefit of nirsevimab.

Table 3: Nirsevimab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Prevention of RSV lower respiratory tract disease in children during their first RSV season who are not addressed in the therapeutic information on RSV antibodies[b]	Watchful waiting	Indication of considerable added benefit

a. Presented is the ACT specified by the G-BA.
b. The present benefit assessment of nirsevimab only covers children without an indication for secondary prophylaxis of lower respiratory tract infections according to AM-RL Appendix IV – Therapeutic information according to §92 para. 2 sentence 7 SGB V. Thus, the following children are not covered by this benefit assessment:
- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically relevant congenital heart defects (e.g. relevant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21
- Children ≤ 6 months of age at the onset of the RSV season who were born prematurely before the completed 35th week of gestation (34 weeks [+ 6 days])

AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee; RSV: respiratory syncytial virus

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of nirsevimab compared with the ACT for the prevention of RSV lower respiratory tract disease in children during their first RSV season who are not addressed in the therapeutic information on RSV antibodies [3].

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of nirsevimab

Therapeutic indication	**ACT**[a]
Prevention of RSV lower respiratory tract disease in children during their first RSV season who are not addressed in the therapeutic information on RSV antibodies[b]	Watchful waiting

a. Presented is the ACT specified by the G-BA.
b. The present benefit assessment of nirsevimab only covers children without an indication for secondary prophylaxis of lower respiratory tract infections according to AM-RL Appendix IV – Therapeutic information according to §92 para. 2 sentence 7 SGB V [3]. Thus, the following children are not covered by this benefit assessment:
- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically relevant congenital heart defects (e.g. relevant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21
- Children ≤ 6 months of age at the onset of the RSV season who were born prematurely before the completed 35th week of gestation (34 weeks [+ 6 days])

AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee; RSV: respiratory syncytial virus

The company followed the specification of the ACT.

The present benefit assessment only covers children who are not addressed in the therapeutic information on the economical prescription of RSV antibodies (Pharmaceutical Directive Appendix IV – Therapeutic information according to §92 para. 2 sentence 7 SGB V) [3] and thus have no indication for secondary prophylaxis.

Thus, the following children are not covered by this benefit assessment:

- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.

- Children with haemodynamically relevant congenital heart defects (e.g. relevant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21
- Children ≤ 6 months of age at the onset of the RSV season who were born prematurely before the completed 35th week of gestation (34 weeks [+ 6 days])

Children with an indication for secondary prophylaxis of lower respiratory tract infections caused by RSV during their first RSV season, according to the therapeutic information, were the subject of a previous benefit assessment [4-6].

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on nirsevimab (status: 2 December 2024)
- Bibliographical literature search on nirsevimab (last search on 4 December 2024)
- Search of trial registries/trial results databases for studies on nirsevimab (last search on 3 December 2024)
- Search on the G-BA website for nirsevimab (last search on 3 December 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on nirsevimab (last search on 10 March 2025); for search strategies, see I Appendix A of the full benefit assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: nirsevimab versus watchful waiting

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
VAS00006 (HARMONIE[c])	No	Yes	No	Yes [7,8]	Yes [9,10]	Yes [11]
D5290C00004 (MELODY[c])	Yes	No[d]	No	Yes [12-14]	Yes [15,16]	Yes [17]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
d. AstraZeneca PLC was the original marketing authorization holder of nirsevimab and conducted the MELODY study. Sanofi Winthrop Industrie took over the marketing authorization on 1 December 2023.

CSR: clinical study report; RCT: randomized controlled trial

I 3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: nirsevimab vs. no intervention or placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
HARMONIE	RCT, open-label, parallel	Healthy children[b, c] aged ≤ 12 months, with ≥ 29 weeks GA, in their first RSV season[d]	Nirsevimab (N = 4038) No intervention (N = 4019)	Screening: ND Treatment: 1 day Observation: up to Day 366 in France and Germany and up to Day 731 in the United Kingdom	235 centres in France, Germany and United Kingdom 8/2022–ongoing Data cut-offs ▪ 28 Feb 2023[e] ▪ 26 Apr 2024[f]	Primary: RSV hospitalization Secondary: morbidity, AEs
MELODY	RCT, double-blind, parallel	Healthy children[b, c] aged ≤ 12 months, with ≥ 35 weeks GA, entering their first RSV season[g]	Nirsevimab (N = 2009) Placebo (N = 1003)	Screening: up to 30 days Treatment: 1 day Observation: until Day 511	211 centres in: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Czech Republic, Estonia, Finland, France, Germany, Israel, Italy, Japan, Latvia, Lithuania, Mexico, New Zealand, Panama, Poland, Russia, South Africa, South Korea, Spain, Sweden, Turkey, Ukraine, United Kingdom, United States 7/2019–3/2023 Data cut-offs: ▪ 11 Mar 2021[h] ▪ 31 Mar 2022[i] ▪ 19 Apr 2023[j]	Primary: RSV lower respiratory tract infection Secondary: morbidity, AEs

Table 6: Characteristics of the studies included – RCT, direct comparison: nirsevimab vs. no intervention or placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. Children for whom palivizumab therapy is not suitable according to local directives. c. Children with an underlying condition such as cystic fibrosis or trisomy 21 but without further risk factors were eligible. d. Children could be enrolled before or during the RSV season; a total of 8020 children were enrolled during the RSV season and 37 children before the RSV season. e. Primary analysis, planned after at least 61 hospitalizations attributable to RSV, or no later than 30 April 2023. f. Analysis conducted after all children had completed the 12-month safety follow-up. g. No information is available on how many children were included in the study before or during the RSV season. Based on the recruitment periods, it is assumed that most children were included before the start of the RSV season (see body text). h. Primary analysis, conducted after the children in the primary cohort (see body text for a description) had completed Day 361. i. Safety analysis, conducted after the children in the safety cohort (see body text for a description) had been observed up to at least Day 151. j. Final analysis, conducted after all children had completed Day 511. AE: adverse event; GA: gestational age; N: number of randomized patients; RCT: randomized controlled trial; RSV: respiratory syncytial virus						

Table 7: Characteristics of the intervention – RCT, direct comparison: nirsevimab vs. no intervention or placebo

Study	Intervention	Comparison
HARMONIE	Nirsevimab IM on Day 1: ▪ 50 mg for children < 5 kg body weight ▪ 100 mg for children ≥ 5 kg body weight	No intervention
	Prohibited prior/concomitant treatment ▪ Immunosuppressant therapy for cancer treatment within 6 months before study start ▪ Long-term systemic corticosteroid therapy (prednisone or equivalent for ≥ 2 consecutive weeks within the 3 months before study start) ▪ Monoclonal antibodies (including palivizumab) ▪ Immunoglobulins, blood or blood-derived products within the 3 months before study start ▪ Any investigational products ▪ Vaccination of the mother with an RSV vaccine during pregnancy **Allowed concomitant treatment** ▪ Any concomitant therapy (with the exception of the above therapies) including routine vaccinations within 14 days before and after randomization, and medication for lower respiratory tract infection during hospitalization	
MELODY	Nirsevimab IM on Day 1: ▪ 50 mg for children < 5 kg body weight ▪ 100 mg for children ≥ 5 kg body weight	Placebo IM on Day 1
	Disallowed pretreatment ▪ Any drug treatment (chronic or other) within 7 days prior to randomization or anticipated use during the study ▪ Current or anticipated use of immunosuppressants including steroids ▪ Previous receipt of blood transfusions or immunoglobulins, or anticipated use during the study ▪ Any investigational products ▪ Palivizumab or other RSV monoclonal antibodies or any RSV vaccines including RSV vaccination of the mother ▪ Monoclonal or polyclonal antibodies (e.g. hepatitis B immunoglobulin, intravenous immunoglobulin) **Allowed concomitant treatment** ▪ Supportive care[a] including routine vitamins and iron ▪ Over-the-counter preparations for the systemic treatment of typical symptoms in infants	

a. Except for the routine administration of vitamins and iron, any concomitant treatment including herbal supplements should be avoided until Day 15 after randomization.

IM: intramuscular; RCT: randomized controlled trial; RSV: respiratory syncytial virus

HARMONIE study

The HARMONIE study is an ongoing randomized, open-label, multicentre study investigating treatment with nirsevimab versus no intervention for the prevention of RSV lower respiratory tract disease in children during their first RSV season. The study enrolled mainly healthy infants ≤ 12 months of age and born at a gestational age of at least 29 weeks. Both preterm and term infants were thus included, according to the study protocol. The children were

enrolled both before and during their first RSV season and, according to the inclusion criteria of the study, should not be eligible for palivizumab as per local guidelines. The children were not allowed to have an active RSV infection or an active lower respiratory tract infection at randomization. Children with moderate or severe illness/infection or febrile illness (temperature ≥ 38°C) could not be included in the study until the condition was resolved.

A total of 8057 children were enrolled in the HARMONIE study and randomized at a 1:1 ratio either to treatment with nirsevimab (N = 4038) or to no intervention (N = 4019). Randomization was stratified according to country (France versus Germany versus United Kingdom) and age of the children at the time of randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months). Treatment with nirsevimab was in compliance with the recommendations of the Summary of Product Characteristics (SPC) [18]. According to the HARMONIE study protocol, children in countries where nirsevimab had already been launched during the study were also allowed to receive nirsevimab outside the study as part of routine treatment (i.e. not as a study medication). As this only affected very few children (4 children in the intervention arm and 12 children in the comparator arm), it was of no consequence for this benefit assessment.

The primary outcome of the study was RSV hospitalization. Patient-relevant secondary outcomes included outcomes in the categories morbidity and side effects (including mortality). Outcomes on health-related quality of life were not recorded.

Data cut-offs

Results from 2 data cut-offs were available for the HARMONIE study:

- Data cut-off on 28 February 2023 (primary analysis), planned after at least 61 RSV hospitalizations, concurring with the end of the RSV season according to the company; included analyses of outcomes in the categories morbidity and side effects up to the data cut-off date
- Data cut-off on 26 April 2024 (1-year analysis): analysis after all children had completed the 12-month safety follow-up (Day 366); included analyses of outcomes in the categories morbidity and side effects at Day 366 as well as analyses of outcomes in the morbidity category at Day 151

The company used different analysis dates depending on the outcome category (see Section “Dates of analysis” below).

MELODY study

The MELODY study is a completed, double-blind RCT, comparing nirsevimab versus placebo for the prevention of RSV lower respiratory tract infections in children. The study enrolled mainly healthy infants ≤ 12 months of age and born at a gestational age of at least 35 weeks. Children with an underlying condition such as cystic fibrosis or trisomy 21 but without further

risk factors were also eligible. Most children were enrolled before their first RSV season (see below) and, according to the eligibility criteria of the study, were not to be eligible for palivizumab as per local guidelines. They were not allowed to have a history of RSV or lower respiratory tract infection, or an active RSV or lower respiratory tract infection prior to or at the time of randomization. Children with fever (temperature ≥ 38°C) or with an acute illness within 7 days prior to randomization were not allowed to participate in the study.

A total of 3012 children were enrolled in the study and randomized at a 2:1 ratio either to treatment with nirsevimab (N = 2009) or to placebo (N = 1003). Randomization was stratified according to hemisphere (northern versus southern) and age of the children at the time of randomization (> 3 months to ≤ 6 months versus > 6 months). Randomization took place in 2 cohorts, at different times. The primary cohort included 1490 children who were included in the study for the 2019/2020 RSV season in the northern hemisphere and for the 2020 RSV season in the southern hemisphere. No further children were included between 15 March 2020 and 9 April 2021 due to the COVID-19 pandemic. The second cohort (called "safety cohort" by the company) included 1522 children who were included in the study for the 2021/2022 RSV season in the northern hemisphere and for the 2021 RSV season in the southern hemisphere. In this benefit assessment, the results of both cohorts of the MELODY study were considered together, analogous to the company's approach, as the suspension of recruitment between 15 March 2020 and 9 April 2021 due to the COVID-19 pandemic had no influence on randomization and blinding. In addition, the subgroup analyses conducted post hoc by the company on the study cohort characteristic did not show any effect modifications.

Treatment with nirsevimab was in compliance with the recommendations of the SPC [18].

The primary outcome of the MELODY study was the occurrence of RSV lower respiratory tract infection. Patient-relevant secondary outcomes included outcomes in the categories morbidity and side effects (including mortality). Outcomes on health-related quality of life were not recorded.

Data cut-offs

Three data cut-offs were available for the MELODY study:

- Data cut-off on 11 March 2021 (primary analysis): conducted after the children in the primary cohort (see above for a description) had completed Day 361; included analyses of the primary cohort for the outcomes in the morbidity category at Day 151 and Day 361, as well as for outcomes in the side effects category at Day 361
- Data cut-off on 31 March 2022 (safety analysis): conducted after the children in the safety cohort (see above for a description) had been observed until at least Day 151; included analyses for outcomes in the morbidity category at Day 151, separately for the

primary cohort and the safety cohort and for the total population of the study, as well as analyses for the outcomes in the side effects category for the total population of the study, based on the safety data of both cohorts collected up to the data cut-off

- Data cut-off on 19 April 2023 (final analysis): conducted after all children had completed Day 511; also included analyses of outcomes in the morbidity category (Day 151 and Day 361) and outcomes in the side effects category (Day 361)

The company used different analysis dates depending on the outcome category (see Section "Dates of analysis" below).

Dates of analysis

Approach of the company

The company used different analysis dates depending on the outcome category. It justified its selection of analysis dates for the outcome category morbidity by stating that the research question of the dossier referred to the period within the RSV season and that infections and thus RSV hospitalizations outside this period tended to be the exception. For the HARMONIE study, the company therefore used the results of the data cut-off of the primary analysis (28 February 2023) to derive the added benefit for outcomes in the morbidity category, as this data cut-off represented the end of the RSV season according to the company (see above). For the MELODY study, the company used the results on Day 151 from the final analysis (data cut-off on 19 April 2023) for outcomes in the morbidity category. According to the company, this analysis date represented an average 5-month RSV season.

For the outcomes in the side effects category, the company used the results on Day 366 (1-year analysis, data cut-off on 26 April 2024) for the HARMONIE study, and the results on Day 361 (final data cut-off on 19 April 2023) for the MELODY study.

Beyond the analysis dates used by the company, results for both studies were available for the morbidity outcomes at Day 361/366, and for the HARMONIE study at Day 151.

Assessment of the company's approach and approach used in this benefit assessment

As described above, the company delimited the RSV season for the morbidity outcomes using a specific date (HARMONIE study) or a defined period (Day 151, MELODY study). Even though it can be assumed that a large proportion of RSV infections occur up to this date or within this period, seasonal and regional differences mean it is not possible to delimit the duration or end of an RSV season with certainty on the basis of specific dates or a 5-month period. In order to obtain a complete picture of the RSV infections that have occurred, an observation period beyond a fixed cut-off date or 5-month period is therefore generally useful.

The studies HARMONIE and MELODY had very similar design (see Table 6), but there was a relevant difference in the time points when the majority of children were enrolled. In the HARMONIE study, almost all children were enrolled during their first RSV season (time of randomization: before the RSV season [n = 37] versus during the RSV season [n = 8020]); no such data were available for the MELODY study. Given the recruitment period of the MELODY study (primary cohort: 1027 children in the northern hemisphere from 23 July 2019 to 30 November 2019; 462 children in the southern hemisphere from 8 January 2020 to 15 March 2020 / safety cohort: 1197 children in the northern hemisphere from 27 April 2021 to 27 October 2021; 325 children in the southern hemisphere from 9 April 2021 to 22 October 2021) however, it can be assumed that a large proportion of the children were enrolled before the start of their first RSV season. Correspondingly, treatment with the study medication was administered mainly during (HARMONIE) or before (MELODY) the RSV season defined by the company. The approach to the inclusion of children in both studies concurred with the health care context, and treatment with the study medication was in compliance with the recommendations of the SPC for nirsevimab and was therefore appropriate.

However, the different dates of study inclusion had consequences for the analysis dates. For the HARMONIE study, analyses of various analysis dates were available for the outcome category morbidity, all of which had limitations. The analysis dates for the data cut-off of the primary analysis, for Day 151 and for Day 366, are considered below. The analysis at the data cut-off date 28 February 2023, which the company described as the end of the RSV season (see above), only covered a mean observation period of approximately 2 months. This was because the majority of the children were included during the RSV season and were therefore only under observation for a relatively short period of time until the data cut-off. This analysis date was therefore not used for the benefit assessment. The analysis date Day 151 represented a uniform and longer observation period for all included children, additionally covered some of the months outside the RSV season defined by the company, and thus contained more information. However, even the analyses at this date did not cover all periods in which RSV infections can occur during the first RSV season. The analysis date on Day 366 provided the most information, but it can be assumed that this covers part of the second RSV season for the children included, which is not part of the given research question.

For the MELODY study, results were available for 2 analysis dates: Day 151 and Day 361. Since the majority of the included children were enrolled before the start of the RSV season defined by the company, the analysis date of Day 151 largely represented the period defined by the company as the RSV season. RSV infections that occurred outside this defined period were therefore not included in the analysis. However, the results at Day 361 showed that RSV infections also occurred to a relevant extent outside the period defined by the company as the RSV season (see Table 13). This means that the analysis date Day 361 contained notably more information. Due to substantial study inclusion prior to the start of the RSV season, it

was assumed that, in contrast to the HARMONIE study, part of the second RSV season was covered for no more than a small proportion of the children included.

Overall, all analysis dates mentioned therefore had limitations regarding the outcomes in the morbidity category, especially in the HARMONIE study. In the given data situation, the analysis dates Day 151 and Day 361/366 for the morbidity outcomes in the studies HARMONIE and MELODY were pooled into one meta-analysis each (see below), considered together and used for the benefit assessment. For the side effect outcomes, the results at the analysis date Day 361/366 were considered, analogous to the company's approach.

Overall, it should be noted that the effect estimates in the morbidity outcomes were consistent across the 3 analysis dates described above, and that the selection of analysis dates therefore had no influence on the conclusion of the benefit assessment.

The total populations of the studies HARMONIE and MELODY included children who are not included in the research question

As described in Chapter I 2, the research question of the present benefit assessment exclusively covers children who are not addressed in the therapeutic information on RSV antibodies [3] and who were not already covered by the research question of the previous benefit assessment procedure on nirsevimab in children with an indication for secondary prophylaxis of RSV lower respiratory tract infections [4-6].

The present research question therefore does not cover:

1) Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
2) Children with haemodynamically relevant congenital heart defects (e.g. relevant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
3) Children with trisomy 21
4) Children ≤ 6 months of age at the onset of the RSV season who were born prematurely before the completed 35th week of gestation (34 weeks [+ 6 days])

Approach of the company

In Module 4 C, the company described that the studies HARMONIE and MELODY did not include any children with bronchopulmonary dysplasia and haemodynamically relevant heart defects. Furthermore, the company described that the studies did include preterm children with a gestational age of 29 weeks or older (HARMONIE) or 35 weeks or older (MELODY) or children with trisomy 21 with an indication for secondary prophylaxis of RSV lower respiratory

tract infection. For this reason, the company presented sensitivity analyses defined post hoc, which excluded 712 children (8.8%) from the HARMONIE study and 156 children (5.2%) from the MELODY study (pooled across both studies: 7.8%). According to the information provided by the company in Module 4 C, the children not included in the sensitivity analyses were those with trisomy 21 or with a gestational age of less than 36 weeks. According to the company, the sensitivity analyses thus only included children without an indication for secondary prophylaxis. The company presented the sensitivity analyses only for the outcomes in the morbidity category. For the derivation of the added benefit, the company used the total populations of the studies on the grounds that the proportion of children not covered by the research question at hand was < 20% in relation to the total populations and that therefore no formal consideration of the subpopulations was required.

Assessment of the company's approach and approach used in this benefit assessment

Children with bronchopulmonary dysplasia and congenital heart disease (except for uncomplicated congenital heart disease such as ductus arteriosus) were excluded from participating in the worldwide MELODY study. This ensured that no children who fall under criteria 1 and 2 mentioned above were included in the MELODY study. Such exclusion criteria were not directly defined for the HARMONIE study conducted in Germany, France and the United Kingdom. However, children were only allowed to participate in the HARMONIE study if they were not eligible for palivizumab as per local guidelines. According to the SPC (both in Europe and the United Kingdom), palivizumab is indicated in children at high risk for RSV disease [19,20]. These include, but are not limited to, children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months, and children less than 2 years of age and with haemodynamically significant congenital heart disease. It was thus also ensured for the HARMONIE study that no children who fall under criteria 1 and 2 mentioned above were included.

Nevertheless, the total populations of HARMONIE and MELODY included children with an indication for secondary prophylaxis. A small proportion of children with trisomy 21 were included in both studies (see Table 9), for example. In addition, children ≤ 6 months of age at the onset of the RSV season who were born prematurely before the completed 35th week of gestation (34 weeks [+ 6 days]), were also included. In Module 4 C, the company therefore presented analyses excluding those children which it considered to have an indication for secondary prophylaxis. These were children with trisomy 21 and children with a gestational age of less than 36 weeks. The exclusion of children with trisomy 21 was appropriate. The blanket exclusion of children with a gestational age of less than 36 weeks was not appropriate, as children born at 35 weeks gestational age or earlier who were older than 6 months at the start of the RSV season are included in the given research question and should therefore be included in the analysis. The number of children affected was unclear. The company potentially excluded children from these analyses who were included in the given research

question. The proportion of 7.8% of children in the total population of both studies who did not correspond to the research question was therefore potentially an overestimate.

It should also be noted that the company only presented analyses for the morbidity outcomes for the previously described subpopulations of the studies HARMONIE and MELODY.

Considering the 2 studies HARMONIE and MELODY together, a maximum of 7.8% of the children did not correspond to the given research question. Therefore, analogous to the company's approach, the total populations of the studies were used for the benefit assessment in the present situation. However, the consideration of children outside the given research question led to a limitation of the certainty of conclusions. Thus, the results of the studies HARMONIE and MELODY allow for the derivation of no more than hints, for example of an added benefit, in each case, and no more than indications, for example of an added benefit, in the meta-analysis of both studies (see also Section I 4.2).

Meta-analysis of the study results

Due to the sufficiently similar designs and patient characteristics of the studies HARMONIE and MELODY, a meta-analytical summary is in principle feasible and useful. Meta-analyses were conducted for the following outcomes: severe RSV lower respiratory tract infection, serious adverse events (SAEs) and severe adverse events (AEs) (see Table 13). No statistically significant heterogeneity was shown for these outcomes.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: nirsevimab vs. no intervention or placebo

Study Outcome category Outcome	Planned follow-up observation
HARMONIE	
Mortality	
All-cause mortality	Up to Day 366 (Germany, France) or Day 731 (United Kingdom)
Morbidity	
Severe RSV lower respiratory tract infection	Up to Day 366 (Germany, France) or Day 731 (United Kingdom)
Health-related quality of life	No outcomes recorded in this category
Side effects	
Non-serious AEs	Up to Day 31
Severe AEs[a], SAEs, AEs of special interest	Up to Day 366 (Germany, France) or Day 731 (United Kingdom)
MELODY	
Mortality	
All-cause mortality	Up to Day 361[b]
Morbidity	
RSV lower respiratory tract infection, severe RSV lower respiratory tract infection	Up to Day 511
Health-related quality of life	No outcomes recorded in this category
Side effects	
All outcomes in the side effects category	Up to Day 361

a. The outcome includes potentially non-serious AEs with a severity grade 3 that were only followed up until Day 31.
b. In Module 4 C, the company stated that AEs resulting in death were documented during the entire study duration (from signing of the informed consent up to Day 511). This information was not available in the study protocol.

AE: adverse event; RCT: randomized controlled trial; RSV: respiratory syncytial virus; SAE: serious adverse event

The observation period for the outcome of non-serious AEs was systematically shortened in the HARMONIE study, as they were only recorded for 30 days after treatment with nirsevimab. However, in order to be able to draw a reliable conclusion about the entire study period, it would be necessary to record this outcome throughout the entire study period.

Characteristics of the study populations

Table 9 shows the characteristics of the children in the studies included.

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: nirsevimab vs. no intervention or placebo (multipage table)

Study Characteristic / Category	HARMONIE		MELODY	
	Nirsevimab	No intervention	Nirsevimab	Placebo
	N = 4038	N = 4019	N = 2009	N = 1003
Age at randomization [months], mean (SD)	4.5 (3.3)	4.5 (3.3)	2.9 (2.2)	2.9 (2.3)
Age category, n (%)				
≤ 3 months	1962 (49)	1953 (49)	1190 (59)	588 (59)
> 3 to ≤ 6 months	959 (24)	954 (24)	636 (32)	323 (32)
> 6 months	1117 (28)	1112 (28)	183 (9)	92 (9)
Sex [F/M], %	48/52	48/52	47/53	50/50
Family origin, n (%)				
White	ND	ND	1052 (52)	541 (54)
Black	ND	ND	299 (15)	138 (14)
Asian	ND	ND	109 (5)	50 (5)
Indigenous	ND	ND	107 (5)[a]	60 (6)[a]
Other	ND	ND	439 (22)[b]	214 (21)[b]
Gestational age [weeks]				
Mean (SD)	38.8 (2.3)	38.9 (2.2)	38.5 (1.6)	38.5 (1.6)
Median [min; max], n (%)	39.3 [28.4; 42.4]	39.3 [28.4; 43.0]	39.0 [35; 42]	39.0 [32; 42]
Missing	33 (< 1)[c]	46 (1)[c]	1 (< 1)	0 (0)
Gestational age category, n (%)				
< 37 weeks[d]	567 (14)	543 (14)	239 (12)	123 (12)[c]
≥ 37 weeks	3438 (85)	3430 (85)	1769 (88)	880 (88)
Missing	33 (< 1)	46 (1)	1 (< 1)	0 (0)
Trisomy 21, n (%)				
Yes	9 (< 1)	6 (< 1)	4 (< 1)	0 (0)
No	4029 (< 100)[c]	4013 (< 100)[c]	2004 (< 100)	1003 (100)
Treatment discontinuation, n (%)[e]	–	–	–	–
Study discontinuation, n (%)	244 (6)[f]	318 (8)[f]	136 (7)[g]	80 (8)[g]

a. Refers to indigenous children from America, Alaska, Hawaii or the Pacific Islands, Institute's calculation.
b. Consisting of the categories "other" and "diverse", Institute's calculation.
c. Institute's calculation.
d. According to inclusion criteria, the gestational age was ≥ 29 weeks in the HARMONIE study and ≥ 35 weeks in the MELODY study.
e. As the study treatment was only administered once, information on treatment discontinuations is not applicable. In the HARMONIE study, 23 children in the intervention arm did not receive treatment, and 1 child in the comparator arm (no intervention) was erroneously immunized. In the MELODY study, 11 children in the intervention arm vs. 7 children in the control arm did not receive any study treatment.
f. A common reason for study discontinuation in the intervention vs. comparator arm (up to Day 366) was lost to follow-up (5% vs. 7%, percentages refer to randomized patients).

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: nirsevimab vs. no intervention or placebo (multipage table)

Study Characteristic Category	HARMONIE		MELODY	
	Nirsevimab	No intervention	Nirsevimab	Placebo
	N = 4038	N = 4019	N = 2009	N = 1003
g. Common reasons for study discontinuation in the intervention vs. comparator arm (final analysis) were lost to follow-up (3% each), discontinuation by parent/guardian: (2% vs. 4%), percentages refer to randomized patients. This also includes 5 children who died in the comparator arm.				
F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation				

HARMONIE

The characteristics of the children were largely balanced between both treatment arms of the HARMONIE study. The children's mean age at randomization was 4.5 months in both treatment arms. About half of the children in the study population (48%) were female. In both treatment arms, most children were ≤ 3 months old at randomization (49%), and around a quarter of the children were between 3 and 6 months old. The proportion of children who were > 6 months old at the time of randomization was 28% in both treatment arms. 14% of the children were born with a gestational age < 37 weeks. The proportion of children with trisomy 21 was below 1% in both treatment arms. The proportion of study discontinuations was 6% in the intervention arm versus 8% in the comparator arm.

MELODY

The characteristics of the children were largely balanced between both treatment arms of the MELODY study. The children's mean age at randomization was 2.9 months in both treatment arms. About half of the children in the study population (48%) were female. In both treatment arms, most children were ≤ 3 months old at randomization (59%), and around a third of the children were between 3 and 6 months old (32%). The proportion of children who were > 6 months old at the time of randomization was 9% in both treatment arms. 12% of the children were born with a gestational age < 37 weeks. The proportion of children with trisomy 21 was less than 1% in the intervention arm, and no children with trisomy 21 were included in the comparator arm. The proportion of study discontinuations was 7% in the intervention arm and 8% in the comparator arm.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: nirsevimab vs. no intervention or placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
HARMONIE	Yes	Yes	No	No	Yes	Yes	Low
MELODY	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies. Limitations resulting from the open-label study design of the HARMONIE study are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

For the HARMONIE study, the company stated that the restriction to the 3 countries of France, Germany and the United Kingdom, where the study was conducted, guaranteed the transferability of the results to the German health care context: 22% of the children enrolled were in Germany, and since the other 78% were in the United Kingdom and France, their health care systems were also comparable to that in Germany, with similar social structures. For the MELODY study, the company stated that it was conducted predominantly in European and North American countries (74% of the study centres were in Europe, the United States and Canada), where health care and social structures are comparable to Germany. The company therefore considered the results of the studies MELODY and HARMONIE to be transferable to the German health care context, without any limitations. According to the company, this also applied to the meta-analysis of both studies.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - RSV lower respiratory tract infection
  - Severe RSV lower respiratory tract infection
- Health-related quality of life
- Side effects
  - SAEs
  - Severe AEs
  - Discontinuation due to AEs
- Other specific AEs, if any

The patient-relevant outcomes selected deviate from those selected by the company, which used additional outcomes in its dossier (Module 4 C).

Table 11 shows for which outcomes data were available in the included studies.

Table 11: Matrix of outcomes – RCT, direct comparison: nirsevimab vs. no intervention or placebo

Study	Outcomes							
	All-cause mortality[a]	RSV lower respiratory tract infection[b]	Severe RSV lower respiratory tract infection[c]	Health-related quality of life	SAEs	Severe AEs	Study discontinuations due to AEs	Specific AEs
HARMONIE	Yes	No[d]	Yes	No[d]	Yes	Yes[e]	Yes	No[f]
MELODY	Yes	Yes	Yes	No[d]	Yes	Yes[g]	Yes	No[h]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Composite outcome consisting of the components hospitalization and outpatient care, each due to RSV lower respiratory tract infection.
c. Operationalized as hospitalization due to RSV lower respiratory tract infection.
d. Outcome not recorded.
e. See body text for operationalization.
f. No suitable analyses on AEs available, a selection of specific AEs is therefore not possible; see the body text for reasons.
g. Operationalized as CTCAE grade ≥ 3.
h. No specific AEs were identified based on the AEs occurring in the relevant study/studies.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; RSV: respiratory syncytial virus; SAE: serious adverse event

Notes on outcomes

RSV lower respiratory tract infection

The composite outcome RSV lower respiratory tract infection was only recorded in the MELODY study; a meta-analysis with the HARMONIE study was therefore not possible. The outcome included the components RSV hospitalization and RSV outpatient care. In contrast to the outcome severe RSV lower respiratory tract infection (operationalized as hospitalization due to RSV lower respiratory tract infection) described below, this outcome provided a complete picture of all relevant RSV lower respiratory tract infections, as additional information on less severe RSV infections that could be treated in an outpatient setting was included in the analysis.

Criteria for confirmed RSV lower respiratory tract infection

To be recorded as RSV lower respiratory tract infection, both the components hospitalization and outpatient care had to meet defined criteria. These criteria specified, in addition to a physical examination, during which it was documented whether the lower respiratory tract was affected and breathing noises (rhonchi, rales, crackles, or wheeze) were present, the

requirement for a positive reverse transcriptase polymerase chain reaction (RT-PCR) assay for RSV infection by a central laboratory after the physical examination or diagnosis by nasal swab. In addition to these 2 criteria, at least one of the following criteria also had to be fulfilled:

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

Increased respiratory rate and clinical signs of severe respiratory disease are patient-relevant criteria. The criterion of hypoxaemia, on the other hand, is the result of a measurement with a pulse oximeter. This is not necessarily patient-relevant. However, the threshold values established in the MELODY study for hypoxaemia were within a range of relevant oxygen deficiency and close to a critical range that may require supplemental oxygen [21]. For this reason, the defined criterion of hypoxaemia was classified as a patient-relevant criterion in this benefit assessment.

Definition of the components RSV hospitalization and RSV outpatient care

As described, the outcome of RSV lower respiratory tract infection had 2 components. The component hospitalization was defined as primary or nosocomial hospitalization. A hospitalization was classified as primary when a child was admitted to hospital for any upper or lower respiratory tract infection and tested positive for RSV infection by RT-PCR within 2 days before or after hospital admission. A hospitalization was classified as nosocomial when an already hospitalized child experienced a documented worsening of respiratory status (requirement for supplemental oxygen or increased need for supplemental oxygen when already receiving oxygen supplementation due to the onset of new symptoms, or need for mechanical ventilation) and had an RSV infection confirmed by a central laboratory using RT-PCR. Children who were hospitalized for upper or lower respiratory tract infection had to have returned to their baseline respiratory status or recovered from the respiratory illness before a new RSV infection was recorded as nosocomial hospitalization.

The component RSV outpatient care was defined as medical attention for an RSV infection in outpatient clinics, urgent and emergency care units.

For the benefit assessment, the analysis dates Day 151 and Day 361 were considered for the outcome RSV lower respiratory tract infection (for justification, see Section I 3.2).

Severe RSV lower respiratory tract infection

This benefit assessment operationalized the outcome severe RSV lower respiratory tract infection as hospitalization due to RSV lower respiratory tract infection. It should be noted that the events of severe RSV lower respiratory tract infection were also included in the composite outcome RSV lower respiratory tract infection described above, which was only recorded in the MELODY study. The events of severe RSV lower respiratory tract infection accounted for approximately a third of the events in the composite outcome (see Table 13). Since the meta-analytical summary of the results for the outcome of severe RSV lower respiratory tract infection from the studies HARMONIE and MELODY yielded greater certainty of results and, in addition, this outcome exclusively represented severe RSV infections and thus a higher grade of severity, it was appropriate to reconsider these events in the present data situation. This aspect was taken into account in the overall assessment of the added benefit (see Section I 5.2).

In the HARMONIE study, RSV respiratory tract infection was the primary study outcome and was defined as follows. All hospitalizations of the children during the first year of the study were reported to the study staff via an electronic patient diary. The investigator then assessed whether a hospitalization was due to an RSV respiratory tract infection. If the attending physician was the investigator, this assessment was done directly based on RSV test results and documented symptoms. If the attending physician was not the investigator, however, this information was collected retrospectively by seeking the required information from the facility where medical attention was sought and transmitting it to the electronic case report form (eCRF).

Testing for RSV was expected to be performed by the hospital as part of routine practice. Based on the data on severe RSV hospitalizations at Day 151 (no data were available for Day 366), the diagnosis was made predominantly (in 44 children) by PCR. For a total of 23 children with severe RSV lower respiratory tract infection, it was unknown which test was used for confirmation of RSV. According to the study protocol, an RSV lower respiratory tract infection was present if, in addition to confirmed RSV, the following symptoms in particular were documented:

- Breathing sounds (rhonchi, rales, crackles or wheeze)
- Increased respiratory rate at rest (age < 2 months: ≥ 60 breaths/min, age 2 to 6 months: ≥ 50 breaths/min, age > 6 months to 2 years: ≥ 40 breaths/min)
- Hypoxaemia (without supplemental oxygen/ventilation: oxygen saturation < 95%); see above for patient relevance

In the MELODY study, the definition of severe RSV lower respiratory tract infections was represented by the component RSV hospitalization of the composite outcome RSV lower respiratory tract infection (see above for definition).

The company additionally included very severe RSV lower respiratory tract infection as a separate outcome in its assessment. This outcome included RSV hospitalizations where oxygen supplementation or intravenous fluid administration was required. However, very severe cases of RSV lower respiratory tract infections were already adequately represented by severe RSV lower respiratory tract infections, which is why the outcome very severe RSV lower respiratory tract infection was not additionally considered separately in this benefit assessment.

Impact of the COVID-19 pandemic on morbidity outcomes

It should be noted that the 2 included studies, HARMONIE and MELODY, were conducted during the COVID-19 pandemic. It cannot be ruled out that the coronavirus protection measures in place at the time prevented (severe) RSV lower respiratory tract infections. As both treatment arms were equally affected, this did not result in any systematic bias in the results presented.

Side effects

In the HARMONIE study, hospitalizations due to lower respiratory tract infections, including hospitalizations due to RSV lower respiratory tract infections, were not to be recorded as SAEs. Overall, only a few clearly disease-related events such as RSV infection and RSV bronchiolitis were included in the analyses of side effects. However, it is unclear whether the analyses also excluded underlying symptoms of an RSV lower respiratory tract infection, coded e.g. using the Preferred Terms (PT) pneumonia, bronchitis or bronchiolitis. The analyses of the overall rates of SAEs and severe AEs in the HARMONIE study thus potentially included events that can be attributed to the symptoms of an RSV lower respiratory tract infection. In the MELODY study, the analyses of the overall rates of SAEs and severe AEs also potentially included events that can be attributed to the symptoms of an RSV lower respiratory tract infection (e.g. PTs pneumonia, bronchitis or bronchiolitis) as well as a few clearly disease-related events, such as RSV infection and RSV bronchiolitis.

For an adequate assessment of the results in the outcome category of side effects, analyses of SAEs and severe AEs without disease-related events are required. In the given data situation, however, it was sufficiently ensured on the basis of the information on common AEs that there was no relevant influence on the results for the overall rates of outcomes in the side effects category (see I Appendix C of the full benefit assessment). The overall rates of SAEs and severe AEs including disease-related events were therefore used for the benefit assessment.

Study discontinuations due to AEs

Since nirsevimab is administered once, and children in the control arm of the studies HARMONIE and MELODY received either no intervention or a single placebo dose, discontinuation of treatment due to AEs could not be determined. For this reason, the outcome study discontinuation due to AEs was considered in this benefit assessment.

Severe AEs

The outcome severe AEs was operationalized differently in HARMONIE and MELODY. In the MELODY study, severity was classified according to the Common Terminology Criteria for Adverse Events [CTCAE], with a severe AE being defined as a grade ≥ 3 AE. This was an adequate operationalization for the benefit assessment. In the HARMONIE study, AEs were categorized into severity grades I to III, with severity grade III indicating a severe AE. The severity grades used to assess the intensity of AEs were based on the FDA's *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* [22] and were adapted for the HARMONIE study. A severe AE (severity grade III) was defined as an AE that interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention. The severity classification was based on the investigator's assessment. There were deviations from the definition of severe AEs according to CTCAE. Against the background of consistent results in both studies (see Table 13), the outcome of severe AEs of the HARMONIE study was also included in the given data situation. The results of both studies were pooled in a meta-analysis.

Specific AEs

In the HARMONIE study, non-serious AEs were only followed up for 30 days after administration of nirsevimab according to the study protocol (see Table 8). In the MELODY study, however, all outcomes in the side effects category were followed up until Day 361. For this reason, the selection of specific AEs was conducted solely on the basis of the MELODY study. The studies HARMONIE and MELODY were used for the selection of specific SAEs and specific severe AEs, as these were comprehensively recorded up to Day 361/366 in both studies. Overall, no specific AEs, specific SAEs and specific severe AEs were identified.

I 4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nirsevimab vs. no intervention or placebo

Study	Study level	Outcomes							
		All-cause mortality[a]	RSV lower respiratory tract infection[b]	Severe RSV lower respiratory tract infection[c]	Health-related quality of life	SAEs	Severe AEs	Study discontinuations due to AEs	Specific AEs
HARMONIE	L	L	–[d]	L	–[d]	L	L[e]	H[f]	–[g]
MELODY	L	L	L	L	–[d]	L	L[h]	L	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Composite outcome consisting of the components hospitalization and outpatient care, each due to RSV lower respiratory tract infection.
c. Operationalized as hospitalization due to RSV lower respiratory tract infection.
d. Outcome not recorded.
e. For operationalization, see Section I 4.1.
f. Lack of blinding in subjective recording of outcomes.
g. No suitable analyses on AEs available, a selection of specific AEs is therefore not possible; see Section I 4.1 for reasons.
h. Severe AEs in the MELODY study are operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; RCT: randomized controlled trial; RSV: respiratory syncytial virus; SAE: serious adverse event

The risk of bias of the results of all patient-relevant outcomes except the outcome study discontinuation due to AEs in the HARMONIE study was assessed as low. The reason for the high risk of bias of the results for the outcome discontinuation due to AEs in the HARMONIE study was the lack of blinding in subjective recording of outcomes. However, there were uncertainties in both studies, HARMONIE and MELODY, regarding the proportion of children included who are not covered by the research question for this benefit assessment (see Section I 3.2). These uncertainties led to a limitation of the certainty of conclusions. The results from the individual studies can therefore at most be used to derive hints, for example of an added benefit. A meta-analytical summary of the results of the studies HARMONIE and MELODY allows for at most the derivation of indications, for example of an added benefit.

I 4.3 Results

Table 13 summarizes the results from the comparison of nirsevimab versus no intervention or placebo for the prevention of RSV lower respiratory tract disease in children who are not addressed in the therapeutic information on RSV antibodies during their first RSV season. Where necessary, calculations conducted by the Institute are provided in addition to the data

from the company's dossier. The results of the studies HARMONIE and MELODY pooled in a meta-analysis were used, provided this was methodologically adequate.

Forest plots of the calculations conducted by the Institute can be found in I Appendix C of the full benefit assessment. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full benefit assessment.

Table 13: Results (mortality, morbidity, side effects) – RCT, direct comparison: nirsevimab vs. no intervention or placebo (multipage table)

Outcome category Outcome	Nirsevimab		No intervention or placebo		Nirsevimab vs. no intervention or placebo
Study	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality[a]					
HARMONIE (Day 366)	4016	0 (0)	4018	0 (0)	–
MELODY (Day 361)	1997	4 (0.2)	997	0 (0)	4.50 [0.24; 83.42]; 0.175[b]
Morbidity					
RSV lower respiratory tract infection (composite outcome)					
HARMONIE (Day 366)	Outcome not recorded				
MELODY (Day 361)	2009	40 (2.0)	1003	67 (6.7)	0.30 [0.20; 0.44]; < 0.001[c]
Hospitalization[d]	2009	11 (0.5)[e]	1003	22 (2.2)[e]	0.25 [0.12; 0.51]; < 0.001[c]
Primary[f]	2009	11 (0.5)[e]	1003	22 (2.2)[e]	
Nosocomial[g]	2009	0 (0)[e]	1003	0 (0)[e]	
Outpatient care	2009	ND	1003	ND	
Emergency outpatient clinic	2009	ND	1003	ND	
Acute care	2009	ND	1003	ND	
Outpatient clinic	2009	ND	1003	ND	
RSV lower respiratory tract infection (composite outcome)					
HARMONIE (Day 151)	Outcome not recorded				
MELODY (Day 151)	2009	24 (1.2)	1003	54 (5.4)	0.22 [0.13; 0.35]; < 0.001[h]
Hospitalization[d]	2009	9 (0.4)	1003	20 (2.0)	0.22 [0.10; 0.48]; < 0.001[h]
Primary[f]	2009	9 (0.4)[e]	1003	20 (2.0)[e]	
Nosocomial[g]	2009	0 (0)[e]	1003	0 (0)[e]	
Outpatient care	2009	ND	1003	ND	
Emergency outpatient clinic	2009	ND	1003	ND	
Acute care	2009	ND	1003	ND	
Outpatient clinic	2009	ND	1003	ND	

Table 13: Results (mortality, morbidity, side effects) – RCT, direct comparison: nirsevimab vs. no intervention or placebo (multipage table)

Outcome category Outcome Study	Nirsevimab		No intervention or placebo		Nirsevimab vs. no intervention or placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Severe RSV lower respiratory tract infection[i]					
HARMONIE (Day 366)	4038	43 (1.1)[e]	4019	96 (2.4)[e]	0.45 [0.31; 0.64]; < 0.001[c]
MELODY (Day 361)	2009	11 (0.5)[e]	1003	22 (2.2)[e]	0.25 [0.12; 0.51]; < 0.001[c]
Total[j]					0.40 [0.29; 0.55]; < 0.001
Severe RSV lower respiratory tract infection[i]					
HARMONIE (Day 151)	4038	12 (0.3)	4019	67 (1.7)	0.18 [0.10; 0.33]; < 0.001[c]
MELODY (Day 151)	2009	9 (0.4)	1003	20 (2.0)	0.22 [0.10; 0.49]; < 0.001[h]
Total[j]					0.19 [0.12; 0.31]; < 0.001
Health-related quality of life				Outcome not recorded	
Side effects					
AEs (supplementary information)					
HARMONIE[k]	4016	3212 (80.0)	4018	3192 (79.4)	–
MELODY (Day 361)	1997	1722 (86.2)	997	843 (84.6)	–
SAEs					
HARMONIE (Day 366)[l]	4016	262 (6.5)	4018	222 (5.5)	1.18 [0.99; 1.40]; 0.071[b]
MELODY (Day 361)	1997	149 (7.5)	997	83 (8.3)	0.90 [0.69; 1.16]; 0.450[b]
Total[m]					1.09 [0.94; 1.25]; 0.264
Severe AEs					
HARMONIE[n] (Day 366)	4016	151 (3.8)	4018	143 (3.6)	1.06 [0.84; 1.32]; 0.681[b]
MELODY[o] (Day 361)	1997	79 (4.0)	997	41 (4.1)	0.96 [0.66; 1.39]; 0.888[b]
Total[m]					1.03 [0.85; 1.25]; 0.745
Study discontinuations due to AEs					
HARMONIE (Day 366)	4016	1 (< 0.1)	4018	1 (< 0.1)	1.00 [0.06; 15.99]; > 0.999
MELODY (Day 361)	1997	0 (0)	997	0 (0)	–

Table 13: Results (mortality, morbidity, side effects) – RCT, direct comparison: nirsevimab vs. no intervention or placebo (multipage table)

Outcome category Outcome Study	Nirsevimab		No intervention or placebo		Nirsevimab vs. no intervention or placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
a. The results on all-cause mortality are based on the information on fatal AEs. b. Institute's calculation, unconditional exact test (CSZ method according to [23]). c. RR, 95% CI and p-value from Institute's calculation; p-value: unconditional exact test (CSZ method according to [23]). d. Corresponds to severe RSV lower respiratory tract infections. e. Institute's calculation. f. For the definition of primary hospitalizations, see Section I 4.1. g. For the definition of nosocomial hospitalizations, see Section I 4.1. h. Poisson regression model with logarithm of the observation period as offset, stratified by hemisphere (northern vs. southern hemisphere), age at randomization (age ≤ 3 months vs. age > 3 to ≤ 6 months vs. age > 6 months) and cohort (primary cohort vs. safety cohort). i. Operationalized as hospitalization due to RSV lower respiratory tract infection; for the definition see Section I 4.1. j. Institute's calculation from meta-analysis, fixed-effect model, Mantel-Haenszel method. k. Different observation periods for AEs: non-serious AEs were observed up to Day 31; medically attended AEs, serious AEs and specific AEs up to Day 361. l. The analysis takes into account SAEs that occurred in children in the United Kingdom between Day 366 and the data cut-off of the 1-year analysis (26 April 2024). This was one SAE per treatment arm. m. Calculated from meta-analysis, fixed-effect model with the inverse variance method. n. For operationalization, see Section I 4.1. o. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; RSV: respiratory syncytial virus; SAE: serious adverse event					

Based on the available information, at most hints, for example of an added benefit, can be determined for all outcomes for which suitable data from only one study were available; and at most indications, for example of an added benefit, for outcomes for which suitable data from both studies were available.

Mortality

All-cause mortality

For the outcome all-cause mortality, 4 events occurred in the intervention arm only in the MELODY study. No statistically significant difference between treatment groups was found. There was no hint of an added benefit of nirsevimab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

RSV lower respiratory tract infection

For the composite outcome of RSV lower respiratory tract infection, which was only recorded in the MELODY study, the analysis both at Day 361 and at Day 151 showed a statistically significant difference in favour of nirsevimab compared with watchful waiting. However, there was an effect modification by the characteristic of age at randomization. For children ≤ 6 months, there was a statistically significant difference in favour of nirsevimab. For children > 6 months, in contrast, there was no statistically significant difference between the treatment groups. However, this effect modification did not lead to a separate derivation of the added benefit for this characteristic in the present benefit assessment (for justification, see Section I 4.4). For this outcome, there was a hint of an added benefit of nirsevimab in comparison with watchful waiting for all children.

Severe RSV lower respiratory tract infection

For the outcome of severe RSV lower respiratory tract infection, operationalized as hospitalization due to RSV lower respiratory tract infection, the meta-analysis showed a statistically significant difference in favour of nirsevimab compared with watchful waiting in the analyses both at Day 361/366 and at Day 151. There was an indication of an added benefit of nirsevimab in comparison with watchful waiting for this outcome.

Health-related quality of life

Outcomes in the category of health-related quality of life were not recorded in the studies HARMONIE and MELODY. There was no hint of an added benefit of nirsevimab in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

The meta-analysis showed no statistically significant difference between treatment groups for the outcomes of SAEs and severe AEs. In each case, there was no hint of greater or lesser harm from nirsevimab in comparison with watchful waiting; an added benefit is therefore not proven.

Study discontinuations due to AEs

Only in the HARMONIE study did one child in each treatment arm discontinue the study. No statistically significant difference between treatment groups was found. There was no hint of greater or lesser harm from nirsevimab in comparison with watchful waiting; greater or lesser harm is therefore not proven for this outcome.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in this assessment:

- Age at randomization (≤ 3 months versus > 3 months to ≤ 6 months versus > 6 months)
- Sex (female versus male)

The subgroup characteristics and cut-off values mentioned were predefined for the outcomes severe RSV lower respiratory tract infection and very severe lower respiratory tract infection in the HARMONIE study and for the outcome RSV lower respiratory tract infection in the MELODY study.

The company conducted separate subgroup analyses for HARMONIE and MELODY. For the morbidity outcomes, Module 4 C contains subgroup analyses for the period up to the primary data cut-off (28 February 2023) for the HARMONIE study, and for the period up to Day 151 for the MELODY study. For the outcomes in the side effects category, the company presented subgroup analyses for Day 361/366. For the meta-analytical summary of both studies, the company also calculated interaction terms for the outcomes of severe RSV lower respiratory tract infection, very severe lower respiratory tract infection and the overall rates of AEs, SAEs, severe AEs and the System Organ Class (SOC) general disorders and administration site conditions.

In addition, the study documents contained subgroup analyses for the morbidity outcomes for the HARMONIE study on Day 151.

There were no subgroup analyses of the morbidity outcomes at the analysis dates Day 361 (MELODY) or Day 366 (HARMONIE), neither for the individual studies nor for the meta-analytical summaries.

In the given data situation, the subgroup analyses on Day 151 were taken into account for outcomes in the morbidity category, and those on Day 361/366 for outcomes in the side effects category.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

Table 14 summarizes the subgroup results from the comparison of nirsevimab versus no intervention or placebo. Forest plots of the presented subgroup results can be found in I Appendix B.1 of the full benefit assessment.

Table 14: Subgroups (morbidity) – RCT, direct comparison: nirsevimab vs. no intervention or placebo

Outcome Characteristic	Nirsevimab		No intervention or placebo		Nirsevimab vs. no intervention or placebo	
Study Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
Morbidity						
RSV lower respiratory tract infection (composite outcome)						
Age at randomization						
HARMONIE (Day 151)	Outcome not recorded					
MELODY (Day 151)						
≤ 3 months	1190	19 (1.6)	588	28 (4.8)	0.33 [0.18; 0.59][a]	< 0.001
> 3 months to ≤ 6 months	636	2 (0.3)	323	21 (6.5)	0.05 [0.01; 0.20][a]	< 0.001
> 6 months	183	3 (1.6)	92	5 (5.4)	0.30 [0.07; 1.27][a]	0.102
Total					Interaction[b]:	0.008

a. Poisson regression model, model unclear.
b. Interaction p-value using a Poisson regression model with robust variance and the interaction of subgroup and study arm.

CI: confidence interval; n: number of patients with (at least) one event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

RSV lower respiratory tract infection

For the outcome of RSV lower respiratory tract infection (composite outcome), which was recorded only in the MELODY study, an effect modification for the subgroup characteristic age at randomization (≤ 3 months, > 3 months to ≤ 6 months, > 6 months) was shown at Day 151. For children ≤ 6 months, there was a statistically significant difference between the treatment groups in favour of nirsevimab. For children > 6 months, in contrast, there was no statistically significant difference between the treatment groups. A complete examination of the observed effect modification for this outcome is not possible, as no subgroup analyses were available for the analysis date Day 361. Furthermore, the outcome was not recorded in the HARMONIE study, which included substantially more children.

However, suitable data from both studies were available for the outcome of severe RSV lower respiratory tract infection (at Day 151). The meta-analysis of the studies HARMONIE and MELODY showed a homogeneous data situation for the outcome of severe RSV lower respiratory tract infection (at Day 151) for this subgroup characteristic (Institute's calculation,

interaction test p = 0.605). Since this outcome was included in the outcome of RSV lower respiratory tract infection (composite outcome) and was also based on the more conclusive meta-analysis, no separate assessment was made according to this subgroup characteristic, as heterogeneity was not confirmed.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 15).

Determination of the outcome category for the morbidity outcomes

It could not be inferred from the dossier whether the following morbidity outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

RSV lower respiratory tract infection

The composite outcome of RSV lower respiratory tract infection included the components hospitalization and outpatient care (see Section I 4.1).

It can be assumed that RSV lower respiratory tract infections that can be treated on an outpatient basis are of minor severity compared to RSV lower respiratory tract infections that lead to hospitalization. Since, in the given data situation, RSV lower respiratory tract infections that lead to hospitalization accounted for only about a third of the events in the outcome RSV lower respiratory tract infection in the MELODY study, the outcome was assigned to the outcome category non-serious/non-severe symptoms/late complications.

Severe RSV lower respiratory tract infection

The outcome of severe RSV lower respiratory tract infection was operationalized as RSV lower respiratory tract infection leading to hospitalization. Hospitalization is a serious event. The outcome of severe RSV lower respiratory tract infection was therefore assigned to the outcome category serious/severe symptoms/late complications.

Table 15: Extent of added benefit at outcome level: nirsevimab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Nirsevimab vs. no intervention or placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality[c]	0.2% vs. 0% RR: 4.50 [0.24; 83.42]; p = 0.175	Lesser benefit/added benefit not proven
Morbidity		
RSV lower respiratory tract infection[d]		
Day 361	2.0% vs. 6.7% RR: 0.30 [0.20; 0.44]; p < 0.001	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Day 151	1.2% vs. 5.4% RR: 0.22 [0.13; 0.35]; p < 0.001 Probability: hint	
Severe RSV lower respiratory tract infection		
Day 361/366	0.5%–1.1% vs. 2.2%–2.4% RR: 0.40 [0.29; 0.55]; p < 0.001	Outcome category: serious/severe symptoms/late complications CI_o < 0.75, risk < 5% Added benefit, extent: considerable
Day 151	0.3%–0.4% vs. 1.7%–2.0% RR: 0.19 [0.12; 0.31]; p < 0.001 Probability: indication	
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	6.5%–7.5% vs. 5.5%–8.3% RR: 1.09 [0.94; 1.25]; p = 0.264	Greater/lesser harm not proven
Severe AEs	3.8%–4.0% vs. 3.6%–4.1% RR: 1.03 [0.85; 1.25]; p = 0.745	Greater/lesser harm not proven
Study discontinuations due to AEs[e]	< 0.1% vs. < 0.1% RR: 1.00 [0.06; 15.99]; p > 0.999	Greater/lesser harm not proven

Table 15: Extent of added benefit at outcome level: nirsevimab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Nirsevimab vs. no intervention or placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if statistically significant differences are present. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. The result is based on only one study (MELODY). No events occurred in the HARMONIE study. d. The result is based on only one study (MELODY). The outcome was not recorded in the HARMONIE study. e. The result was based on only one study (HARMONIE). No events occurred in the MELODY study. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event		

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of nirsevimab vs. watchful waiting

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Severe RSV lower respiratory tract infection: indication of an added benefit – extent: considerable Non-serious/non-severe symptoms/late complications ▪ RSV lower respiratory tract infection: hint of an added benefit – extent: considerable	–
No data are available for the outcomes of health-related quality of life	
RSV: respiratory syncytial virus	

Overall, only positive effects were shown for nirsevimab in comparison with watchful waiting. In the category of serious/severe symptoms/late complications, there was an indication of considerable added benefit for the outcome of severe RSV lower respiratory tract infection. There was also a hint of a considerable added benefit for the outcome of RSV lower respiratory tract infections in the category of non-serious/non-severe symptoms/late complications. However, it should be noted that this outcome includes events that were already included in the outcome of severe RSV lower respiratory tract infection, so these are not completely independent outcomes.

In summary, there is an indication of a considerable added benefit of nirsevimab versus the ACT for the prevention of RSV lower respiratory tract disease in children during their first RSV season who are not addressed in the therapeutic information on RSV antibodies.

Table 17 summarizes the result of the assessment of the added benefit of nirsevimab in comparison with the ACT.

Table 17: Nirsevimab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Prevention of RSV lower respiratory tract disease in children during their first RSV season who are not addressed in the therapeutic information on RSV antibodies[b]	Watchful waiting	Indication of considerable added benefit

a. Presented is the ACT specified by the G-BA.
b. The present benefit assessment of nirsevimab only covers children without an indication for secondary prophylaxis of lower respiratory tract infections according to AM-RL Appendix IV – Therapeutic information according to §92 para. 2 sentence 7 SGB V [3]. Thus, the following children are not covered by this benefit assessment:
- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically relevant congenital heart defects (e.g. relevant left-to-right and right-to-left shunt diseases, and patients with pulmonary hypertension or pulmonary venous congestion)
- Children with trisomy 21
- Children ≤ 6 months of age at the onset of the RSV season who were born prematurely before the completed 35th week of gestation (34 weeks [+ 6 days])

AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee; RSV: respiratory syncytial virus

The assessment described above differs from that by the company, which derived proof of a major added benefit based on the results of the individual studies HARMONIE and MELODY and their meta-analytical summaries.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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