Nirsevimab (secondary prophylaxis of RSV disease of the lower respiratory tract)

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

EXTRACT

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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

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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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
BPD	bronchopulmonary dysplasia
CHD	congenital heart defect
CPAP	continuous positive airway pressure
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)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) 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 4 March 2024.

Research question

The aim of this report is to assess the added benefit of nirsevimab compared with the appropriate comparator therapy (ACT) in children during their 1st respiratory syncytial virus (RSV) season with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV.

The research questions shown in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of nirsevimab

Research question	Therapeutic indication	ACT[a, b]
1	Children during their 1st RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is indicated[d]	Palivizumab
2	Children during their 1st RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated[d]	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. No ACT is determined for nirsevimab for the prevention of lower respiratory tract infections caused by RSV in paediatric patients at the beginning of their 1st RSV season that is not a secondary prophylaxis, as this therapeutic indication currently does not fall within the scope of §35 a SGB V.
c. For certain children, the intervention is a secondary prophylaxis:
- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the last 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically significant congenital heart defect (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 up to the completed 35th week of gestation (34 weeks [+ 6 days])

d. The therapeutic advice on RSV antibodies (AM-RL Appendix IV - Therapeutic advice in accordance with §92 [para. 2, sentence 7] SGB V) dated 2 November 2023 must be taken into account. With regard to research question 2, the G-BA specified that this patient group currently comprises only patients with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant congenital heart defect, who were not born prematurely up to the completed 35th week of gestation (34 weeks [+ 6 days]).

AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee; RSV: respiratory syncytial virus; SGB: Social Code Book V

For better readability, the present benefit assessment uses the following terms for the patient populations of the research questions presented in Table 2:

- Research question 1: children in whom secondary prophylaxis with palivizumab is indicated
- Research question 2: children in whom secondary prophylaxis with palivizumab is not indicated

The company followed the G-BA's specification of the ACT for research questions 1 and 2, but deviated from the G-BA in the allocation of the patient population to the research questions. The approach of the company is not appropriate.

Allocation of the patient populations to research question 1 and research question 2 according to the G-BA and approach of the company

In accordance with the G-BA's note, the therapeutic advice on RSV antibodies (Pharmaceutical Directive Appendix IV – therapeutic advice according to §92 [para. 2, sentence 7] SGB V) with resolution of 2 November 2023 must be taken into account for the allocation of the patient populations to research questions 1 and 2. According to this, the use of nirsevimab is indicated at the onset of the RSV season for the following children ≤ 12 months of age at high risk of a severe course of infection:

- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the last 6 months before the onset of the RSV season; these measures included supplemental oxygen, steroids, bronchodilators or diuretics
- Children with haemodynamically significant congenital heart defect (CHD) (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 up to the completed 35th week of gestation (34 weeks of gestation [+ 6 days])

According to the above-mentioned therapeutic advice and the approval of palivizumab, treatment with palivizumab is suitable for all these children, with the exception of children with trisomy 21. They are therefore covered by research question 1. With regard to research question 2, the G-BA specified in its notes on the ACT that this patient group currently comprises only children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant CHD, who were not born prematurely up to the completed 35th week of gestation (34 weeks [+ 6 days]).

In deviation from the specification of the G-BA, the company used the therapeutic advice on palivizumab from 2008 and the S2k guideline "Guideline on the prophylaxis of severe respiratory syncytial virus (RSV) disease in high-risk children" from 2018 for the allocation of children to research questions 1 and 2 in addition to the approval of palivizumab. For the company, this results in the following allocation to the 2 research questions:

- Research question 1 (children in whom secondary prophylaxis with palivizumab is indicated):
  - Children in their 1st year of life and with haemodynamically significant CHD
  - Children in their 1st year of life and with bronchopulmonary dysplasia (BPD)
  - Preterm infants ≤ 6 months of age at the onset of the RSV season and with a gestational age of < 29 weeks of pregnancy
- Research question 2 (children in whom secondary prophylaxis with palivizumab is not indicated):
  - Children in their 1st year of life and with an underlying neuromuscular disease, severe chronic lung disease such as cystic fibrosis, trisomy 21, or immunodeficiency
  - Premature children with a gestational age between 29 and 35 weeks of pregnancy (it is assumed that the company only included children ≤ 6 months of age, in accordance with the 2008 therapeutic advice on palivizumab)

The company justified its approach by stating that, in line with the German Regulation for Early Benefit Assessment of New Pharmaceuticals, a consideration of the health care situation without the drug to be assessed (in this case nirsevimab) was appropriate for the assessment of added benefit and that therefore the previous therapeutic advice on palivizumab from 2008 had to be taken into account. The company's assessment and the inconsistent approach in the dossier are not appropriate. For the present benefit assessment, the therapeutic advice that reflects the current health care situation must be taken into account. Accordingly, the therapeutic advice dated 2 November 2023 is taken into account.

The assessment is carried out for the patient populations specified by the G-BA in comparison with the respective ACTs. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit.

Research question 1: children in whom secondary prophylaxis with palivizumab is indicated

Study pool and study design

The MEDLEY study was included in the benefit assessment of nirsevimab.

The MEDLEY study is a double-blind RCT comparing nirsevimab with palivizumab in children in their 1st year of life entering their 1st RSV season. The study comprises 2 cohorts: a preterm cohort and a cohort with children with either BPD or haemodynamically significant CHD (hereinafter referred to as "BPD/CHD cohort"). According to the study protocol, the preterm cohort included children born at ≤ 35 weeks gestational age who were eligible to receive palivizumab in accordance with national or local guidelines. In accordance with the country-specific approval of palivizumab, only preterm infants between the ages of 6 and 12 months and with a gestational age of 29 to 35 weeks were included in Japan.

A total of 925 children were included in the study, 615 children in the preterm cohort and 310 children in the BPD/CHD cohort. 616 children were randomized to the intervention arm and 309 to the comparator arm. The planned follow-up observation for all children was 360 days after the 1st dose (i.e. until Day 361). Only children in the BPD/CHD cohort received study medication also in the 2nd RSV season. The 2nd RSV season is irrelevant for the benefit assessment and is no longer considered hereinafter.

The present benefit assessment uses the results of the total population. However, this also includes preterm infants aged > 6 months at randomization or born at a gestational age of > 35 weeks and in whom secondary prophylaxis with palivizumab is therefore not indicated. Since, in contrast to the subpopulation presented by the company, the total population also includes children with a gestational age between 29 and 35 weeks in whom secondary prophylaxis with an RSV antibody is indicated, and, in addition, the proportion of children who do not correspond to the present research question is not larger than 15%, the results of the total population are used in the present benefit assessment.

Nirsevimab and palivizumab were each dosed in compliance with the Summary of Product Characteristics (SPC). Palivizumab was administered in a total of 5 doses every 4 weeks. Since nirsevimab is administered in a single dose, the children in the intervention arm also received an intramuscular placebo injection once a month on Days 31, 61, 91 and 121 to maintain blinding. The children also received supportive care where necessary.

The primary benefit outcome of the study was the composite outcome of RSV lower respiratory tract infection. Patient-relevant secondary outcomes were all-cause mortality and outcomes from the side effects category.

Risk of bias

The risk of bias across outcomes was rated as low for the MEDLEY study. The risk of bias for the results of the outcomes of all-cause mortality, RSV lower respiratory tract infection, serious adverse events (SAEs) and severe adverse events (AEs), as well as discontinuation due to AEs was also rated as low.

Results

The present benefit assessment uses the analyses at the Day 361 Visit with the data cut-off on 30 April 2022 for all included outcomes.

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of an added benefit of nirsevimab in comparison with palivizumab; an added benefit is therefore not proven.

Morbidity

RSV lower respiratory tract infection

There was no statistically significant difference between treatment groups for the composite outcome of RSV lower respiratory tract infection, consisting of hospitalization and outpatient care due to this infection, or for the individual components. There is no hint of an added benefit of nirsevimab in comparison with palivizumab; an added benefit is therefore not proven.

Health-related quality of life

Outcomes in the category of health-related quality of life were not recorded in the MEDLEY study. There is no hint of an added benefit of nirsevimab in comparison with palivizumab; an added benefit is therefore not proven.

Side effects

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. There is no hint of greater or lesser harm of nirsevimab in comparison with palivizumab; greater or lesser harm is therefore not proven for these outcomes.

Research question 2: children in whom secondary prophylaxis with palivizumab is not indicated

Results

The company presented analyses of the studies D5290C00003 and HARMONIE. These include results on the total populations, subpopulations, and a meta-analytical summary of the subpopulations of both studies.

Data presented by the company

Study D5290C00003 is a completed, randomized, double-blind, multicentre study comparing nirsevimab with placebo for the prevention of RSV lower respiratory tract infections. It included healthy preterm infants born with a gestational age between 29 weeks of pregnancy + 0 days

and 34 weeks of pregnancy + 6 days. At the time of study inclusion, the children had to be before their 1st RSV season and not be eligible for secondary prophylaxis with palivizumab based on the criteria of the American Academy of Pediatrics or other local guidelines. A total of 1453 children were randomized in a 2:1 ratio; 969 children were included in the nirsevimab arm and 484 children in the placebo arm. They received one intramuscular injection of 50 mg nirsevimab or placebo and were subsequently observed for another 360 days. In study D5290C00003, the subpopulation of children with a body weight < 5 kg at the time of randomization received an approval-compliant dosage. This subpopulation comprised 570 children in the nirsevimab arm and 290 children in the placebo arm. The primary outcome of the study was the incidence of medically attended RSV lower respiratory tract infection over the duration of the 5-month RSV season. Other outcomes included outcomes on side effects, among others.

The HARMONIE study is a randomized, open-label, multicentre study investigating treatment with nirsevimab to prevent RSV hospitalizations in comparison with no intervention. A total of 8058 infants ≤ 12 months of age and with a gestational age of at least 29 weeks of pregnancy were included, 4037 of whom in the nirsevimab arm. No intervention was given to 4021 children. In accordance with the study protocol, both preterm and term infants were included. At the time of study inclusion, the children had to be before their 1st RSV season and, according to eligibility criteria, not be eligible for secondary prophylaxis with palivizumab based on local guidelines. Treatment with nirsevimab was in compliance with the recommendations of the SPC. Primary outcome of the study was RSV hospitalization. Secondary outcomes included the outcome of very severe RSV lower respiratory tract infections and side effect outcomes. The study started in 2022 and is still ongoing. For the HARMONIE study, the company presented results of the subpopulation of preterm infants born at a gestational age of 29 to 35 weeks of pregnancy. The company considered this subpopulation of 317 children in the nirsevimab arm and 299 children in the comparator arm to comprise those children for whom RSV secondary prophylaxis is indicated and for whom, in addition, palivizumab treatment is not suitable.

Studies D5290C00003 and HARMONIE are unsuitable for the benefit assessment

The analyses presented by the company for research question 2 of the present benefit assessment are not suitable for deriving conclusions on the added benefit of nirsevimab compared with the ACT for children with indication for secondary prophylaxis of RSV lower respiratory tract infections in whom palivizumab is not indicated. Study D5290C00003 included only healthy preterm infants born in their 1st year of life with a gestational age between 29 weeks of pregnancy + 0 days and 34 weeks of pregnancy + 6 days. According to the 2023 therapeutic advice on palivizumab, these preterm infants are candidates for secondary prophylaxis with palivizumab (in accordance with research question 1 of the present benefit assessment), provided they are ≤ 6 months old at the onset of the 1st RSV season. The presented subpopulation of the D5290C00003 study of 570 children in the

nirsevimab arm and 290 children in the placebo arm therefore does not correspond to the patient population determined by the G-BA for research question 2, for whom secondary prophylaxis with palivizumab is not indicated. Accordingly, the total population of study D5290C00003 is also not relevant, with the additional factor that some of the children received a nirsevimab dose that is not in compliance with the approval.

The subpopulation of the HARMONIE study presented by the company for the benefit assessment also exclusively comprised preterm infants with a gestational age of 29 to 35 weeks of pregnancy. Around 20% of the children were already > 6 months old at the time of randomization, and secondary prophylaxis of RSV lower respiratory tract infections is not indicated for these children according to the current therapeutic advice on RSV antibodies. For all preterm infants in the subpopulation aged ≤ 6 months, however, not only is secondary prophylaxis indicated according to the current therapeutic advice, but they are also eligible for palivizumab treatment. The presented subpopulation of the HARMONIE study therefore also does not correspond to the patient population determined by the G-BA for research question 2. In summary, the data presented by the company do not represent the population according to research question 2 and are therefore not suitable for the benefit assessment.

Results on added benefit

No suitable data are available for the assessment of the added benefit of nirsevimab compared with watchful waiting in children with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated. There is no hint of an added benefit of nirsevimab in comparison with the ACT; an added benefit is therefore not proven for this patient group.

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

Research question 1: children in whom secondary prophylaxis with palivizumab is indicated

Overall, neither positive nor negative effects were found for nirsevimab in comparison with palivizumab. Data on health-related quality of life are not available.

In summary, there is no hint of an added benefit of nirsevimab as secondary prophylaxis in comparison with the ACT palivizumab for children with indication for secondary prophylaxis

[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].

of lower respiratory tract infections caused by RSV in whom palivizumab is indicated; an added benefit is therefore not proven for this patient group.

Research question 2: children in whom secondary prophylaxis with palivizumab is not indicated

As no suitable data are available for the assessment of the added benefit of nirsevimab compared with the ACT in children with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated, an added benefit of nirsevimab is not proven for this patient group.

Probability and extent of added benefit – summary

The result of the assessment of the added benefit of nirsevimab in comparison with the ACT is summarized in Table 3.

Table 3: Nirsevimab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Children during their 1st RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is indicated[d]	Palivizumab	Added benefit not proven
2	Children during their 1st RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated[d]	Watchful waiting	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. No ACT is determined for nirsevimab for the prevention of lower respiratory tract infections caused by RSV in paediatric patients at the beginning of their 1st RSV season that is not a secondary prophylaxis, as this therapeutic indication currently does not fall within the scope of §35 a SGB V.
c. For certain children, the intervention is a secondary prophylaxis:
- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the last 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically significant congenital heart defect (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 up to the completed 35th week of gestation (34 weeks [+ 6 days])

d. The therapeutic advice on RSV antibodies (AM-RL Appendix IV - Therapeutic advice in accordance with §92 [para. 2, sentence 7] SGB V) dated 2 November 2023 must be taken into account. With regard to research question 2, the G-BA specified that this patient group currently comprises only patients with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant congenital heart defect, who were not born prematurely up to the completed 35th week of gestation (34 weeks [+ 6 days]).

AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee; RSV: respiratory syncytial virus; SGB: Social Code Book V

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 in children during their 1st RSV season with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV.

The research questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of nirsevimab

Research question	Therapeutic indication	ACT[a, b]
1	Children during their 1st RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is indicated[d]	Palivizumab
2	Children during their 1st RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated[d]	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. No ACT is determined for nirsevimab for the prevention of lower respiratory tract infections caused by RSV in paediatric patients at the beginning of their 1st RSV season that is not a secondary prophylaxis, as this therapeutic indication currently does not fall within the scope of §35 a SGB V.
c. For certain children, the intervention is a secondary prophylaxis:
- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the last 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically significant congenital heart defect (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 up to the completed 35th week of gestation (34 weeks [+ 6 days])

d. The therapeutic advice on RSV antibodies (AM-RL Appendix IV - Therapeutic advice in accordance with §92 [para.2 2, sentence 7] SGB V) dated 2 November 2023 [3] must be taken into account. With regard to research question 2, the G-BA specified that this patient group currently comprises only patients with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant congenital heart defect, who were not born prematurely up to the completed 35th week of gestation (34 weeks [+ 6 days]).

AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee; RSV: respiratory syncytial virus; SGB: Social Code Book V

For better readability, the present benefit assessment uses the following terms for the patient populations of the research questions presented in Table 4:

- Research question 1: children in whom secondary prophylaxis with palivizumab is indicated

- Research question 2: children in whom secondary prophylaxis with palivizumab is not indicated

The company followed the G-BA's specification of the ACT for research questions 1 and 2, but deviated from the G-BA in the allocation of the patient population to the research questions. The approach of the company is not appropriate; this is justified below.

Allocation of the patient populations to research question 1 and research question 2 according to the G-BA and approach of the company

In accordance with the G-BA's note, the therapeutic advice on RSV antibodies (Pharmaceutical Directive Appendix IV – therapeutic advice according to §92 [para. 2, sentence 7] SGB V) with resolution of 2 November 2023 [3] must be taken into account for the allocation of the patient populations to research questions 1 and 2. According to this, the use of nirsevimab is indicated at the onset of the RSV season for the following children ≤ 12 months of age at high risk of a severe course of infection:

- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the last 6 months before the onset of the RSV season; these measures included supplemental oxygen, steroids, bronchodilators or diuretics
- Children with haemodynamically significant CHD (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 up to the completed 35th week of gestation (34 weeks of gestation [+ 6 days])

According to the above-mentioned therapeutic advice and the approval of palivizumab [4], treatment with palivizumab is suitable for all these children, with the exception of children with trisomy 21. They are therefore covered by research question 1. With regard to research question 2, the G-BA specified in its notes on the ACT that this patient group currently comprises only children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant CHD, who were not born prematurely up to the completed 35th week of gestation (34 weeks [+ 6 days]).

In deviation from the specification of the G-BA, the company used the therapeutic advice on palivizumab from 2008 [5]and the S2k guideline "Guideline on the prophylaxis of severe respiratory syncytial virus (RSV) disease in high-risk children" from 2018 [6] for the allocation of children to research questions 1 and 2 in addition to the approval of palivizumab [4]. For the company, this results in the following allocation to the 2 research questions:

- Research question 1 (children in whom secondary prophylaxis with palivizumab is indicated):
  - Children in their 1st year of life and with haemodynamically significant CHD
  - Children in their 1st year of life and with bronchopulmonary dysplasia
  - Premature infants ≤ 6 months of age at the onset of the RSV season and with a gestational age of < 29 weeks of pregnancy
- Research question 2 (children in whom secondary prophylaxis with palivizumab is not indicated):
  - Children in their 1st year of life and with an underlying neuromuscular disease, severe chronic lung disease such as cystic fibrosis, trisomy 21, or immunodeficiency
  - Premature children with a gestational age between 29 and 35 weeks of pregnancy (it is assumed that the company only included children ≤ 6 months of age, in accordance with the 2008 therapeutic advice on palivizumab [5])

The company justified its approach by stating that, in line with the German Regulation for Early Benefit Assessment of New Pharmaceuticals, a consideration of the health care situation without the drug to be assessed (in this case nirsevimab) was appropriate for the assessment of added benefit and that therefore the previous therapeutic advice on palivizumab from 2008 had to be taken into account. In contrast to this, the company based the allocation of the patient populations on the current therapeutic advice with the resolution dated 2 November 2023 for the determining the patient numbers in Module 3 A. The company's assessment and the inconsistent approach in the dossier are not appropriate. For the present benefit assessment, the therapeutic advice that reflects the current health care situation must be taken into account. Accordingly, the therapeutic advice dated 2 November 2023 is taken into account.

For children with other underlying diseases such as immunodeficiency, underlying neuromuscular diseases or severe chronic lung diseases, it should also be noted that the current therapeutic advice on RSV antibodies does not provide for general eligibility for secondary prophylaxis with palivizumab, but that palivizumab treatment is possible in individual cases with justification in the patient file on the basis of weighing up the individual risk of severe RSV disease [3,7]. The company's deviation with regard to the general allocation of children with other underlying diseases such as immunodeficiency, underlying neuromuscular diseases or severe chronic lung diseases to research question 2 remains without consequence, as only healthy preterm infants with a gestational age of 29 to 35 weeks of pregnancy were included in the studies presented by the company for research question 2 (see Chapter I 4).

The assessment is carried out for the patient populations specified by the G-BA in comparison with the respective ACTs. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: children in whom secondary prophylaxis with palivizumab is indicated

I 3.1 Information retrieval and study pool

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

- study list on nirsevimab (status: 19 December 2023)
- bibliographical literature search on nirsevimab (last search on 19 December 2023)
- search in trial registries/trial results databases for studies on nirsevimab (last search on 19 December 2023)
- search on the G-BA website for nirsevimab (last search on 19 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on nirsevimab (last search on 14 March 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: nirsevimab vs. palivizumab

Study	Study category			Available sources		
	Study for the approval 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])
D5290C00005 (MEDLEY[c])	Yes	Yes	No	Yes [8-10]	Yes [11,12]	Yes [13]

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.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that selected by the company.

I 3.1.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: nirsevimab vs. palivizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MEDLEY	RCT, double-blind, parallel	Children in their 1st year of life[b] entering their 1st RSV season: Preterm cohort: ▪ preterm infants with a GA of ≤ 35 weeks, without BPD/CHD, eligible to receive palivizumab in accordance with local or national guidelines BPD/CHD cohort: ▪ children with a prenatal diagnosis of BPD who required therapeutic measures within the 6 months prior to randomization[c] ▪ children with haemodynamically significant CHD	Nirsevimab (N = 616)[d] Palivizumab (N = 309)[e]	Screening: up to 30 days Treatment: up to and including Day 121[f] Observation: Until Day 361[f]	126 study centres in: Austria, Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Japan, Latvia, Lithuania, Mexico, Poland, Russia, South Africa, South Korea, Spain, Sweden, Turkey, Ukraine, United Kingdom, United States 7/2019–1/2023 Data cut-offs: ▪ Primary analysis[g]: 3 May 2021 ▪ Secondary analysis[h]: 30 April 2022 ▪ Final analysis[i]: 20 January 2023	Primary: safety Secondary: morbidity, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: nirsevimab vs. palivizumab (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 consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Contrary to the European approval of palivizumab, in Japan, only children between the ages of 6 and 12 months, and with a GA of 29 to 35 weeks, were included in accordance with the local approval.
c. For example, supplemental oxygen, bronchodilators, or diuretics.
d. 407 children in the preterm cohort and 209 children in the BPD/CHD cohort were randomized to the nirsevimab arm.
e. 208 children in the preterm cohort and 101 children in the BPD/CHD cohort were randomized to the palivizumab arm.
f. Lasting 2 years, the study comprised 2 RSV seasons, which were analysed separately. In the 2nd RSV season, all children in the BPD/CHD cohort in the nirsevimab arm of the 1st RSV season were retreated with nirsevimab. In contrast, children in the palivizumab arm of the 1st RSV season were randomized in a 1:1 ratio to treatment with nirsevimab or palivizumab. Only the results of the 1st RSV season until Day 361 are relevant for the benefit assessment.
g. The primary analysis was performed after all children had completed at least 150 days of follow-up after the 1st dose.
h. The secondary analysis was performed after all children in the BPD/CHD cohort had completed the Day 151 Visit of the 2nd RSV season. It also includes analyses of benefit and harm outcomes up to 360 days after the 1st dose (1st RSV season Day 361 Visit).
i. The final analysis was performed after all children in the BPD/CHD cohort had completed a 360-day follow-up of the 2nd RSV season (2nd RSV season Day 361 Visit).

AE: adverse event; BPD: bronchopulmonary dysplasia; CHD: congenital heart defect; 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. palivizumab

Study	Intervention	Comparison
MEDLEY	Nirsevimab IM on Day 1[a] ▪ 50 mg for < 5 kg body weight ▪ 100 mg for ≥ 5 kg body weight Placebo IM on Days 31, 61, 91 and 121	palivizumab 15 mg/kg body weight IM an Days 1, 31, 61, 91 and 121[a]
	Disallowed pretreatment ▪ any investigational product ▪ palivizumab or other RSV monoclonal antibody or any RSV vaccine, including maternal RSV vaccination ▪ any monoclonal or polyclonal antibody (e.g. hepatitis B immunoglobulin or IV immunoglobulin) **Allowed concomitant treatment** ▪ Supportive care including routine vitamins and iron; from Day 15 after consultation with the investigator, e.g. antibiotics, anti-emetics, anti-diarrheals, and analgesics ▪ supportive care including transfusions of blood and blood products, and other care in accordance with institutional guidelines **Disallowed concomitant treatment** ▪ monoclonal or polyclonal antibody ▪ anticipated cardiac surgery < 6 months after randomization	

a. After unplanned cardiopulmonary bypass surgery < 90 days after receipt of the 1st dose but prior to receipt of the last dose, children in the BPD/CHD cohort in both arms received a replacement dose according to the protocol-specified dosing schedule. In cardiopulmonary bypass surgery ≥ 90 days after receipt of the 1st dose but prior to receipt of the last dose, children in the nirsevimab arm received a replacement dose of nirsevimab of 50 mg, and children in the palivizumab arm received a replacement dose of palivizumab of 15 mg/kg body weight. When determined by the investigator to be medically stable for an IM injection, the children could receive a replacement dose of the study drug to which they had been randomized immediately following the surgery. A total of 8 children in the nirsevimab arm and 7 in the palivizumab arm received a replacement dose.

BPD: bronchopulmonary dysplasia; CHD: congenital heart defect; IM: intramuscular; IV: intravenous; RCT: randomized controlled trial; RSV: respiratory syncytial virus

The MEDLEY study is a completed double-blind RCT comparing nirsevimab with palivizumab in children in their 1st year of life entering their 1st RSV season. The study comprises 2 cohorts: a preterm cohort and a cohort with children with either BPD or haemodynamically significant CHD (hereinafter referred to as “BPD/CHD cohort”). According to the study protocol, the preterm cohort included children born at ≤ 35 weeks gestational age who were eligible to receive palivizumab in accordance with national or local guidelines. In accordance with the country-specific approval of palivizumab, only preterm infants between the ages of 6 and 12 months and with a gestational age of 29 to 35 weeks were included in Japan. For inclusion in the study, neither BPD nor haemodynamically relevant CHD was permitted in the preterm cohort. However, children with uncomplicated small atrial or ventricular septal defects or patent ductus arteriosus, or aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone could be included in the preterm cohort. The BPD/CHD cohort included infants with BPD

requiring medical intervention within the 6 months prior to randomization, such as supplemental oxygen, bronchodilators, or diuretics, as well as infants with haemodynamically significant CHD that was unoperated or partially corrected. In accordance with the country-specific approval of palivizumab, children with trisomy 21 without pre-existing medical condition could also be included in the BPD/CHD cohort in Japan. Infants with haemodynamically significant acyanotic cardiac lesions had to have pulmonary hypertension (≥ 40 mmHg measured pressure in the pulmonary artery) or the need for daily supportive medication. All children included in the MEDLEY study were not allowed to have an active lower respiratory tract infection or RSV infection prior to, or at the time of, randomization.

A total of 925 children were included in the study, 615 children in the preterm cohort and 310 children in the BPD/CHD cohort. The children were randomly allocated to the treatment arms in a 2:1 ratio. 616 children were randomized to the intervention arm and 309 to the comparator arm. Randomization was stratified by the factors of region (northern hemisphere and southern hemisphere) and age when entering the 1st RSV season (≤ 3 months, > 3 months to ≤ 6 months, > 6 months). The planned follow-up observation for all children was 360 days after the 1st dose (i.e. until Day 361). Only children in the BPD/CHD cohort received study medication also in the 2nd RSV season: children in the BPD/CHD cohort who had been assigned to the intervention arm in the 1st RSV season received an additional dose of nirsevimab, and children who had been assigned to the comparator arm in the 1st RSV season were re-randomized in a 1:1 ratio to the nirsevimab arm or palivizumab arm. The 2nd RSV season is irrelevant for the benefit assessment and is no longer considered hereinafter.

Nirsevimab and palivizumab were each dosed in compliance with the SPC [4,14]. Palivizumab was administered in a total of 5 doses every 4 weeks. According to the SPC, there is no time limit of 5 months for the administration of palivizumab. However, it is described that most experience has been gained with 5 monthly injections during an RSV season [4], which is why the restriction of palivizumab administration to 5 doses remains without consequence. Since nirsevimab is administered in a single dose, the children in the intervention arm also received an intramuscular placebo injection once a month on Days 31, 61, 91 and 121 to maintain blinding. The children also received supportive care where necessary. According to the study protocol, this included transfusions of blood and blood products, antibiotics, anti-emetics, anti-diarrheals, and analgesics. If necessary, continuous positive airway pressure (CPAP) ventilation, supplemental oxygen, or administration of bronchodilators, steroids, or cardiac drugs could and were also used.

The primary benefit outcome of the study was the composite outcome of RSV lower respiratory tract infection. Patient-relevant secondary outcomes were all-cause mortality and outcomes from the side effects category.

Data cut-offs

The following data cut-offs were planned for the MEDLEY study:

- Data cut-off dated 3 May 2021 (primary analysis): analysis after all children had completed a follow-up of 150 days after the 1st dose (1st RSV season Day 151 Visit); includes analyses on the benefit outcome of RSV lower respiratory tract infection; also includes results on side effects in children who were observed for more than 151 days at this point in time
- Data cut-off dated 30 April 2022 (Season 2 analysis, referred to as "secondary analysis" by the company in Module 4 A): analysis after all children in the BPD/CHD cohort had completed the Day 151 Visit of the 2nd RSV season; also includes analyses of benefit and harm outcomes up to 360 days after the 1st dose (1st RSV season Day 361 Visit)
- Data cut-off dated 20 January 2023 (final analysis). analysis after all children in the BPD/CHD cohort had completed a 360-day follow-up after the 1st dose of the 2nd season (2nd RSV season Day 361 Visit)

The 2nd RSV season is not part of the present research question; therefore the final analysis is not relevant for the benefit assessment and is not considered further in the following.

In Module 4 A, the company presented the results for the RSV season Day 151 Visit (data cut-off from 3 May 2021) for the benefit outcomes and used these to derive the added benefit. It justified this by stating that RSV infections outside the RSV season are the exception. For outcomes on side effects, the company used the analyses of the 1st RSV season Day 361 Visit (data cut-off from 30 April 2022).

In deviation from the company's procedure, since RSV lower respiratory tract infections can also occur outside the 5-month RSV season, the analyses of the Day 361 Visit with data cut-off on 30 April 2022 are used for the present benefit assessment for all included outcomes, as this covers the longest available observation period.

Relevant population for the benefit assessment

For the MEDLEY study, the company presented results for the total population as well as for a subpopulation. The subpopulation comprised 245 children in the intervention arm and 118 children in the comparator arm. In the subpopulation, the company fully considered the BPD/CHD cohort and restricted the preterm cohort to preterm infants born at a gestational age of < 29 weeks and aged ≤ 6 months at the onset of the RSV season. It therefore did not take into account preterm infants with a gestational age between 29 and 35 weeks and aged ≤ 6 months, who are also eligible for treatment with palivizumab according to the current therapeutic advice [3] and approval of palivizumab [4]. The company justified the restriction regarding gestational age by stating that, at the time of the approval of nirsevimab, there was

no clear recommendation in Germany for RSV prophylaxis with palivizumab or nirsevimab for these preterm infants, and referred to the therapeutic advice for palivizumab applicable at that time [5] and the S2k guideline with the last update in 2018 [6] (see also Chapter I 2).

The exclusion of preterm infants aged ≤ 6 months and born between the 29th and 35th week of pregnancy is not appropriate. According to the current therapeutic advice on monoclonal antibodies [3] and the current S2k guideline on the prophylaxis of severe respiratory syncytial virus (RSV) disease in high-risk children [15], there is a therapeutic indication for secondary prophylaxis with palivizumab for preterm infants aged ≤ 6 months at the onset of the 1st RSV season and born up to the completed 35th week of pregnancy (34 weeks [+ 6 days]). Thus, secondary prophylaxis with palivizumab is also indicated for these children, who are not included in the subpopulation formed by the company. The exclusion of preterm infants aged > 6 months from the subpopulation formed by the company is appropriate.

The present benefit assessment uses the results of the total population. This also includes preterm infants aged > 6 months at randomization or born at a gestational age of > 35 weeks and in whom secondary prophylaxis with palivizumab is therefore not indicated. However, the proportion in relation to the total population is 11% (103 children > 6 months old at randomization) or a maximum of 4% (39 children with gestational age ≥ 35 weeks), so that the proportion of children not comprised by the present question is a maximum of 15% (with no overlap of the 2 characteristics). Since, in contrast to the subpopulation presented by the company, the total population also includes children with a gestational age between 29 and 35 weeks in whom secondary prophylaxis with an RSV antibody is indicated, and, in addition, the proportion of children who do not correspond to the present research question is not larger than 15%, the results of the total population are used in the present benefit assessment. In accordance with the country-specific approval of palivizumab, children with trisomy 21 without pre-existing medical condition could also be included in the BPD/CHD cohort in Japan (see above). According to the current therapeutic advice on RSV antibodies dated 2 November 2023 [3], palivizumab is not suitable for children with trisomy 21 without BPD or a haemodynamically significant CHD and born from the 36th week of pregnancy. However, this only affects one child in the BPD/CHD cohort and is therefore of no consequence for the benefit assessment.

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nirsevimab vs. palivizumab (multipage table)

Study **Characteristic** **Category**	**Nirsevimab** **N[a] = 616**	**Palivizumab** **N[a] = 309**
MEDLEY		
Age at randomization [months], mean (SD)	3.9 (2.6)	3.8 (2.5)
Sex [F/M], %	52/48	57/43
Age category, n (%)		
≤ 3 months	274 (45)	144 (47)
> 3 months to ≤ 6 months	210 (34)	101 (33)
> 6 months[b]	132 (21)	64 (21)
Family origin, n (%)		
White	483 (78)	249 (81)
Black	59 (10)	29 (9)
Asian	36 (6)	14 (5)
Other[c]	38 (6)[d]	16 (5)[d]
GA [weeks]; N		
Mean (SD)	31.7 (3.7)	31.4 (3.7)
Median (min; max)	32.0 (22; 41)	32.0 (23; 40)
GA category, n (%)		
< 29 weeks	130 (21)	70 (23)
≥ 29 to < 35 weeks	390 (63)[d]	197 (64)[d]
≥ 35 weeks[e]	96 (16)	42 (14)
Congenital heart defect, n (%)		
Yes	70 (11)	34 (11)
No	546 (89)	275 (89)
Bronchopulmonary dysplasia, n (%)		
Yes	147 (24)	70 (23)
No	469 (76)	239 (77)
Trisomy 21, n (%)		
Yes	9 (1)[f]	3 (< 1)
No	607 (99)	306 (99)
Treatment discontinuation, n (%)[g]	11 (2)	3 (< 1)
Study discontinuation, n (%)[h]	73 (12[d])	46 (15[d])

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nirsevimab vs. palivizumab (multipage table)

Study Characteristic Category	Nirsevimab N[a] = 616	Palivizumab N[a] = 309
a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. A proportion of 17% of the preterm cohort without bronchopulmonary dysplasia or congenital heart defect (corresponding to 11% of the total population) was > 6 months of age at the time of randomization. c. The category includes the following family origins in the intervention vs. control arm: indigenous (America/Alaska) 2% vs. 2%, indigenous (Hawaii/Pacific Islands) < 1% vs. < 1%, other 3% vs. 2%, diverse < 1% vs. 1%. d. Institute's calculation. e. In the preterm cohort, 8% in the intervention arm vs. 3% in the control arm were born at ≤ 35 weeks GA. f. In the preterm cohort, one child in the intervention arm had trisomy 21 without bronchopulmonary dysplasia or congenital heart defect. g. With the exception of one child who discontinued treatment due to an AE, no information is available on the reasons for treatment discontinuation. h. The most common reason for study discontinuation in the intervention arm vs. control arm was withdrawal by parents or guardians (7% vs. 9%). In the intervention vs. control arm, < 1% vs. < 1% discontinued the study due to the COVID-19 pandemic, and < 1% vs. 2% for "other reasons". AE: adverse event; GA: gestational age; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation		

The characteristics of the children are largely balanced between both treatment arms of the MEDLEY study. The children's mean age was 3.9 months in the intervention arm and 3.8 months in the comparator arm. At 52% and 57% respectively, slightly more than half of the children included in the study were girls. In both arms, most children were ≤ 3 months old at randomization (45% versus 47%) and around 1 third of the children were between 3 and 6 months old (34% vs. 33%). The proportion of children who were > 6 months old at the time of randomization was 21% in both treatment arms. At 63% in the intervention arm and 64% in the comparator arm, the majority of children were born at a gestational age between 29 and 35 weeks of pregnancy. The proportion of children with pre-existing medical conditions was comparable in both treatment arms. In both treatment arms, 11% of the children had a haemodynamically significant CHD, and 24% and 23% respectively had BPD. The proportion of treatment discontinuations was low in both treatment arms (2% vs. < 1%). The proportion of treatment discontinuations was 12% versus 15%.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: nirsevimab vs. palivizumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
MEDLEY	Yes	Yes	Yes	Yes	Yes	No[a]	Low

a. At the time of the study, scheduled visits may not have been performed, and administration of the study drug may have been delayed due to the COVID-19 pandemic. In addition, the coronavirus protection measures also influenced the spread of RSV and thus the risk of RSV infection. As a result, changes were made to the study protocol and the planned analyses. These measures and the comparable situation for all participating children regardless of the study medication do not result in an increased risk of bias at study level.

RCT: randomized controlled trial; RSV: respiratory syncytial virus

The risk of bias across outcomes is rated as low for the MEDLEY study.

Transferability of the study results to the German health care context

The company stated that the majority of the 25 study centres (85%) were located in Europe, the United States and Canada, and that health care and social structures of the countries were comparable to those in Germany. According to the company, transferability was guaranteed for the subpopulation it used, as the subpopulation was formed on the basis of the European approval of palivizumab and the German recommendations prior to the approval of nirsevimab and therefore corresponded to the definition of palivizumab suitability based on German criteria. According to the company, the results of the MEDLEY study are transferable to the German health care context without limitations.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity

- RSV lower respiratory tract infection
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs
  - discontinuation due to AEs
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: nirsevimab vs. palivizumab

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

a. Recorded within the scope of safety as AEs resulting in death.
b. Consisting of the components of hospitalization and outpatient care, each due to RSV lower respiratory tract infection.
c. Includes potentially disease-related events; however, in the present data situation, there is no relevant influence on the results on the overall rates.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. No outcomes in the outcome category were recorded.
f. No specific AEs were identified based on the AEs occurring in the relevant study.

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 outcome of RSV lower respiratory tract infection is a composite outcome. It comprises the components of hospitalization due to RSV and outpatient care due to RSV.

Criteria for confirmed RSV lower respiratory tract infection

To be recorded as RSV lower respiratory tract infection, the 2 components of 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, cracles, or wheeze) were present, there also had to be 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, the children in the preterm cohort also had to fulfil at least one of the following criteria:

- 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)
- hypoxemia: 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

Children in the BPD/CHD cohort had to meet at least one of the following criteria in addition to the 2 criteria mentioned above:

- increase in baseline respiratory rate by ≥ 20% at rest and that rate is greater than the above-mentioned thresholds for the preterm cohort
- hypoxaemia: oxygen saturation < 95% in room air or oxygen saturation drop of 5% from baseline in children with baseline oxygen saturation < 95% in room air, or acute documented need for supplemental oxygen or increased oxygen requirement compared with baseline
- 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

- prescription of new or increased dose of medications from baseline (e.g. bronchodilators, steroids, diuretics, cardiac medications)

For both cohorts, 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 established cohort-specific threshold values for hypoxaemia are in a range of relevant oxygen deficiency and close to a critical range that may require supplemental oxygen [16]. For this reason, the defined criterion of hypoxaemia is classified as a patient-relevant criterion in the present benefit assessment. For the criterion specifically applicable to the BPD/CHD cohort of prescription of new or increased dose of medications from baseline, it should be noted that a dose escalation of existing bronchodilators, diuretics or cardiac medications, or initiation of these drug classes is not necessarily associated with an RSV lower respiratory tract infection and, as a sole criterion, also does not necessarily mean a noticeable worsening for the children. In total, 7 children in the 2 study arms of the BPD/CHD cohort had RSV lower respiratory tract infection by Day 361; 4 of these children had a dose escalation or initiation of drugs. However, based on the available information on the existing symptoms, it is sufficiently certain that the majority of children in the BPD/CHD cohort in whom an RSV lower respiratory tract infection was recorded had at least one other symptom (e.g. intercostal retractions). Thus, this uncertainty regarding the patient relevance of this criterion has no consequences for the present benefit assessment.

Definition of the components RSV hospitalization and RSV outpatient care

As already described, the outcome of RSV lower respiratory tract infection has 2 components. The component of 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 in already existing 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 return to their baseline respiratory status or be clearly resolving the preceding respiratory illness before a new RSV infection was recorded as nosocomial hospitalization.

The component of RSV outpatient care was composed of the number of children requiring medical attention due to an RSV infection in outpatient clinics, urgent and emergency care units.

Relevant analysis of the composite outcome

RSV lower respiratory tract infections leading to hospitalization are potentially more severe than RSV lower respiratory tract infections that can be treated in an outpatient setting. In the present benefit assessment, however, the occurrence of any RSV lower respiratory tract infection, regardless of the developing severity, is relevant. Therefore, the composite benefit outcome is used in its entirety in the present benefit assessment. With regard to the component of hospitalization, no information is available on how many children had a primary or nosocomial hospitalization by Day 361. By Day 151 (1st RSV season), no nosocomial and 2 primary hospitalizations were recorded in each of both treatment arms. By Day 361, a total of 5 children were hospitalized in the intervention arm and 3 children in the comparator arm (primary and nosocomial).

Contrary to the procedure in the present benefit assessment, the company used analyses of the composite outcome until the Day 151 Visit of the 1st RSV season in Module 4 A (see also Section I 3.1.2). At this date of analysis, 4 children in the intervention arm and 3 children in the comparator arm had RSV lower respiratory tract infection, and an additional 8 children in the intervention arm and 4 children in the comparator arm had events between Day 151 and Day 361. After the end of the 5-month RSV season, RSV lower respiratory tract infections still occurred to a relevant extent; the analyses on Day 361 therefore are more informative and are relevant for the benefit assessment. It should be noted that the results of the comparison between intervention and comparator arm are not statistically significant on the analysis dates Day 151 and Day 361.

It should be noted that the MEDLEY study was conducted during the COVID-19 pandemic. Due to the coronavirus protection measures in place at the time, it cannot be ruled out that RSV lower respiratory tract infections were prevented.

RSV hospitalization

In Module 4 A, the company used RSV hospitalization as an independent benefit outcome in the morbidity category. However, the outcome of RSV hospitalization was already recorded as a component of the composite outcome of RSV lower respiratory tract infection and is presented as such in the present benefit assessment.

No information is available on overall hospitalization.

Side effects

The analyses of the overall rates of SAEs and severe AEs potentially include events that can be attributed to the symptoms of RSV lower respiratory tract infection, such as the Preferred Terms (PTs) pneumonia, bronchitis or 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 present data situation, however, it is sufficiently ensured on the basis of the information on common AEs that there is no relevant influence on the results for the outcomes in the side effects category (see I Appendix B of the full dossier assessment). The overall rates of SAEs and severe AEs including disease-related events are therefore used for the benefit assessment.

I 3.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nirsevimab vs. palivizumab

Study		Outcomes						
	Study level	All-cause mortality[a]	RSV lower respiratory tract infection[b]	Health-related quality of life	SAEs	Severe AEs[c]	Discontinuation due to AEs	Specific AEs[e]
MEDLEY	L	L	L	–[d]	L	L	L	–

a. Recorded within the scope of safety as AEs resulting in death.
b. Consisting of the components of hospitalization and outpatient care, each due to RSV lower respiratory tract infection.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. No outcomes in the outcome category were recorded.
e. No specific AEs were identified based on the AEs that occurred in the relevant study.

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

The risk of bias for the results of the outcomes of all-cause mortality, RSV lower respiratory tract infection, SAEs and severe AEs, as well as discontinuation due to AEs was rated as low.

I 3.2.3 Results

Table 12 summarizes the results of the comparison of nirsevimab with palivizumab in children with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is indicated. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix B of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: nirsevimab vs. palivizumab

Study Outcome category Outcome	Nirsevimab		Palivizumab		Nirsevimab vs. palivizumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
MEDLEY (Day 361)					
Mortality					
All-cause mortality	614	5 (0.8)	304	1 (0.3)	2.48 [0.29; 21.10]; 0.449[a]
Morbidity					
RSV lower respiratory tract infection (composite outcome)	616	12 (1.9)	309	7 (2.3)	0.86 [0.34; 2.16][d]; 0.791[a]
Hospitalization	616	5 (0.8)	309	3 (1.0)	0.84 [0.20; 3.48][d]; 0.866[a]
Primary[b]	616	–	309	–	–
Nosocomial[c]	616	–	309	–	–
Outpatient care	616	11 (1.8[d])	309	4 (1.3[d])	1.38 [0.44; 4.30][d]; 0.617[a]
Emergency outpatient clinic	616	6 (0.1[d])	309	0 (0.0[d])	6.53 [0.37; 115.57][d]; 0.089[a]
Acute care	616	3 (0.5[d])	309	1 (0.3[d])	1.50 [0.16; 14.41][d]; 0.791[a]
Outpatient clinic	616	5 (0.8[d])	309	3 (0.1[d])	0.84 [0.20; 3.48][d]; 0.866[a]
Health-related quality of life	Outcomes from this category were not recorded				
Side effects					
AEs (supplementary information)	614	444 (72.3)	304	215 (70.7)	–
SAEs	614	80 (13.0)	304	38 (12.5)	1.04 [0.73; 1.50]; 0.870[a]
Severe AEs[e]	614	50 (8.1)	304	25 (8.2)	0.99 [0.63; 1.57]; 0.979[a]
Discontinuation due to AEs	614	1 (0.2)	304	0 (0.0)	1.49 [0.06; 36.41]; 0.599[a]

a. Institute's calculation; unconditional exact test (CSZ method according to [17]).
b. No data are available on the proportion of primary hospitalizations by Day 361. By Day 151, there were 2 primary hospitalizations in each of the 2 treatment arms. For the definition of primary hospitalizations, see Section I 3.2.1.
c. No data are available on the proportion of nosocomial hospitalizations by Day 361. There were no nosocomial hospitalizations by Day 151. For the definition of nosocomial hospitalizations, see Section I 3.2.1.
d. Institute's calculation.
e. 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; RCT: randomized controlled trial; RR: relative risk; RSV: respiratory syncytial virus; SAE: serious adverse event

Based on the available information, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of an added benefit of nirsevimab in comparison with palivizumab; an added benefit is therefore not proven.

Morbidity

RSV lower respiratory tract infection

There was no statistically significant difference between treatment groups for the composite outcome of RSV lower respiratory tract infection, consisting of hospitalization and outpatient care due to this infection, or for the individual components. There is no hint of an added benefit of nirsevimab in comparison with palivizumab; an added benefit is therefore not proven.

Health-related quality of life

Outcomes in the category of health-related quality of life were not recorded in the MEDLEY study. There is no hint of an added benefit of nirsevimab in comparison with palivizumab; an added benefit is therefore not proven.

Side effects

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. There is no hint of greater or lesser harm of nirsevimab in comparison with palivizumab; greater or lesser harm is therefore not proven for these outcomes.

I 3.2.4 Subgroups and other effect modifiers

The following subgroups were considered in the present assessment:

- age at randomization (≤ 3 months; > 3 months to ≤ 6 months; > 6 months)
- sex (female; male)
- study inclusion criterion (BPD/ haemodynamically significant CHD; preterm birth)

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 one 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 presented only if there is a statistically significant and relevant effect in at least one subgroup.

For the outcomes included in the benefit assessment, subgroup analyses on the above-mentioned characteristics for the period until the Day 361 Visit (1st RSV season) are only available for outcomes on side effects. For the outcome of all-cause mortality, which was recorded in the context of AEs, the company stated that the requirements for calculating the interaction p-value were not met due to the small number of events that occurred, so that no subgroup analyses were conducted. This is appropriate. Using the methods described above, there were no statistically significant effect modifications for the characteristics of age at randomization, sex, and study inclusion criterion for the outcomes in the side effects category.

For the composite outcome of RSV lower respiratory tract infection, the company only considered results from the Day 151 Visit (1st RSV season) in Module 4 A. Due to few events occurring in this outcome, the company did not conduct any subgroup analyses. Subgroup analyses for the subgroup characteristics of age at randomization and sex that cover the period until the Day 361 Visit (1st RSV season) considered for the benefit assessment are not available for the outcome mentioned. Until the Day 151 Visit (1st RSV season), the very low number of events was distributed evenly across the subgroups. Since only a small number of events occurred for the outcome of RSV lower respiratory tract infection in relation to the total population and thus across subgroups by Day 361 (12 children with event in the intervention arm versus 7 in the control arm), it is assumed that there were also no effect modifications relevant to the conclusion for the subgroup characteristics of age at randomization and sex on Day 361. For the subgroup characteristic of study inclusion criterion, there was no statistically significant effect modification for the outcome of RSV lower respiratory tract infection on Day 361.

I 3.3 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 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 13).

Table 13: Extent of added benefit at outcome level: nirsevimab vs. palivizumab

Outcome category **Outcome**	**Intervention vs. comparator** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**
Mortality		
All-cause mortality	0.8% vs. 0.3% RR: 2.48 [0.29; 21.10]; p = 0.449	Lesser/added benefit not proven
Morbidity		
RSV lower respiratory tract infection	1.9% vs. 2.3% RR: 0.86 [0.34; 2.16]; p = 0.791	Lesser/added benefit not proven
Health-related quality of life	Outcomes from this category were not recorded	
Side effects		
SAEs	13.0% vs. 12.5% RR: 1.04 [0.73; 1.50]; p = 0.870	Greater/lesser harm not proven
Severe AEs	8.1% vs. 8.2% RR: 0.99 [0.63; 1.57]; p = 0.979	Greater/lesser harm not proven
Discontinuation due to AEs	0.2% vs. 0% RR: 1.49 [0.06; 36.41]; p = 0.599	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.

AE: adverse event; CI: confidence interval; RR: relative risk; RSV: respiratory syncytial virus; SAE: serious adverse event

I 3.3.2 Overall conclusion on added benefit

Table 14 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of nirsevimab in comparison with palivizumab

Positive effects	**Negative effects**
–	–
Data on health-related quality of life are not available.	

Overall, neither positive nor negative effects were found for nirsevimab in comparison with palivizumab. Data on health-related quality of life are not available.

In summary, there is no hint of an added benefit of nirsevimab as secondary prophylaxis in comparison with the ACT palivizumab for children with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is indicated; an added benefit is therefore not proven for this patient group.

This deviates from the company's assessment, which derived an indication of non-quantifiable added benefit for research question 1.

I 4 Research question 2: children in whom secondary prophylaxis with palivizumab is not indicated

I 4.1 Information retrieval and study pool

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

- study list on nirsevimab (status: 19 December 2023)
- bibliographical literature search on nirsevimab (last search on 19 December 2023)
- search in trial registries/trial results databases for studies on nirsevimab (last search on 19 December 2023)
- search on the G-BA website for nirsevimab (last search on 19 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on nirsevimab (last search on 14 March 2024); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified for assessing the added benefit of nirsevimab in comparison with watchful waiting.

The company, in contrast, identified the RCTs D5290C00003 [18-21] and HARMONIE [22-25] comparing nirsevimab with placebo or no intervention, and used them to derive the added benefit.

The analyses of the studies D5290C00003 and HARMONIE presented by the company are unsuitable for deriving conclusions on the added benefit of nirsevimab in comparison with watchful waiting. The decisive factor for non-eligibility is that the children included in the studies were candidates for palivizumab and that watchful waiting was not an ACT. Below, the studies are described, and reasoning is provided for their exclusion.

I 4.1.1 Evidence provided by the company

Study D5290C00003

Study D5290C00003 is a completed, randomized, double-blind, multicentre study comparing nirsevimab with placebo for the prevention of RSV lower respiratory tract infections. It included healthy preterm infants born with a gestational age between 29 weeks of pregnancy + 0 days and 34 weeks of pregnancy + 6 days. The children had to be before their 1st RSV season at the time of inclusion in the study and were therefore not allowed to be > 1 year old at the time of screening. From Protocol Amendment 1 for the European Union dated 15 May 2018 they had to be ≤ 8 months old at the time of screening if they enrolled at a European study centre. According to study eligibility criteria, the included children were not

eligible for secondary prophylaxis with palivizumab based on the criteria of the American Academy of Pediatrics [26] or other local guidelines. No acute illness was allowed at the time of randomization, and upper respiratory tract illness within 7 days prior to randomization also led to exclusion from participation in the study. Children with active RSV infection or prior history of RSV infection were also excluded from participation in the study.

Between November 2016 and the end of the study in December 2018, a total of 1453 children were randomized in a ratio of 2:1. Randomization was stratified by northern or southern hemisphere and age at the time of randomization. 969 children were included in the nirsevimab arm and 484 children in the placebo arm. They received one intramuscular injection of 50 mg nirsevimab or placebo and were subsequently observed for another 360 days. According to the SPC, nirsevimab is given based on body weight [14]. Children with a body weight < 5 kg receive a dose of 50 mg nirsevimab, children with a body weight of 5 kg or higher receive a dose of 100 mg nirsevimab. In study D5290C00003, the subpopulation of children with a body weight below 5 kg thus received an approval-compliant dosage. This subpopulation comprised 570 children in the nirsevimab arm and 290 children in the placebo arm.

The primary outcome of the study was the incidence of medically attended RSV lower respiratory tract infection over the duration of the 5-month RSV season. Other outcomes included outcomes on side effects, among others.

For the present benefit assessment, the company presented results of the final analysis, i.e. after all children had completed the last study visit and thus Day 361.

HARMONY study

The HARMONIE study is a randomized, open-label, multicentre study investigating treatment with nirsevimab to prevent RSV hospitalizations in comparison with no intervention. Infants ≤ 12 months of age and with a gestational age of at least 29 weeks of pregnancy were included. In accordance with the study protocol, both preterm and term infants were thus included. At the time of study inclusion, the children had to be before their 1st RSV season and, according to eligibility criteria, not be eligible for secondary prophylaxis with palivizumab based on local guidelines. At the time of randomization, children were not allowed to have an active RSV infection or an active lower respiratory tract infection. 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 8058 children were enrolled in the HARMONIE study and randomized at a 1:1 ratio either to treatment with nirsevimab (N = 4037) or to no intervention (N = 4021). Randomization was stratified by country and age of the children. Treatment with nirsevimab was in compliance with the recommendations of the SPC [14].

Primary outcome of the study was RSV hospitalization. Secondary outcomes included the outcome of very severe RSV lower respiratory tract infections and side effect outcomes.

The study started in 2022 and is still ongoing. At the time of the benefit assessment, results of the data cut-off from 28 February 2023 were available. This is the data cut-off for the prespecified primary analysis of the study.

Further information on the characteristics of the studies D5290C00003 and HARMONIE can be found in Table 20 in I Appendix C of the full dossier assessment.

Approach of the company

For the D5290C00003 study, the company presented results from both the total population and the subpopulation with a body weight < 5 kg to ensure that the children in the nirsevimab arm received an approval-compliant dosage (50 mg). The subpopulation of healthy preterm infants < 5 kg with a gestational age of 29 weeks of pregnancy + 0 days to 34 weeks of pregnancy + 6 days comprises infants who the company considered ineligible for treatment with palivizumab. This subpopulation comprised 570 children in the nirsevimab arm and 290 children in the placebo arm.

For the HARMONIE study, the company presented results of the subpopulation (referred to by the company as “dossier population”) of preterm infants born at a gestational age of 29 to 35 weeks of pregnancy. The company considered this subpopulation of 317 children in the nirsevimab arm and 299 children in the comparator arm to comprise those children for whom RSV secondary prophylaxis is indicated and for whom, in addition, palivizumab treatment is not suitable.

In addition, it pooled the results of the presented subpopulations of both studies in a meta-analysis.

The company used all results presented in Module 4 A to derive the added benefit.

I 4.1.2 Assessment of the evidence presented by the company

The analyses presented by the company for research question 2 of the present benefit assessment are not suitable for deriving conclusions on the added benefit of nirsevimab compared with the ACT for children with indication for secondary prophylaxis of RSV lower respiratory tract infections in whom palivizumab is not indicated. This is further explained below.

For preterm infants born until the completed 35th week of pregnancy (34 weeks of pregnancy [+ 6 days]) and who are 6 months or younger at the onset of the RSV season, secondary prophylaxis of RSV lower respiratory tract infections is indicated according to the current

therapeutic advice on RSV antibodies from 2 November 2023 [3] and the approval of palivizumab [4] (see Chapter I 2).

Study D5290C00003 included only healthy preterm infants born in their 1st year of life with a gestational age between 29 weeks of pregnancy + 0 days and 34 weeks of pregnancy + 6 days. According to the 2023 therapeutic advice on palivizumab [3], these preterm infants are candidates for secondary prophylaxis with palivizumab (in accordance with research question 1 of the present benefit assessment), provided they are ≤ 6 months old at the onset of the 1st RSV season. Secondary prophylaxis is no longer an option for preterm infants aged > 6 months. In the total population of study D5290C00003, this affected 207 of the 1453 children included (14.3%). In the subpopulation with < 5 kg at the time of randomization presented by the company, who were treated in compliance with the SPC of nirsevimab, only 2 children were > 6 months old. The presented subpopulation therefore does not correspond to the patient population determined by the G-BA for research question 2, for whom secondary prophylaxis with palivizumab is not indicated. Accordingly, the total population of study D5290C00003 is also not relevant, with the additional factor that some of the children received a nirsevimab dose that is not in compliance with the approval.

The subpopulation of the HARMONIE study presented by the company for the benefit assessment also exclusively comprised preterm infants with a gestational age of 29 to 35 weeks of pregnancy. Around 20% of the children were already > 6 months old at the time of randomization (see Table 21 in I Appendix C of the full dossier assessment), and secondary prophylaxis of RSV lower respiratory tract infections is not indicated for these children according to the current therapeutic advice on RSV antibodies. For all preterm infants in the subpopulation aged ≤ 6 months, however, not only is secondary prophylaxis indicated according to the current therapeutic advice, but they are also eligible for palivizumab treatment. The presented subpopulation of the HARMONIE study therefore also does not correspond to the patient population determined by the G-BA for research question 2.

The therapeutic advice on RSV antibodies dated 2 November 2023 [3] named various groups of children at high risk of severe courses of infection for whom secondary prophylaxis is indicated, including children with trisomy 21. In this respect, the G-BA specified in its notes on the ACT that this patient group currently comprises only patients with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant CHD, who were not born prematurely up to the completed 35th week of gestation (34 weeks [+ 6 days]) (see also Chapter I 1). According to the approval of palivizumab [4], these patients are not covered by the therapeutic indication for palivizumab. Treatment with palivizumab is therefore not suitable for these children. It can be inferred from the clinical study report that the total study population of the HARMONIE study contains few children with trisomy 21. However, it is not clear from the available data how many children in this small group of a maximum of

15 children (9 in the intervention arm and 6 in the comparator arm) had a gestational age of ≥ 36 weeks of pregnancy and thus correspond to the patient population defined by the G-BA for research question 2. The company presented no analyses on these children.

Information on the characterisation of the presented subpopulation of study D5290C00003 with approval-compliant dosing in the intervention arm and the "dossier population" of the HARMONIE study used by the company can be found in Table 21 in I Appendix C of the full dossier assessment.

In summary, the data presented by the company do not represent the population according to research question 2 and are therefore not suitable for the benefit assessment.

I 4.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of nirsevimab compared with watchful waiting in children with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated. There is no hint of an added benefit of nirsevimab in comparison with the ACT; an added benefit is therefore not proven for this patient group.

I 4.3 Probability and extent of added benefit

As no suitable data are available for the assessment of the added benefit of nirsevimab compared with the ACT in children with indication for secondary prophylaxis of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated, an added benefit of nirsevimab is not proven for this patient group.

This deviates from the company's assessment, which derived proof of a considerable added benefit for research question 2.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of nirsevimab in comparison with the ACT is summarized in Table 15.

Table 15: Nirsevimab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Children during their 1st RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is indicated[d]	Palivizumab	Added benefit not proven
2	Children during their 1st RSV season with indication for secondary prophylaxis[c] of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated[d]	Watchful waiting	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. No ACT is determined for nirsevimab for the prevention of lower respiratory tract infections caused by RSV in paediatric patients at the beginning of their 1st RSV season that is not a secondary prophylaxis, as this therapeutic indication currently does not fall within the scope of §35 a SGB V.
c. For certain children, the intervention is a secondary prophylaxis:
- Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the last 6 months before the onset of the RSV season. These measures included supplemental oxygen, steroids, bronchodilators or diuretics.
- Children with haemodynamically significant CHD (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 up to the completed 35th week of gestation (34 weeks [+ 6 days])

d. The therapeutic advice on RSV antibodies (AM-RL Appendix IV - Therapeutic advice in accordance with §92 [para.2 2, sentence 7] SGB V) dated 2 November 2023 [3] must be taken into account. With regard to research question 2, the G-BA specified that this patient group currently comprises only patients with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically significant congenital heart defect, who were not born prematurely up to the completed 35th week of gestation (34 weeks [+ 6 days]).

AM-RL: Pharmaceutical Directive; G-BA: Federal Joint Committee; RSV: respiratory syncytial virus; SGB: Social Code Book V

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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